investigations, including chest radiographs, blood cultures and blood counts.[3] No clinical benefit has been reported and may result in overtreatment and increased resource cost without altering the disease or admission course.[13] Despite this, we described around 40% of infants undergoing at least one investigation, most commonly phlebotomy. Similarly, there remain variations in antibiotic prescribing practices in bronchiolitis worldwide. Our study shows only 10% of infants received antibiotics, compared to higher rates in other centers.[14,15] Interestingly we reported that antibiotics were administered more frequently to infants between 12 and 24 weeks old testing positive for hMPV compared to RSV. The same cohort was more frequently discharged on antibiotics, however, whilst statistically significant, the sample size was small and may account for this variation in the findings. Further education and guideline reinforcement may be required to minimize the use of ineffective and/or unnecessary testing.

CONCLUSION

In a cohort of bronchiolitis with a high incidence of viral testing, RSV and hMPV cases were compared. Our findings suggest RSV affects a younger population, appears to require hydration support more often, and tends to have longer hospital admissions when compared to infants with hMPV bronchiolitis. These findings remained constant on age stratification. Further investigation into precise mechanisms or drivers that lead to these differences, may aid intervention practices and preventative measures.

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EPIDEMIOLOGY AND CLINICAL CHARACTERISTICS OF HUMAN METAPNEUMOVIRUS INFECTIONS IN HOSPITALIZED CHILDREN IN TWO CONSECUTIVE POSTPANDEMIC YEARS

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Abstract: We assessed human metapneumovirus infections in children hospitalized between 2011 and 2023 and compared the strongest pre- and postpandemic seasons. After the COVID-19 pandemic, we observed offseason cases and loss of the alternating pattern of the human metapneumovirus season magnitude. Incidence rate ratio of 0- to 11-month-old versus 12- to 23-month-old children was 2.1 (95% CI: 1.0–4.8) before and 1.3 (95% CI: 0.6–2.9) after the pandemic.

Key Words: HMPV, COVID-19, epidemiology, children, hospitalized

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Human metapneumovirus (HMPV) was first described 20 years ago and is a common cause of upper and lower respiratory tract infections in infants and children.[1] Most children with HMPV infection develop a mild upper respiratory tract infection; however, more severe clinical courses, including life-threatening severe bronchiolitis and pneumonia, are possible.[1] Globally, HMPV is detected in approximately 3%–10% of hospitalizations of younger children (<5 years of age) with acute lower respiratory tract infections.[1] Symptomatic treatment varies depending on the clinical course but may include intensive care unit (ICU) treatment and mechanical ventilation in severe cases.[2] In the Northern Hemisphere, HMPV infections typically peak in March, with seasonal occurrence from late winter to spring (January–March).[3]

Nonpharmaceutical interventions (NPI) due to the COVID-19 pandemic lead to broad changes in the epidemiology of respiratory viruses, such as a significant decrease in the circulation of respiratory syncytial virus (RSV), influenza virus, parainfluenza virus

and HMPV,[4] as well as a decrease in bacterial infections.[5] However, resurgence and offseason occurrence of these infections were observed after NPIs were relaxed, as has been reported for RSV[6,7] and invasive group A Streptococcal infections.[8]

We hypothesized that COVID-19 NPIs might not only alter HMPV seasonality but also change the clinical presentation potentially leading to more severe infections. We thus compared the clinical presentation of children hospitalized with HMPV infections at the University Children's Hospital Bern before and after the COVID-19 pandemic and assessed seasonality of infections.

METHODS

Study Design

We performed a single-center retrospective study among children (<17 years) admitted to the University Children's Hospital Bern with HMPV infection between July 2011 and June 2023. We identified children from our institution's microbiology database and retrieved demographic and clinical data [age, sex, clinical diagnosis, relevant comorbidities, duration of hospitalization, duration of respiratory support, oxygen treatment, high-flow treatment, mechanical ventilation, ICU treatment, viral and bacterial codetections, C-reactive protein (CRP), antimicrobial therapy, catecholamines and death] from the electronic health records of the patients. The local competent ethics committee (project no. 2022-00138) approved this study.

Immunofluorescence Assay of Nasopharyngeal Specimens

HMPV infection was diagnosed by positive immunofluorescence assay of nasopharyngeal swabs or nasopharyngeal aspirates (Main Supplemental Digital Content 1, http://links.lww.com/INF/F355).[9] Every patient admitted with acute respiratory symptoms between 2011 and 2023 was tested systematically, except during the period from May 2015 until April 2020, when testing was performed on an individual basis at the discretion of the treating physician (eg, children with severe clinical courses, such as ICU treatment, ventilation or prolonged hospitalization).

Epidemiologic Definitions

We defined a surveillance year from July 1 to June 30 of the following year.[10] We identified the typical HMPV season using the average epidemic curve, which represents the usual level of HMPV activity calculated as the average of several epidemic years, providing a baseline for typical seasonal variation and is based on the World Health Organization surveillance standards.[11] We determined in-season cases by defining a prepandemic seasonal threshold, defined as 1.645 standard deviations above the mean detection rate in years with systematic testing,[11] and compared monthly HMPV detections to this threshold.

Statistical Analyses

We compared the numbers of hospitalizations from 2011 to 2023 to assess the HMPV disease burden by season. To investigate potential changes in the clinical presentation after the COVID-19 pandemic, we compared the largest HMPV seasons at our hospital prepandemic to the largest HMPV season postpandemic. The primary outcomes were duration of hospitalization in days and duration of any respiratory support (oxygen treatment, high-flow treatment, continuous positive airway pressure and mechanical ventilation) in days. The secondary outcomes were age, ICU admission, maximum CRP level,

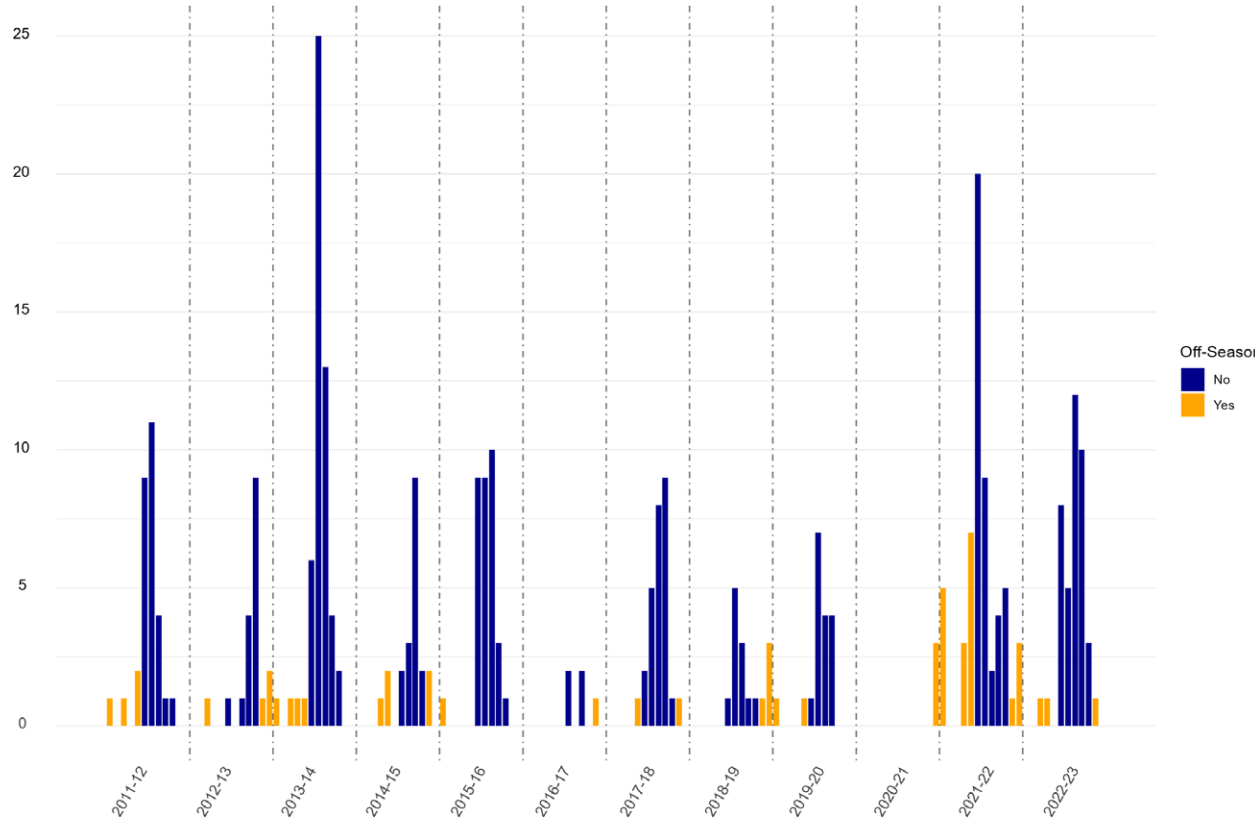

FIGURE 1. Epidemiology of HMPV infections at the University Children's Hospital Bern, 2011–2023. Monthly case counts of children hospitalized with HMPV infection at the University Children's Hospital Bern. Vertical lines on the x-axis indicate the different seasons (July–June of the following year). Yellow color displays offseason occurrences.

TABLE 1. Characteristics of Hospitalized Children With HMPV Respiratory Tract Infection

Characteristic	2013/2014, N = 51*†	2021/2022, N = 59*†	*P* Value‡
Age (years)	1.88 (0.60, 2.30)	2.92 (0.85, 3.45)	0.068
0–11 months	23 (45.1)	17 (28.8)	
12–23 months	11 (21.6)	13 (22)	
>23 months	17 (33.3)	29 (49.2)	
Sex (male)	28 (55)	25 (42)	0.2
Hospitalization (days)	4.35 (3, 5)	5.00 (2, 5)	0.5
Respiratory support with oxygen (days)	2.71 (1, 4)	3.56 (1, 4)	0.9
CPAP required	1 (1.8)	2 (3.4)	
Mechanic ventilation	0	2 (3.4)	
High flow	Not done§	9 (15.5)	
CRP (mg/L)	43.8 (10, 50)	69.18 (6, 102)	0.73
ICU (number of cases)	2 (3.9)	7 (12)	0.11
Antibiotic therapy	22 (43)	20 (34)	0.3
Any codetection	4 (7.8)	11 (18.6)	0.022
Bacterial codetection	2 (3.9)	2 (3.4)	
Viral codetection	2 (3.9)	9 (15)	0.048
RSV	2 (3.9)	0	
Rhino-/enterovirus	0	2 (3.4)	
Parainfluenza virus	0	1 (1.7)	
Rotavirus	0	1 (1.7)	
SARS-CoV-2¶	0	5 (8.5)	
Main diagnosis			0.056
Pneumonia	19 (37)	29 (49)	
Bronchitis	12 (24)	12 (20)	
Bronchiolitis	17 (33)	8 (14)	
URTI	3 (5.9)	10 (17)	
Underlying chronic disease	11 (22)	19 (32)	0.2
Catecholamines (number of cases)	0	1 (1.7)	
Death	0	0	

*Mean (IQR); n (%).
†Children with unclear primary reason for hospitalization were excluded (2013/2014, n = 3; 2021/2022, n = 1).
‡Wilcoxon rank-sum test; Pearson χ^2 test; Fisher exact test.
§High-Flow not available in 2013/2014.
¶SARS-CoV-2 was tested with PCR, only in 2021/2022.
CPAP indicates continuous positive airway pressure; IQR, interquartile range; PCR, polymerase chain reaction; URTI, upper respiratory tract infection.

presence of any codetections and viral codetections, antimicrobial therapy, catecholamines, mechanical or noninvasive ventilation and death. We performed Wilcoxon rank-sum test, Pearson χ^2 test or Fisher exact test depending on data distribution and calculated incidence rate ratios (IRRs) for age groups. Confidence intervals of IRR were calculated with the "Exact Poisson Method" [MedCalc Statistical Software version 22.009 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020), comparison of 2 rates, https://www.medcalc.org/calc/rate_comparison.php (Version 22.009; accessed August 23, 2023)]. For all other statistical analyses and graphs, we used R Statistical Software (v4.1.2; Vienna, Austria; R Core Team 2021; https://www.R-project.org/). Statistical significance was defined as $P < 0.05$.

RESULTS

Seasonality of HMPV Hospitalizations

We identified HMPV infections in 403 children hospitalized at the University Children's Hospital Bern from 2011 to 2023. The typical HMPV season spanned from December to April. Between months May and November, the mean number of cases was <1 per month in prepandemic seasons with systematic testing (2011–2014) (Figure, Supplemental Digital Content 1, http://links.lww.com/INF/F391). We observed seasonal fluctuations of HMPV detections with a mean (range) of 27.2 (3, 60) cases per season (Fig. 1 and Table, Supplemental Digital Content 1, http://links.lww.com/INF/F391). After the institution of COVID-19 NPIs in Switzerland in mid-March 2020,[12] we did not record a single HMPV case between April 2020 and May 2021. This was followed by a larger than usual offseasonal occurrence of HMPV cases in summer 2021 [n = 19 cases vs. mean (range) = 4 (4, 5) cases per season in prepandemic years] (Fig. 1).

Clinical Course of HMPV Infections Before and After the Pandemic

To assess potential changes in disease presentation after the COVID-19 pandemic, we compared the clinical courses of HMPV infections in the seasons with the highest case numbers 2013/2014 (n = 51) and 2021/2022 (n = 59), in each period, respectively (Table 1). In 2021/2022, more children older than 12 months were hospitalized than in 2013/2014. IRR of 0- to 11-month-old children compared to 12- to 23-month-old children was 2.1 (95% CI: 1.0–4.8) before and 1.3 (95% CI: 0.6–2.9) after the pandemic and IRR of 0- to 2-year-old children compared with 3- to 4-year-old children was 3.4 (95% CI: 1.6–7.7) before and 1.8 (95% CI: 0.9–3.4) after the pandemic. Although viral codetections occurred more often in 2021/2022, there was no difference in the clinical course (Table 1). Severe courses, which required ICU admission and catecholamines or antimicrobial treatment, rarely occurred, with no significant difference between the pre- and postpandemic periods (Table 1).

DISCUSSION

We found no difference in the presentation of HMPV infections in hospitalized children before and after the COVID-19 pandemic, despite an offseason resurgence after lifting the NPI and an increase in patient age.

After HMPV hospitalizations were completely suppressed during the pandemic NPIs period (spring 2020 until spring 2021), we observed the highest case numbers in the past 11 years and an increased offseasonal occurrence in 2021/2022, followed by another season with relatively high case numbers in 2022/2023. Our findings in the first postpandemic season are in line with other

studies that observed strong rebounds of HMPV after NPI-associated reduction and a delayed peak in HMPV case numbers.[13] However, we saw 2 seasons with comparably high case numbers in consecutive years (2021/2022 and 2022/2023), which was unexpected in our setting, where HMPV seasons usually alternate with RSV seasons.[9] Conceivably, the circulation of HMPV during the first postpandemic season was insufficient to restore population immunity, as has been the case after seasons in prepandemic years. One could also hypothesize that the massive cocirculation of different respiratory viruses [RSV, severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2)], which has resulted in more frequent viral codetections, interfered with the induction of robust immune responses. It is interesting to note that also for RSV, the 2022/2023 season was marked by much greater hospitalization rates than the 2021/2022 season (data on file).

When comparing the largest prepandemic season (2013/2014) to the largest postpandemic season (2021/2022), we found no major differences in the clinical course of HMPV infections, which is in line with reports on RSV.[14] In contrast, one study from Spain has reported more severe clinical courses of HMPV infections in children.[15] Like the study from Spain, we found an increase in the average age of children hospitalized with HMPV infection after the COVID-19 pandemic.[15] This might be explained by decreased population immunity due to lack of exposure in an age group, which is normally dealing with respiratory viruses regularly.[6] Under normal circumstances, most children are seropositive for HMPV by the age of 2 years.[16] Temporary suppression of virus circulation during the early pandemic likely prevented exposure to HMPV and deferred the first contact with this pathogen to the second or third year of life. Similar findings have been reported from Spain[15] and for RSV.[17]

To the best of our knowledge, our study is the first study to extend the observation period to 2 postpandemic years. Owing to systematic testing for several years, we have a comprehensive dataset for our institution, which is the sole provider of pediatric inpatient care for a stable population of approximately 160,000 individuals below 16 years of age. However, the overall low number of cases of HMPV hospitalizations limits our study. Moreover, we did not perform systematic testing in the years 2015–2019, which may have underestimated the true case load in these years.

After 2 HMPV seasons with comparably high case numbers in consecutive years, we expect a mild season in the coming winter, as general immunity in the population should have been restored. However, surveillance is required to assess whether HMPV and other respiratory viruses return to prepandemic seasonality.

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