Vpliv pandemije Covid-19 na epidemiologijo in etiologijo okužb spodnjih dihal pri otrocih

Impact of Covid-19 pandemic on the epidemiology and etiology of lower respiratory tract infections in children

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IZVLEČEK

Namen: *Spremembe v epidemiologiji nalezljivih bolezni pri otrocih so ena od neposrednih in merljivih posledic pandemije COVID-19, zato smo želeli oceniti vpliv te pandemije na epidemiologijo in etiologijo drugih okužb spodnjih dihal pri otrocih.*

Metode: *Izvedli smo retrospektivno študijo in vključili vse otroke, ki so bili hospitalizirani zaradi okužb spodnjih dihal (izključujoč COVID-19) v letih 2019 in 2021. Pri vseh otrocih smo opravili bris nosno-žrelnega prostora in s pomočjo verižne reakcije s polimerazo določili povzročitelja okužbe spodnjih dihal.*

Rezultati: *Leta 2019 je bilo zaradi okužb spodnjih dihal hospitaliziranih 356 otrok, leta 2021 pa 250, kar je 29,8 % manj. Delež otrok, ki so bili hospitalizirani zaradi atipične pljučnice, se je zmanjšal*

ABSTRACT

Purpose: *Changes in the epidemiology of communicable diseases in children are one of the direct and measurable consequences of the coronavirus disease 2019 (COVID-19) pandemic. Therefore, this study aimed to evaluate the impact of the recent pandemic on the epidemiology of lower respiratory tract infections and the relevant causative pathogens other than severe acute respiratory syndrome coronavirus 2.*

Methods: *In this retrospective study, all children hospitalized due to lower respiratory tract infections in 2019 and 2021 were enrolled. The nasopharyngeal swab test was performed using polymerase chain reaction to identify prevalent respiratory viruses and atypical bacteria.*

Results: *A total of 356 children were hospitalized due to lower respiratory tract infections in 2019 and 250 children in 2021 (a reduction*

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iz 10,1 % v letu 2019 na 2,8 % v letu 2021, delež otrok z bakterijsko pljučnico pa iz 21,9 % v letu 2019 na 12,0 % v letu 2021 (p < 0,01). V pandemičnem letu 2021 smozasledili popolno izginotje virusa gripe in močno zmanjšanje deleža vzorcev, pozitivnih na Mycoplasma pneumoniae, iz 9,0 % v letu 2019 na 2,7 % v letu 2021 (p < 0,01). Delež vzorcev, pozitivnih na rinovirus, pa se je povečal iz 8,2 % v letu 2019 na 41,2 % v letu 2021 (p < 0,01).

Zaključek: *Pandemija COVID-19 je vplivala na pojavnost in etiologijo okužb spodnjih dihal z drugimi povzročitelji. V primerjavi z obdobjem pred pandemijo se je močno zmanjšala pojavnost atipične in bakterijske pljučnice. Virus gripe je med epidemijo COVID-19 povsem izginil inobčutno se je spremenila sezona pojavljanja okužb z respiratornim sincicijskim virusom. Ta opažanja so pomembna za načrtovanje zdravstvenih virov in preventivnih ukrepov za prihodnje pandemije, do katerih bo nedvomno še prišlo.*

of 29.8%). The proportion of children hospitalized due to atypical pneumonia and bacterial pneumonia decreased from 10.1% and 21.9% in 2019 to 2.8% and 12.0% in 2021, respectively (P <0.01 for both). A complete disappearance of influenza viral infections was observed in 2021. Moreover, a profound decrease in the proportion of Mycoplasma pneumoniae–positive specimens from 9.0% in 2019 to 2.7% in 2021 was observed (P <0.01). However, the proportion of rhinovirus-positive specimens increased from 8.2% in 2019 to 41.2% in 2021 (P <0.01).

Conclusions: *The COVID-19 pandemic affected the incidence and etiology of lower respiratory tract infections in children, resulting in a decrease in atypical and bacterial pneumonia, a complete disappearance of influenza, and a seasonal shift in the epidemiology of the respiratory syncytial virus. These observations are important for planning healthcare resources and preventive measures for future pandemics, which will undoubtedly occur.*

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic and the associated preventive measures, such as social distancing, travel restrictions, school and kindergarten closures, and use of masks and hand hygiene, have been found to be associated with a significant reduction in other respiratory infections in children; these included respiratory syncytial virus (RSV) and influenza infections, particularly during the winter season in the Northern Hemisphere (1, 2).

Some epidemics of respiratory infections, such as RSV-related bronchiolitis in infants, occurred much later than expected and outside the typical season, namely, in the late spring or even in the summer of 2020 and 2021. This epidemiological shift likely resulted from a decrease in COVID-related protective measures during the summer months (3, 4). Respiratory tract infections (other than COVID-19) and outpatient visits among Chinese children decreased by more than 50% during the first few winter months after the onset of the COVID-19 pandemic in 2020. Moreover, the incidence of most of the main respiratory viruses (RSV, influenza, adenovirus, and metapneumovirus) was lower than in the same winter months in 2018 and 2019. The incidence of these viruses remained significantly lower during the remainder of 2020. Even greater decreases in LRTIs, including pneumonia and viral infection–induced wheezing, in infants were observed in Israel and Poland. However, lower respiratory tract infections (LRTIs) caused by parainfluenza and rhinovirus sharply increased after the reopening of schools in China in the summer of 2020, which completely compensated for the decrease in winter (5, 6, 7, 8).

The COVID-19 pandemic and related preventive measures have also decreased the incidence of community-acquired pneumonia (CAP) caused by bacteria, including the most common pathogens, such as *Streptococcus pneumoniae* (9). The detection rate of *Mycoplasma pneumoniae*, which is the most common cause of atypical pneumonia in children, also decreased sharply worldwide, and the pathogen did not reappear as expected after lifting COVID-19-related restrictions (10).

Slovenia was one of the countries most affected by COVID-19. The reported incidences of 58,000 cases and 400 deaths per 100,000 population were the third and fourth highest, respectively, among European Union countries (11). Correspondingly, the prevention measures, such as travel restrictions and school and kindergarten closures, have also been comparable to those in other heavily affected European countries (12, 13).

The impact of the COVID-19 pandemic on other LRTIs in Western, Central, and Southern Europe has not been reported. Therefore, we performed a retrospective study to evaluate the impact of the COVID-19 pandemic on the incidence of viral LRTIs and CAP in hospitalized children. Furthermore, we aimed to compare the prevalence and seasonal occurrence of different respiratory viruses and *M. pneumoniae*, as causes of LRTIs, in hospitalized children between the pre-pandemic year of 2019 and the pandemic year of 2021.

MATERIALS AND METHODS

Participants

This retrospective study included 606 patients, aged 1 month to 18 years, hospitalized in Department of Pediatrics, University Medical Centre Maribor from January 1 to December 31, 2019 (n = 350), and from January 1 to December 31, 2021 (n = 256). The patients had acute LRTI with a diagnosis of acute bronchiolitis, acute bronchitis, viral infection–induced wheezing, and CAP. We also included and separately analyzed 56 patients who were hospitalized due to acute laryngitis. Data were collected from the medical records, and the final diagnosis (at discharge) was considered for the statistical analysis.

Patients previously diagnosed with asthma or other chronic pulmonary diseases (e.g., cystic fibrosis, primary ciliary dyskinesia, immune deficiencies, and congenital pulmonary malformations) were not included. Moreover, patients born prematurely (before 37 weeks of gestational age) and patients with neurological impairment, heart diseases, or other known chronic conditions that can predispose them to LRTI symptoms (e.g., gastroesophageal reflux disease) were excluded.

Diagnostics

Nasopharyngeal swabs were collected for detecting the eight most common respiratory viruses (influenza A, influenza B, parainfluenza, RSV, adenovirus, metapneumovirus, rhinovirus, and coronavirus) and three atypical bacteria (*M. pneumoniae*, *Bordetella pertussis*, and *Chlamydophila pneumoniae*). FilmArray, a polymerase chain reaction (PCR)-based assay, was used for detecting COVID-19 in most (94.8%) patients hospitalized in 2019 and in all patients hospitalized in 2021 when COVID-19 was added to the assay. For the statistical analysis, we recorded all pathogens detected by PCR. Serological testing for *M. pneumoniae* and *C. pneumoniae* was performed when atypical bacterial LRTI was suspected.

Chest x-ray (CXR) and/or lung ultrasound (LUS) were performed when clinically appropriate.

CAP was diagnosed using CXR and/or LUS based on the British Thoracic Society criteria and when pneumonia was undoubtedly acquired outside the hospital. A patient was diagnosed with pneumonia when infiltrate(s) was detected on CXR and/or hypoechoic consolidation with hyperechoic air bronchograms detected using LUS (14–16).

Atypical bacterial LRTIs were considered when atypical bacteria were detected in nasopharyngeal swabs and/or when immunoglobulin M against *M. pneumoniae* or *C. pneumoniae* was detected in blood serum (17).

When no viruses or atypical bacteria were detected, either leukocytosis (white blood cell count >15 × 109/L) or consolidation (alveolar infiltrate) on CXR and/or large (>20 mm) single consolidation detected using LUS was sufficient for a diagnosis of bacterial CAP (16, 18, 19). Bacterial CAP (superinfection) was considered in patients with both leukocytosis and a large single consolidation (detected with either CXR or LUS), even when viruses were detected in nasopharyngeal swabs.

Viral infection–induced wheezing was considered in a patient with at least one previous episode of wheezing associated with upper respiratory tract infection in the last year before hospitalization and responded to the beta2-agonist (20). All other patients with signs and/or symptoms of LRTIs were considered to have bronchitis/bronchiolitis after the exclusion of CAP.

When more than one virus (or atypical bacteria) was detected in the same patient (coinfection), each pathogen was considered a separate case for comparing the incidence of different respiratory pathogens between 2019 and 2021.

Statistical analysis

Statistical analysis was performed using SPSS 26.0 statistical software (IBM Inc., IL, USA). The Kolmogorov–Smirnov test was used first to evaluate the normality of data distributions. The median and the interquartile range (IQR) were calculated for quantitative variables. The relative proportions of hospitalizations due to different LRTIs (e.g., acute bronchitis, acute bronchiolitis, viral infection–induced wheezing, and CAP) and acute laryngitis between the pre-pandemic and pandemic years were compared using the Fischer's exact test or chi-squared test. The odds ratio (OR) with a 95% confidence interval (CI) was calculated for 2021 where applicable. The same tests were used to compare the proportions of nasopharyngeal swabs that were positive for the most common respiratory pathogens between 2019 and 2021. The Mann–Whiney U test was performed to compare quantitative variables such as the median age and the length of stay. The α level for all tests was set to 0.05, and the P values were presented for two-tailed tests.

Data availability

The data presented in the article are not publicly available but can be obtained from the corresponding author upon reasonable request.

Statement of ethics

This study was conducted following the 1964 Declaration of Helsinki and its subsequent amendments and was approved by the ethics committee of the University Medical Centre Maribor on September 14, 2022 (protocol number: UKC-MB-KME-47/22).

RESULTS

LRTIs and acute laryngitis

A total of 606 children were hospitalized due to LRTIs (including CAP and viral infection–induced wheezing) in 2019 and 2021, 275 (45.4%) of which were females, with a median age of 23 months (IQR, 28 months). In addition, 56 children (22 or 39.3% were females) were hospitalized in both years due to laryngitis (median age, 27 months; IQR, 31 months).

In 2021, 250 children were admitted due to LRTIs, which was 29.8% less than the year before the pandemic, when 356 children were admitted. The median age of patients in 2021 and 2019 was 22 and 25 months, respectively ($P = 0.15$). The number of children admitted due to acute laryngitis decreased by 72.7% (from 44 in the pre-pandemic year to 12 in 2021).

A comparison of the epidemiological and clinical characteristics of children admitted due to LRTIs in 2021 and 2019 is presented in Table 1. The monthly admission rates (LRTI and acute laryngitis combined) in 2019 and 2021 are presented in Figure 1.

Only 29 (11.1% of all annual cases) patients were hospitalized due to LRTI or acute laryngitis in the first four months of 2021 compared with 229 (57.3%) in the same period in 2019 ($P < 0.01$). However, in 2021, 19,

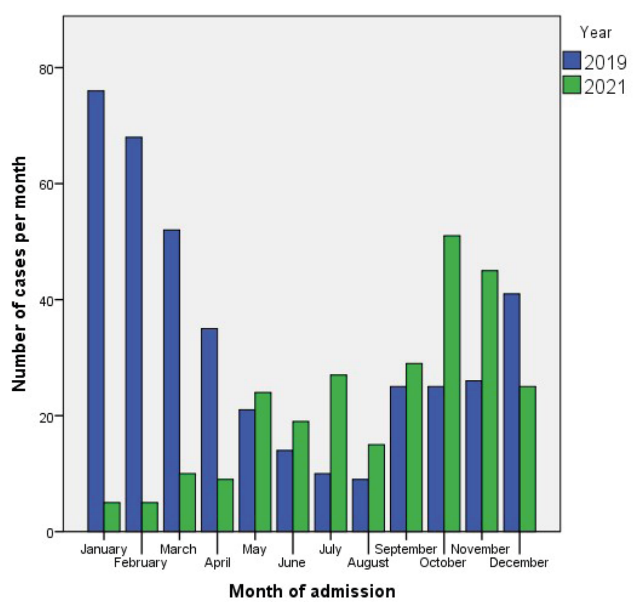

Figure 1. *Monthly admission rate due to lower respiratory tract infections and acute laryngitis in children in 2019 and 2021.*

Table 1. Comparison of epidemiological and clinical characteristics of children hospitalized due to lower respiratory tract infections in 2021 and 2019

Characteristic [n (%)] *	Year 2019 (N ** = 356)	Year 2021 (N = 250)	p value ***	Odds ratio (95% confidence interval) ****
Sex (female)	162 (45.6)	113 (45.2)	1.00	1.00 (0.84–1.20)
Viral infection-induced wheezing	19 (5.3)	24 (9.6)	0.05	1.88 (1.01–3.52)
Bronchitis/bronchiolitis	196 (55.1)	164 (65.6)	0.01	1.56 (1.11–2.17)
Viral pneumonia	30 (8.4)	36 (14.4)	0.02	1.21 (0.73–2.02)
Atypical pneumonia	36 (10.1)	7 (2.8)	< 0.01	0.26 (0.11–0.58)
Bacterial pneumonia	78 (21.9)	30 (12.0)	< 0.01	0.49 (0.31–0.77)

**Number of participants with a particular characteristic (percentage in parentheses).*
***Number of patients hospitalized due to lower respiratory tract infection*
****P value refers to the comparison of the relative proportion of patients hospitalized due to a particular clinical entity (between 2021 and 2019).*
*****Odds ratio was calculated where applicable and for 2021.*

27, 15, 29, and 50 patients (altogether 140 or 53.4%) compared with 14, 10, 9, 25, and 25 patients (altogether 83 or 20.8%) in 2019 were hospitalized in June, July, August, September, and October, respectively (P < 0.01).

Seasonal occurrence of respiratory pathogens

A comparison of the relative proportions of detected specific respiratory viruses between 2021 and 2019 is presented in Table 2.

M. pneumoniae was detected in the nasopharyngeal swabs from 34 (9.0% of all specimens collected) and 7 (2.7%) patients in 2019 and 2021, respectively (P < 0.01; OR = 0.94; 95% CI, 0.90–0.97).

The seasonal occurrence of the two most common respiratory viruses (RSV and rhinovirus) is presented in Figures 2 and 3. In the first 4 months (January–April) of 2019, we detected 91 cases of RSV infection from 220 collected nasopharyngeal swabs. The proportion of positive results was 41.4%, which was significantly higher (P < 0.01) compared with only one RSV-positive result out of 29 swabs collected (3.5%) during the same period in 2021. From August to November 2019, only one patient (from 78 collected swabs, 1.3%) was confirmed to have an RSV infection compared with 77 patients (from 136 collected swabs, 56.6%) during the same period in 2021 (P < 0.01).

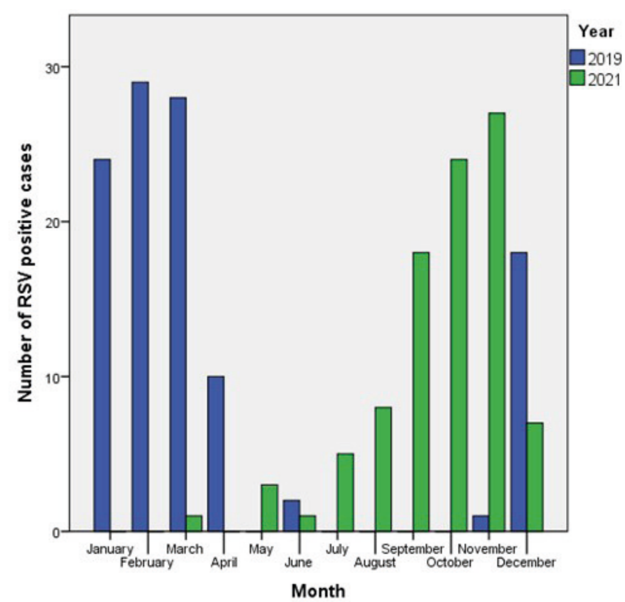

***Figure 2.** Seasonal occurrence of respiratory syncytial virus (RSV) in 2019 and 2021.*

We detected nine cases of rhinovirus infection with 4.1% of total swabs testing positive for rhinovirus in the first 4 months (January–April) of 2019 compared with 10 cases with 34.4% of total swabs

Table 2. Comparison of relative proportions of specimens (nasopharyngeal swab) that were positive for respiratory viruses

Respiratory virus [n (%)] *	Year 2019 (N ** = 379)	Year 2021 (N ** = 257)	p value***	Odds ratio (95% confidence interval) ****
Influenza	66 (17.4)	0 (0)	< 0.01	
RSV	111 (29.3)	93 (36.2)	0.07	1.14 (0.99–1.32)
Rhinovirus	31 (8.2)	107 (41.6)	< 0.01	3.11 (2.27–4.27)
Parainfluenza	10 (2.6)	38 (14.8)	0.51	3.01 (1.73–5.25)
Metapneumovirus	7 (1.8)	19 (7.4)	< 0.01	2.26 (1.20–4.26)
Adenovirus	11 (2.9)	14 (5.4)	0.15	1.37 (0.88–2.14)
Coronavirus (non-COVID-19)	0 (0)	17 (6.7)	< 0.01	

**Number of patients infected with specific respiratory pathogens (percentage of positive specimens in parentheses).*
***Number of collected specimens (nasopharyngeal swab).*
****P value refers to the comparison of relative proportions of positive specimens (between 2021 and 2019).*
*****Odds ratio was calculated where applicable and for 2021.*

testing positive for rhinovirus in 2021 (P < 0.01). From August to November 2019, we detected 18 cases of rhinovirus infection (accounting for 12.8% of positive swabs). In the same period in 2021, we detected 54 cases of rhinovirus infection with 39.7% of total swabs testing positive for rhinovirus (P < 0.01).

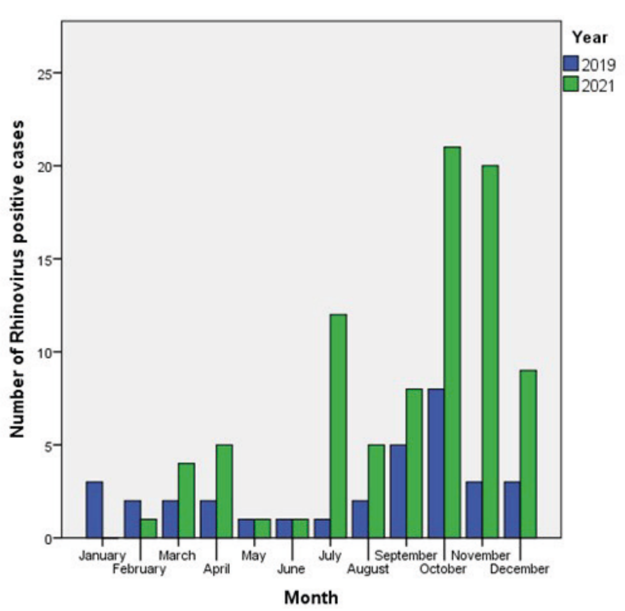

***Figure 3.** Figure 3. Seasonal occurrence of rhinovirus in 2019 and 2021.*

DISCUSSION

In this study, significant differences in the incidence of clinical entities in children hospitalized due to LRTIs were observed between the pre-pandemic year 2019 and 2021, when the COVID-19 pandemic and related preventive measures reached their peak. The differences in the incidence and seasonal occurrence of different respiratory pathogens that cause LRTI were even more profound. The hospitalization rates for acute laryngitis and atypical and bacterial pneumonia decreased by more than 60% in 2021 compared with those in 2019. However, the hospitalization rates of children with viral infection–induced wheezing, acute bronchitis/bronchiolitis, and viral pneumonia in 2021 remained comparable to those in the pre-pandemic year. Moreover, the relative proportions of these clinical entities among all LRTIs even increased in 2021.

The decrease of 29.8% in the overall incidence of hospitalizations due to LRTIs in 2021 (compared with 2019) in our study was less pronounced than that observed in other countries. Rosenfeld et al. reported a reduction in hospitalization due to LRTIs and pneumonia by approximately 80% and a reduction of 40% for wheezing episodes in infants in Israel born in the first months of 2019 compared with those born in the first months of 2020 (7). Grochowska et al.

reported an 81% decrease in the hospitalization rate due to LRTIs in Polish children from April 2020 to March 2021 compared with the same period in 2019/2020 (8). The lower decrease observed in our study was probably due to the comparison of different time frames, as all of the aforementioned studies included the first months of the pandemic in 2020 when preventive measures were most strict, and (unlike our study) did not include the second half of 2021, when we observed the resurgence of hospitalization due to LRTIs, as presented in Figure 1. Northern Italy was one of the regions most affected during the first months of the pandemic and was comparable with Slovenia regarding the incidence of reported cases of COVID-19 and related deaths per 100,000 inhabitants (12, 21). Barbiellini Amidei et al. reported an approximately 50% decrease in emergency department visits among children under 14 years of age in 2020 compared with 2019 in the northern Italy region of Veneto (22). Unfortunately, they did not specifically analyze the effects of the pandemic on LRTIs in children. Our study was novel in analyzing the impact of the COVID-19 pandemic on the incidence of LRTIs in children in Western, Central, and Southern Europe.

We observed a 63.5% decrease in hospitalizations due to bacterial CAP in 2021 compared with 2019, which was similar to the 71.5% reduction in admissions due to CAP reported by Rybak et al. in French children but less than 82% decrease in hospitalizations due to CAP reported by Friedrich et al. in Brazilian children (23, 24).

We also observed the almost complete and persistent disappearance of *M. pneumoniae*, with a decrease of 79.5%, as a cause of LRTIs in the children in our study during the pandemic year 2021 compared with 2019. A similar persistent disappearance of *M. pneumoniae* was reported by Meyer Sauteur et al. They analyzed data from 20 countries worldwide and found a reduction in the global incidence of *M. pneumoniae* infections by more than 80% during the first year of the pandemic. Moreover, no resurgence of infections was observed when preventive measures were discontinued in the second year of the pandemic, which can be explained by the slow spread of *M. pneumoniae* compared with respiratory viruses (10). However, the observed and lasting decrease in LRTIs caused by *M. pneumoniae* can also be explained by a large natural variation in the annual incidence of this pathogen, with peaks occurring every 3–7 years (25). Regarding RSV infections, we observed an almost complete disappearance of the virus during the winter months of 2021, when we would expect the highest incidence based on the seasonal occurrence of RSV in Slovenia in the pre-pandemic era (26). From June to November 2021, the incidence of admissions due to LRTIs caused by RSV increased sharply and almost fully compensated for the decrease in winter. This seasonal shift in the peak of RSV infections has not been observed in Slovenia before. Similar observations were reported by Grochowska et al., who detected an unexpected 20-fold increase in RSV-positive cases among children hospitalized due to LRTIs in August 2021 in Poland compared with that during the same month in the pre-pandemic years. However, they used a tiny sample (8). Foley et al. reported an inter-seasonal resurgence of RSV in Australian children with a magnitude that was 2.5 times higher than the average seasonal peak of RSV in the pre-pandemic years (4). This seasonal shift could be attributed to the impacts of the COVID-19 pandemic and related preventive measures. Wearing masks, social distancing, improved hand hygiene, and lockdowns contributed not only to a significant reduction in severe acute respiratory syndrome coronavirus 2 transmission but also negatively influenced the spread of other respiratory viruses, such as RSV. Nonexposure to a particular virus during its usual previous season and a consequent immune naivety probably also contributed to the increased susceptibility of children even outside the usual season.

Our study found that rhinovirus was the least affected of all the respiratory pathogens during the COVID-19 epidemic. Moreover, the relative proportion of rhinovirus-positive specimens among children hospitalized due to LRTIs increased from 8.2% in 2019 to 41.6% in 2021. As shown in Figure 3, rhinovirus did not disappear during the lockdown in winter and early spring of 2021, and we observed long-lasting peaks of rhinovirus infections in the summer and autumn months of 2021, far exceeding the proportion of rhinovirus-positive specimens during the same period of 2019. Therefore, our results confirmed the previous findings of "resistance" of rhinovirus to preventive measures during the COVID-19 pandemic (2). Unlike all other respiratory pathogens, the Centers for Disease Control and Prevention reported an almost unaffected prevalence of rhinovirus from all specimens collected in the United States during the peaks of the COVID-19 pandemic (2). However, contrary to our results, the proportion of rhinovirus-positive specimens during the pandemic did not exceed percentages from pre-pandemic years (2). Jia et al. analyzed the proportion of rhinovirus-positive specimens collected from the upper airways of children hospitalized or treated as outpatients due to LRTI at the University Children's Hospital in Shanghai, China. They reported an increase in the proportion of rhinovirus-positive specimens from 26.7% in 2019 to 52.5% in 2020, consistent with our study (27). The increase in the prevalence of rhinoviruses from specimens collected in hospital settings and not in specimens from community surveillance systems can be explained by the prevalence of human rhinovirus A serotypes that cause more serious LRTIs in children (27).

Our study had several limitations. First, diagnoses were based mostly on completed medical records. Variability in diagnostic procedures (e.g., performing or omitting a CXR) and establishing a final diagnosis among treating physicians is very probable. Second, we included the entire year of 2021, although preventive measures were relaxed during the summer of 2021, and most of the studies from other countries included only the winter and spring months of 2021. However, by including the summer and autumn months of 2021, we obtained insight into the longer-lasting effects of the pandemic on the prevalence of respiratory pathogens that cause LRTIs in children. Third, we included only hospitalized children, which does not necessarily reflect the complete epidemiological spectrum of respiratory tract infections and their causative pathogens in children. In conclusion, the COVID-19 pandemic had several and diverse effects on children's health (28). It significantly impacted the incidence of LRTIs in hospitalized children, with a decrease in the incidence of atypical and bacterial pneumonia. The observed impact of the pandemic and related preventive measures on the (seasonal) occurrence of respiratory pathogens was even more profound. Some viruses (e.g., influenza) completely disappeared from the collected specimens and did not reemerge despite removingmost preventive measures in the second half of 2021. A similar but not as profound effect was observed for *M. pneumoniae*. The incidence of LRTI caused by RSV paralleled the course of preventive measures, with a drastic decrease during the lockdown and a rapid resurgence after its end. Almost no effect of preventive measures was observed on the incidence of LRTI caused by rhinovirus, and a sharp increase occurred after the end of the lockdown, far exceeding the incidence in the pre-pandemic years and almost completely compensating for the diminished occurrence of some other respiratory pathogens. Although the impact of the COVID-19 pandemic might be waning, these observations are important for planning healthcare resources and preventive measures for future pandemics, which will undoubtedly occur. Similar changes in the incidence of respiratory infections can be expected in any prolonged epidemic (of respiratory and other diseases), requiring large-scale preventive measures such as wearing masks, social distancing, and school and kindergarten closures.

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