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Very Low Incidence of SARS-CoV-2, Influenza and RSV but High Incidence of Rhino-, Adeno- and Endemic Coronaviruses in Children With Acute Respiratory Infection in Primary Care Pediatric Practices During the Second and Third Wave of the SARS-CoV-2 Pandemic

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Abstract: Respiratory viruses were detected by multiplex-polymerase chain reaction from oropharyngeal swabs in 114/168 (67.9%) children with acute respiratory infection presenting to 5 pediatric practices in Germany between November 2020 and April 2021. In contrast to rhino- (48.8%), adeno- (14.3%) and endemic coronaviruses (14.9%), SARS-CoV-2 and influenza virus were detected only once; respiratory syncytial virus was not detected. This demonstrates differing impacts of pandemic infection control measures on the spread of respiratory viruses.

Key Words: primary care, pediatric practices, SARS-CoV-2, pandemic, acute viral respiratory infection, respiratory virus

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During the first wave of the SARS-CoV-2 pandemic, hygiene measures such as physical distancing, regular hand washing and wearing of masks were implemented in Germany from spring 2020 onwards, to minimize transmission of SARS-CoV-2.[1] During this time, pediatric primary care practices and emergency rooms of pediatric hospitals reported significant lower number of patients overall. This drop in pediatric patients might be explained by the parents' concern that the child may be exposed to SARS-CoV-2 in medical settings as well as a reduced occurrence of respiratory infections due to the general enforced infection control measures in society.[2]

However, in autumn 2020, during the second wave of the pandemic, the incidence of pediatric patients with acute respiratory infections increased again but remained on a low level, with a reduction by approximately 50% compared with pre-pandemic years.[3] Still, data from the European Centre for Disease Prevention and Control showed a 99.5% decrease in influenza infections in all age groups in autumn and winter 2020/2021.[4] In the German nationwide physician-based sentinel surveillance system, consisting of approximately 590 primary care practices including general practitioners (59%), internists (12%) and pediatricians (23%), only 3 patients with a respiratory syncytial virus (RSV) infection had been registered from calendar week 40/2020 to calendar week 18/2021.[5] Similarly, a significantly shortened influenza and RSV season and a reduction in number of infected children was seen in several countries.[6–8]

At present, most studies addressing the occurrence and etiology of acute respiratory infections (ARI) during the SARS-CoV-2 pandemic in children and adolescents were conducted in hospitalized patients.[9] However, children admitted to hospital care are more likely to suffer from underlying diseases and/or a more severe course of infection, whereas children seeking medical attention in primary care practices usually reflect the spreading of viruses in the general pediatric population more accurately. Therefore, we investigated the occurrence of SARS-CoV-2 in relation to other respiratory viruses in children with ARI presenting to primary care pediatric practices during the second and third pandemic wave.

METHODS

We conducted a prospective, multicenter observational study in five primary care pediatric practices in the city of Wuerzburg (total population: approximately 144,604 inhabitants with 16,349 children and adolescents). Respiratory sampling (one primary care practice per weekday, every 2 weeks) was performed from November 09, 2020, to April 30, 2021. The first 8 children (up to 14 years of age) presenting at the respective pediatric primary care practice with ARI on the predefined study day were included after parent informed consent. Only patients with onset of symptoms within 14 days prior to presentation at the practice were included, and an oropharyngeal swab was taken for viral diagnostics.

Demographic and clinical data were collected through questionnaires on the day of presentation and after 7 and 14 days by a telephone interview.

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Viral Diagnostics

Viral diagnostics were performed at the Central Laboratory of the Institute of Virology and Immunobiology, University of Wuerzburg. The oropharyngeal swabs were placed in a viral transport medium (COPAN ITALIA SPA, Brescia, Italy or biocomma, Guandong, China) and screened for viral pathogens using a commercial multiplex-polymerase chain reaction (PCR; FTD Respiratory pathogens 21, Fast Track Diagnostics, Luxembourg).

Preliminary extraction was performed using the NucliSENS easyMAG (bioMérieux) extraction kit. The FTD-21 test kit identified the following viral pathogens: influenza virus A and B, RSV, human parainfluenza virus 1–4, human coronavirus NL63, OC43, HKU1 and 229E, human metapneumovirus, human bocavirus, adenovirus, rhinovirus, enterovirus and parechovirus.

SARS-CoV-2-RNA was identified by reverse transcription quantitative PCR according to the recommendations of the World Health Organization and the manufacturer's instructions. As described by Corman et al, primers in the SARS-CoV-2 E-gene[10] and the FTD SARS-CoV-2 test kit (Siemens Healthineers, Erlangen, Germany) were used. Cycle thresholds ≥40 were considered negative.

Statistical Analysis

Data were entered into IBM SPSS 26.0 for statistical analysis. Data were analyzed descriptively (frequency, percentage and median with IQR).

Ethical Considerations and Data Protection

The study was approved by the Ethics Committee of the Medical Faculty at the University of Wuerzburg (183/20-sc). Parents provided written informed consent. Only pseudonymous data were reported to the study coordination center at the Department of Pediatrics, University Hospital of Wuerzburg.

RESULTS

A total of 168 children and adolescents (median age 3 years; IQR 1–5) with ARI were included; 45.8% of participants were female (n=77). Chronic pulmonary (including bronchopulmonary dysplasia, asthma and/or other chronic lung disease) n=39 (23.2%) and cardiac n=15 (8.9%) diseases were the most common underlying chronic conditions described. Children with a history of prematurity accounted for 7.7% (n=13). Other underlying diseases included allergies (n=11/6.5%), renal (n=7/4.2%) and neurologic diseases (n=4/2.4%), primary immune deficiency (n=1/0.6%) and oncologic disease (n=1/0.6%).

The most common acute diagnoses were upper (defined as rhinitis, otitis media, conjunctivitis, sinusitis, tonsillitis, pharyngitis, laryngitis; n=133/79.2%) or lower respiratory infection (defined as bronchitis, bronchiolitis, pneumonia, laryngotracheitis; n=3/1.8%) or a combination of both (n=32/19%), either with (n=81/48.2%) or without fever (n=87/51.8%). The median duration of onset of ARI symptoms before presentation to a primary care pediatric practice was 3 days (IQR 1–5). Three (1.8%) patients were hospitalized. The median duration of illness was 7 days (IQR 5.5–10).

At least one respiratory virus was detected in 114 of 168 ARI patients (67.9%; Figure 1): SARS-CoV-2 (n=1/0.6%); rhinovirus (n=82/48.8%), adenovirus (n=24/14.3%), coronavirus-NL63 (n=24/14.3%), coronavirus-229E (n=1/0.6%), parainfluenza virus 3 (n=2/1.2%), influenza virus (n=1/0.6%), bocavirus (n=1/0.6%) and parechovirus (n=1/0.6%). In 18.4% (n=21) 2 or more viruses (n=1/0.6%) were detected simultaneously. Co-detections included rhinovirus and adenovirus (n=15/8.9%), rhinovirus and coronavirus-NL63 (n=3/1.8%), adenovirus and coronavirus-NL63 (n=2/1.2%), rhinovirus and parainfluenza virus 3 (n=1/0.6%) as well as rhino-, adeno- and bocavirus (n=1/0.6%). RSV, human metapneumovirus and enterovirus were not found. Median age of children with

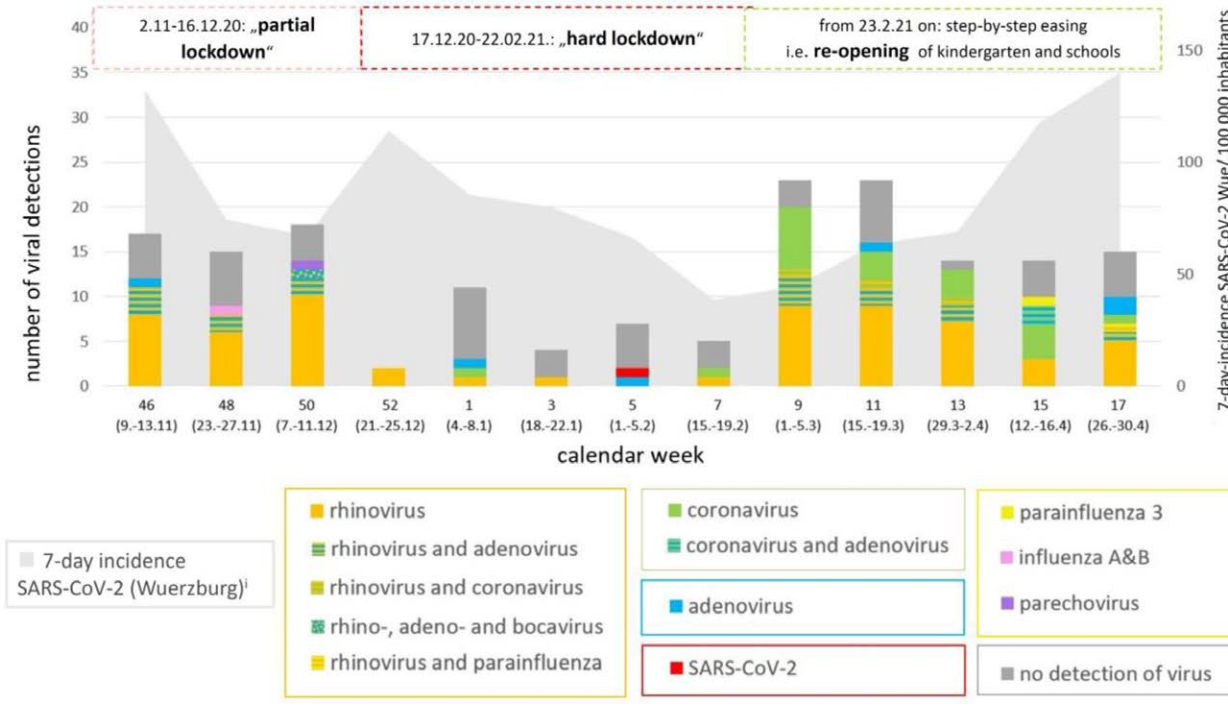

Figure 1. Detection of respiratory viruses among 168 patients with acute respiratory infection in 5 primary care pediatric practices in Wuerzburg, Germany. Depicted in gray: 7-day-incidence SARS-CoV-2 per 100,000 inhabitants of the total population in the city of Wuerzburg[1] https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Daten/Fallzahlen_Kum_Tab.html (last accessed 14.10.2021).

detection of rhino-, adeno- or endemic coronaviruses was comparable (rhinovirus 2 years, IQR 1–4; adenovirus 2 years, IQR 1–3; endemic coronaviruses 3 years, IQR 2–6). Throughout the study, the number of viruses detected was lowest during the "strict lockdown" (end of December 2020 to end of February 2021). The number of viral detections increased subsequently in March 2021 as the strict infection control and distancing measures were reduced.

DISCUSSION AND CONCLUSION

In this sample of children presenting with ARI in primary care pediatric practices, rhinovirus, adenovirus and endemic coronaviruses were the predominant viral pathogens detected in 62.5% of all study participants between November 2020 and April 2021. In contrast, SARS-CoV-2 was detected only once although this study covered the SARS-CoV-2 peak incidences during the second and third wave of the pandemic. RSV was not detected at all and influenza virus was only detected in one child although our study covered the usual annual winter RSV/Influenza season (November–April) The low incidence of SARS-CoV-2, RSV and Influenza in children may be either due to the effective prevention by various infection control measures, but in the case of SARS-CoV-2, also due to a limited susceptibility of children.

The high incidence of rhinoviruses can be explained on the one hand by the predominant transmission via contact/smear infection and probable inadequate handwashing technique by small children[11] and on the other hand by the year-round occurrence with presence of more than 160 serotypes that allow repeated infections with short-term and type-specific immunity. Similarly, endemic coronaviruses[12] and adenoviruses are transmitted by contact/smear infections and adenoviruses are additionally resistant to many disinfectants.[13]

In respiratory samples from end of September 2020 to mid-May 2021 collected in children and adults with ARI by the German physician-based sentinel surveillance system, rhinovirus (22%) and endemic coronavirus (7%) were detected less frequently; however, SARS-CoV-2 was detected more frequently, most probably due to higher incidences in older age groups at that time.[5]

Increase in the incidence of respiratory viruses were observed in several countries once COVID-19-related infection control measures were reduced. For example, the incidence of respiratory syncytial virus infections sharply increased off-season in Australia, France, South Africa, the United States and the United Kingdom. In comparison, rhinovirus infections increased in New Zealand and Finland once strict restrictions were removed,[11,14] whereas their incidence remained unchanged in other countries as Japan and South Korea.[7,8] These observations underline that SARS-CoV-2, RSV and influenza infections are—at least partially—preventable by hygiene measures and may re-increase once these are removed.[15] In contrast, rhinovirus infections, and to a lesser extent endemic human coronavirus infections, seem to be continuously transmitted even during periods with strict infection control measures. Further studies on the transmission ability, ecologic fitness and virus-virus interaction are needed to better understand the continuous transmission of endemic human coronaviruses.[16]

A limitation of our study is the relatively small number of primary care practices, which might reflect only the local situation in the city of Wuerzburg. Nevertheless, the apparently low incidence of SARS-CoV-2 infections in the pediatric populations has been confirmed in several studies in hospitalized patients.[9,17] Furthermore, all of our patients were seen in an outpatient setting reflecting the general pediatric population and infection activity more accurately than hospitalized patients do.

In the future, variants of the pandemic coronavirus may evolve with an increased infectiousness and transmissibility. At the same time, other viruses will continue to spread (rhinovirus, adenovirus, human coronavirus) or may reappear outside their usual season (influenza, RSV), once the strict preventive hygienic measures have been eased. Hence, in the coming winter season a sharp increase of ARI in children can be expected, which will put high pressure on the healthcare system and on the health of children. In the future, in addition to SARS-CoV-2, continuous surveillance of respiratory pathogens in primary care pediatric practices is important to better understand the burden and transmission of virus-associated respiratory diseases in children.

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