The Effect of the COVID-19 Pandemic on Pediatric Respiratory Hospitalizations

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ABSTRACT **Background:** During coronavirus disease 2019 (COVID-19) pandemic, less isolation of common winter viruses was reported in the southern hemisphere.

Objectives: To evaluate annual trends in respiratory disease-related admissions in a large Israeli hospital during and before the pandemic.

Methods: A retrospective analysis of medical records from November 2020 to January 2021 (winter season) was conducted and compared to the same period in two previous years. Data included number of admissions, epidemiological and clinical presentation, and isolation of respiratory pathogens.

Results: There were 1488 respiratory hospitalizations (58% males): 632 in 2018–2019, 701 in 2019–2020, and 155 in 2020–2021. Daily admissions decreased significantly from a median value of 6 (interquartile range [IQR] 4–9) and 7 per day (IQR 6–10) for 2018–2019 and 2019–2020, respectively, to only 1 per day (IQR 1–3) in 2020–2021 (*P*-value < 0.001). The incidence of all respiratory viruses decreased significantly during the COVID-19 pandemic, with no hospitalizations due to influenza and only one with respiratory syncytial virus. There was also a significant decline in respiratory viral and bacterial co-infections during the pandemic (*P*-value < 0.001).

Conclusions: There was a significant decline in pediatric respiratory admission rates during the COVID-19 pandemic. Possible etiologies include epidemiological factors such as mask wearing and social distancing, in addition to biological factors such as viral interference. A herd protection effect of adults and older children wearing masks may also have had an impact.

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Every winter, pediatric outpatient clinics and hospital wards are inundated with children who present with infectious respiratory diseases such as respiratory syncytial virus (RSV) bronchiolitis, influenza A and B, and other respiratory pathogens causing upper and lower respiratory tract infections (URTI, LRTI, respectively) [1,2].

RSV is the leading cause of acute LRTI in children. By the age of 1 year, 60–70% of children have been infected at least once. Hospitalization rates are as high as 2–3%. The estimated past RSV hospitalization burden in Israel, according to a large national database, was highest among infants < 1 year of life (1218.4 per 100,00) [3]. In Israel, influenza affects an average of 20–30% of the pediatric population annually [4]. It usually begins in December, peaks in January, and extends over February [5], while with RSV most cases are reported from early November to late February [6].

The COVID-19 pandemic, originating during December 2019, rapidly spread worldwide with increasing and alarming morbidity and mortality. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has since infected over 224 million people worldwide, resulting in more than 4.6 million deaths globally [7]. The accumulating knowledge concerning this pandemic, as well as previous epidemiological and public health data, has led to the development of widespread infection prevention strategies including mandatory wearing of face masks, hand sanitation, and social distancing. To control the spreading disease, the Israeli government imposed three nationwide quarantine orders (14 March–9 May 2020, 18 September–17 October 2020, and 8 January–7 February 2021), closing all educational facilities and airports with limitations on travel, canceling all social events, and significantly reducing out-of-house employment.

Globally, such measures raised questions regarding how the current 2020–2021 winter season would develop in terms of respiratory infectious illnesses other than COVID-19-related disease. Several assumptions were made based on expert opinion and data from the southern hemisphere, which saw a significant reduction in respiratory disease-related hospital admissions [8,9]. The aims of this study are to assess the number and profile of hospitalizations due to respiratory diseases before and during

the pandemic, specifically during the winter season, compared to the same time period during previous years.

PATIENTS AND METHODS

This retrospective observational study was conducted at Schneider Children's Medical Center, the largest, university-affiliated, tertiary pediatric hospital in Israel. We analyzed electronic medical records (EMR) of children aged 0–18 years old who were hospitalized due to respiratory diseases in all three general wards. The study period was during the winter months of 1 November 2020 to 31 January 2021 (season 3) and was compared to the same period in 2018–2019 (season 1) and 2019–2020 (season 2) as no COVID-19 cases were recorded in Israel before February 2020.

We used the hospital database and filtered the search according to ICD-9 codes for *pneumonia*, *wheezing*, *asthma*, *viral infection*, *bronchiolitis*, *dyspnea or tachypnea*, *RSV*, *influenza*, *adenovirus* as well as hospitalizations due to COVID-19. Each case was reviewed by the researchers. Demographic, clinical, and microbiological data were collected. URTI was diagnosed when the main complaints were nasal discharge with or without coughing [10] as well as stridor. LRTI was defined when wheezing or increased breath sounds over the lungs or signs of inflammation over the lung parenchyma in chest X-ray were detected [11] as well as new hypoxemia in room air. Bacterial pneumonia was defined as respiratory symptoms, fever above 37.5°C or a history of fever at home, and a radiological diagnosis of pneumonia (defined as a confluent area of consolidation) [12]. Co-infection was defined as a diagnosis of bacterial pneumonia together with the isolation of a viral pathogen. Identification of a microbiological pathogen was made using polymerase chain reaction (PCR) from nasal secretions or bacterial sputum cultures. We used AllplexTM RV essential assay kit for screening seven major viral pathogens of respiratory infections (adenovirus, influenza A, influenza B, human metapneumovirus, parainfluenza, RSV, and human rhinovirus A/B/C) (Seegene Inc., Korea).

Our hospital's policy during the pandemic included screening patients for SARS-CoV-2 at all pediatric admissions, even without fever or respiratory complaints. We included hospitalizations associated with COVID-19 but made the distinction between admissions due to COVID-19 respiratory related symptoms or due to other pediatric causes with a subsequent positive PCR test for COVID-19. Re-admission under what was suspected to be the same infectious disease was considered as one hospitalization. If the child was admitted due to a different respiratory disease, we considered it as a separate admission. In addition, children hospitalized in our pediatric intensive care unit (PICU) due to severe respiratory disease are transferred to the general pediatric ward for further care after they are clinically stable, and thus were a part of our patient cohort.

The primary outcome was the number of daily admissions due to respiratory diseases during the study period compared to the previous two winter seasons. The secondary outcomes were a comparison of the clinical and microbiological characteristics of hospitalized children in the COVID-19 era, compared to the same period in the previous 2 years.

STATISTICAL ANALYSIS

Continuous variables with normal distribution are shown as mean ± standard deviation, continuous variables with non-normal distribution or ordinal variables as median and interquartile range (IQR), and categorical data as sum and percentage. Univariate comparisons among groups were performed with appropriate tests. Specifically, nominal variables such as sex and pathogen isolation per admission were compared via Pearson's chi-square test. Continuous variables that fulfilled parametric criteria were compared via Student's *t*-test; and ordinal and continuous non-parametric variables, such as daily respiratory admission, were compared via Mann-Whitney U test.

We designed a regression model to assess the risk of daily respiratory admissions during the winter season of the COVID-19 pandemic (November 2020–January 2021) in comparison with the same period during the two years prior. Incidence rate ratio (IRR) was calculated via negative binomial regression, due to the dispersed nature of our outcome – daily respiratory admissions. Risk for daily respiratory admissions during winter season of the COVID-19 pandemic is presented as IRR with a 95% confidence interval (95%CI). Analysis was performed using IBM® SPSS software version 24 (IBM Corp, Armonk, New York, United States of America). Significance was set as $P \leq 0.05$.

The study protocol was approved by our institutional review board committee.

RESULTS

During the study period, there were 1488 respiratory disease-related hospitalizations in the three general pediatric wards (632 in 2018–2019, 701 in 2019–2020, and 155 in 2020–2021); 58% were males [Table 1]. Total respiratory admissions declined by 75.5% and 77.9% during the COVID-19 pandemic season compared to the winter seasons of 2018–2019 and 2019–2020, respectively. Daily respiratory admissions also declined significantly; median (and IQR) daily respiratory admissions were 6 (4–7), 7 (6–10), and 1 (1–3) during the winter seasons of 2018–2019, 201–2020, and 2020–2021, respectively [Figures 1, 2].

Negative binomial regression showed a significant decrease in daily admissions during the COVID-19 pandemic season. The IRR for daily admissions due to respiratory complaints during the pandemic season in comparison with the two prior winter seasons was 0.235, (95%CI 0.174–0.318, $P < 0.001$).

Median age at admission was 1.0 years old during 2018–2019 (IQR 0.33–2.17), 1.17 years during 2019–2020 (IQR 0.5–2.58), and 1.58 years during 2020–2021 (IQR 0.92–3.92), $P < 0.001$.

Hospitalizations due to LRTI were more common throughout

Table 1 – Respiratory admissions during winter season of Covid-19 pandemic and two years prior; Univariate analysis

	Season #1, (November 2018–January 2019), **n=632**	**Season #2,** (November 2019–January 2020), **n=701**	**Season #3,** (November 2020–January 2021), **n=155**	***P*-value, #1 vs. #2**	***P*-value, #1 vs. #3**	***P*-value, #2 vs. #3**	**Total N=1488**
Sex (male), n(%)	364 (57.6)	396 (56.5)	103 (66.5)	0.684	0.044	0.023	863 (58.0)
Age in years, median (IQR)	1.00 (0.33–2.17)	1.17 (0.50–2.58)	1.58 (0.92–3.92)	0.022	< 0.001	< 0.001	1.17 (0.5–2.5)
Daily respiratory admissions, median (IQR)	6 (4–9)	7 (6–10)	1 (1–3)	0.018	< 0.001	< 0.001	6 (3–8)
URTI, n (%)	102 (16.1)	219 (31.2)	50 (32.3)	< 0.001	< 0.001	0.805	371 (24.9)
LRTI, n (%)	538 (85.1)	484 (69.0)	106 (68.4)	< 0.001	< 0.001	0.873	1,128 (75.8)
Adenovirus, n (%)	69 (10.9)	70 (10)	8 (5.2)	0.578	0.031	0.059	147 (9.9)
HMPV, n (%)	25 (4)	3 (0.4)	1 (0.6)	< 0.001	0.039	0.720	29 (1.9)
Influenza, n (%)	63 (10.0)	186 (26.5)	0	< 0.001	< 0.001	< 0.001	249 (16.7)
RSV, n (%)	285 (45.1)	240 (34.2)	1 (0.6)	< 0.001	< 0.001	< 0.001	526 (35.3)
Parainfluenza, n (%)	35 (5.5)	29 (4.1)	7 (4.5)	0.232	0.612	0.831	71 (4.8)
Rhinovirus, n (%)	1 (0.2)	11 (1.6)	19 (12.3)	0.006	< 0.001	< 0.001	31 (2.1)
SARS-CoV-2, n (%)	0	0	4 (2.6)	–	–	–	4 (0.3)
Bacterial pneumonia: total, n (%)	177 (28.0)	193 (27.5)	43 (27.7)	0.847	0.948	0.958	412 (27.8)
Respiratory co-infections, n (%)	91 (14.4%)	142 (20.3%)	7 (4.5%)	0.005	0.001	< 0.001	240 (16.1%)

HMPV = human metapneumovirus, IQR = inter quartile range, LRTI = lower respiratory tract infection, RSV = respiratory syncytial virus, URTI = upper respiratory tract infection

Figure 1. Daily respiratory admission during winter seasons (2018–2021)

COVID-19 = coronavirus disease 2019

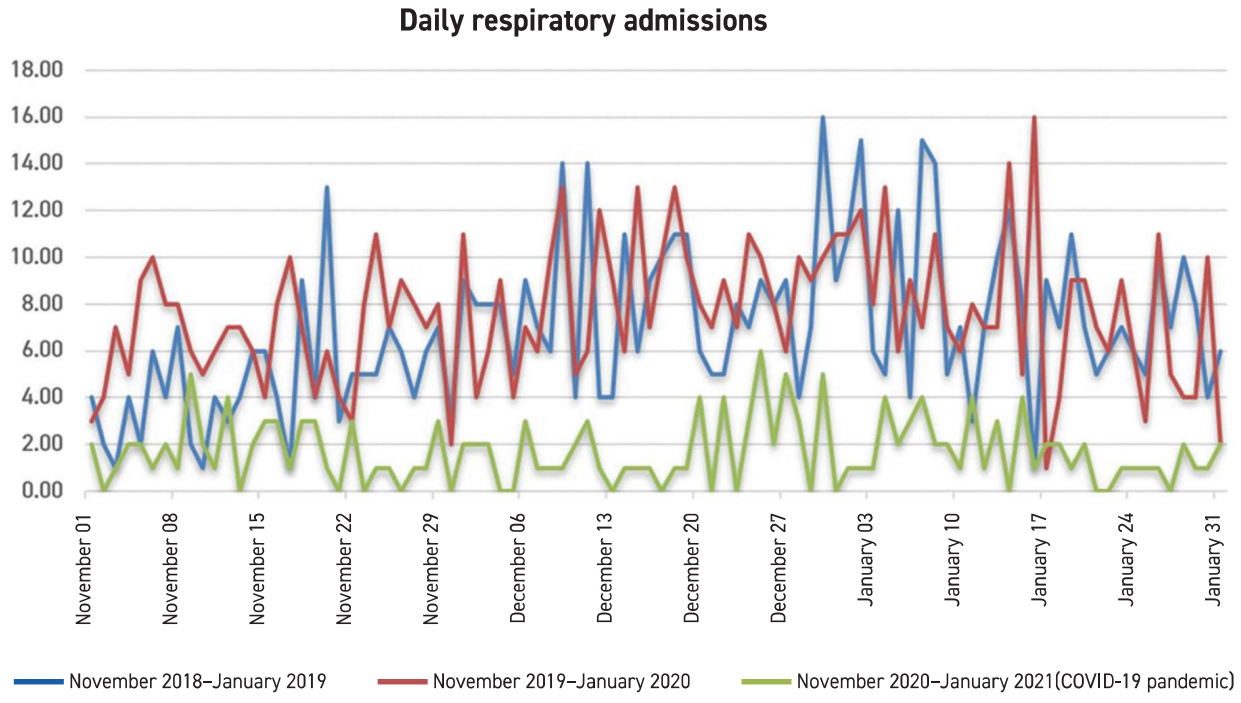
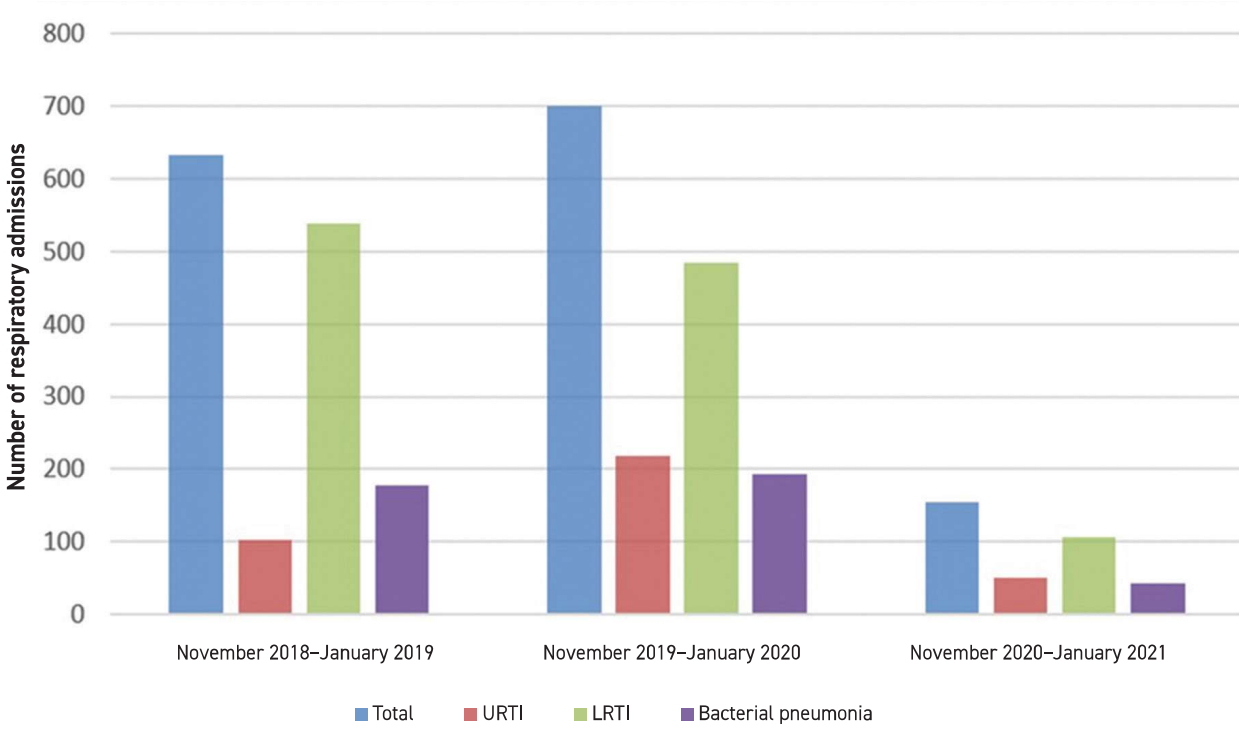


Figure 2. Respiratory admissions and types of infections during the winter seasons (2018–2021)

LRTI = lower respiratory tract infections, URTI = upper respiratory tract infections



the studied periods. There were 538 LRTI admissions in 2018–2019 (85.1%), 484 in 2019–2020 (69%), and 106 in 2020–2021 (68.4%) [Figure 2].

Microbiological analysis revealed a statistically significant decrease in incidence of all viruses in 2020–2021 compared to previous seasons. Rhinovirus was introduced into the general pediatric viral respiratory PCR panel in our hospital in the 2019–2020 season; thus, it was only possible to compare seasons 2 and 3 for this aspect. Rhinovirus prevalence was the only virus found to have increased during the pandemic [Figure 3]. Influenza virus infections were more common in season 2 (P-value < 0.001) compared to season 1, with no hospitalizations due to the virus in season 3. Even though there was an absolute decline in the number of hospitalizations due to bacterial pneumonia during season 3 compared to seasons 1 and 2 (177 and 193 vs. 43, respectively) [Figure 2], their relative percentage of respiratory admission did not change during the study periods. Interestingly, there was a significant decline in the percentage of bacterial and viral co-infections (P value < 0.001) [Figure 3].

In total, there were four hospitalizations due to a respiratory disease attributed to COVID-19, the diagnosis in three was LRTI and one for URTI.

DISCUSSION

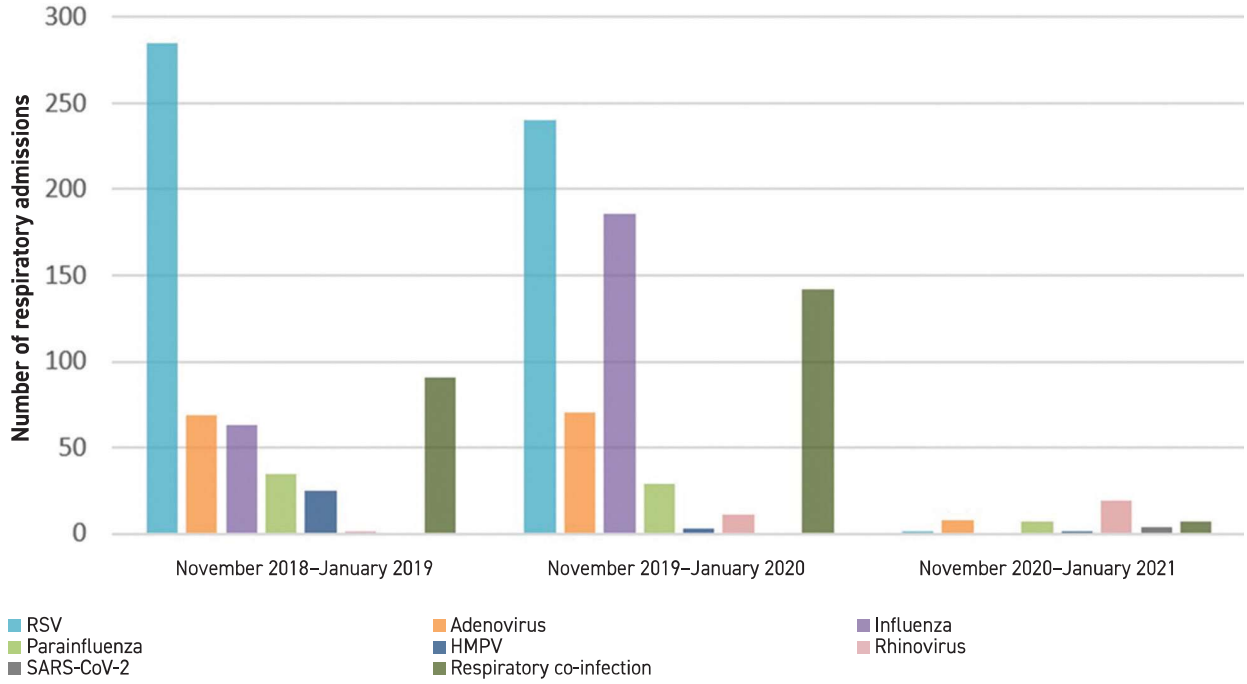
During the COVID-19 pandemic, we found a significant decline in pediatric hospitalizations due to respiratory illnesses, and for all respiratory viruses except rhinovirus. Surprisingly, even during our peak season there was no isolation of influenza virus and only one isolated case of RSV in our hospital. Similarly, the primary physician consultation rates due to URTI and pneumonia during the first wave of COVID-19 in Israel were significantly lower than expected [13].

We assume that the drop in hospitalizations for respiratory diseases was primarily due to epidemiological factors such as wearing facemasks and adhering to hand hygiene, recurrent lock downs, and closure of schools, kindergartens, and childcare institutions. As days of vacation and holidays were similar during the winter seasons, we assume they did not affect the number of hospitalizations.

The high transmission rate and epidemic nature of respiratory tract viruses implies that effective public health measures, such as wearing facemasks, could have reduced transmission and had a substantial role in their prevention [14]. Soon after the beginning of the COVID-19 pandemic, the U.S. Centers for Disease Control and Prevention (CDC) recommended that people older than 2 years should wear masks in public settings, with emphasis on teachers, staff, and students [15]. RSV is a

Figure 3. Respiratory admissions per pathogen during the winter seasons (2018–2021)

HMPV = human metapneumovirus, RSV = Respiratory syncytial virus, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2



highly contagious virus that is transmitted mainly via direct contact with respiratory droplets. Strict hand hygiene, including frequent hand washing or use of alcohol-based hand solutions, is recommended for transmission prevention [16]. The dramatic decline in RSV isolations during the COVID-19 pandemic raises the question whether RSV prevention precautions should include not only contact but also droplet precautions.

Johnson and associates [17] assessed in vivo the efficacy of surgical masks and N95 respirators to filter influenza virus particles in patients with laboratory confirmed acute influenza. They found that surgical masks and respirators were equally effective in filtering influenza, and no virus particles could be detected by reverse transcription PCR in any participant [17]. In contrast, a comprehensive review of eight trials, which examined effectiveness of masks in preventing transmission of respiratory viruses, concluded that surgical masks did not decrease risk for respiratory illness [18].

Indoor crowded places during rainy seasons or cooler months might facilitate transmission of viruses. Furthermore, bronchiolitis is believed to spread in childcare facilities and schools. Avoidance of large crowds in childcare settings may decrease the risk of RSV infection [16]. We assume childcare facility and school closures due to the COVID-19 pandemic had a significant, maybe greater impact, on the transmission of other viruses in addition to its impact on SARS-CoV-2.

A Brazilian study described the impact of social isolation due to the COVID-19 pandemic on the seasonal incidence of respiratory illnesses. They found an average monthly reduction of 38 hospitalizations with a diagnosis of respiratory diseases in the period of social isolation, even though most pediatric respiratory illnesses occurred among children younger than 5 years of age. The younger children presented behavioral and technical challenges in wearing face masks correctly, and for prolonged yet necessary periods of time [19]. Thus, other factors such as lock downs; social distancing; and closures of childcare facilities, schools, and airports were probably more pivotal to the decline in respiratory diseases. Another possible explanation for this decrease could be the herd effect of masks worn by adults and older siblings, who are assumed to be more cooperative and persistent in their mask wearing and social distancing.

There is emerging evidence indicating that viral and bacterial infections act synergistically in many cases and increase the severity of community acquired pneumonia [20]. Influenza virus for example, using several mechanisms such as destruction of respiratory epithelium, decreased mucociliary velocity, and transient immunosuppression, can set the stage for secondary bacterial infections [21,22]. Thus, the decline in viral infections could have mitigated the reduction in both bacterial pneumonias and viral and bacterial co-infection cases observed during the 2020–2021 season [Figures 2 and 3].

Several other intriguing observations arise, including the relative increase in URTIs versus LRTIs during 2020–2021 compared

to 2018–2019, but without an increase in 2019–2020 [Figure 3]. While respiratory infections were scarcer during the 2020–2021 season, there was a relative persistence of viruses typically causing more upper respiratory symptoms such as parainfluenza and rhinovirus. The question why these viruses were more common while influenza and RSV were not, is important. The relative high prevalence of rhinovirus during COVID-19 portrayed in our study was also described by Poole and colleagues [23]. One possible explanation is that rhinoviruses are non-enveloped, making them moderately resistant to soaps and sanitizers and more stable on surfaces, thus allowing greater transmission among children [8]. Wu et al. [24] showed that previous rhinovirus infection can suppress subsequent influenza infection. Possible mechanisms for this phenomenon include direct blockage of viral entry receptors for one virus by another virus, viral competition for host cell resources, and viral induction of innate or adaptive immune responses that protect against a related or distinct virus. This finding raises the question whether COVID-19 by itself or with of rhinoviruses, via viral interference, could mitigate the dramatic decrease in other viral infections in general, and influenza virus specifically.

The main limitation of our study is its retrospective nature. We described the respiratory illnesses in only one center in a hospital setting, which does not necessarily represent the situation in community clinics. Nevertheless, as the largest pediatric center in Israel, we assume our results reflect hospitalizations in other medical centers.

The Israeli Center of Disease Control (ICDC) reports weekly on respiratory viral isolations. During January 24–30, 2021, no influenza activity was identified in the community, and the downward trend of influenza-like illness was low [25].

CONCLUSIONS

During the COVID-19 pandemic there was a dramatic decline in hospital admissions due to pediatric respiratory illnesses, as reflected by only one isolated case of RSV and no isolation of influenza during a period of 4 months. We observed a concomitant significant decrease in the prevalence of human metapneumovirus, parainfluenza, and adenovirus infections, with an increase in the prevalence of rhinovirus isolations. These findings may be explained by various epidemiological factors such as social distancing, recurrent lock downs, facemask wearing, as well as viral interference.

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