



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



ELSEVIER

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

SARS-CoV-2 infection in children in Moscow in 2020: clinical features and impact on circulation of other respiratory viruses

SARS-CoV-2 infection in children in Moscow in 2020

Alexander S. Yakovlev^a, Ilmira K. Belyaletdinova^a, Lyudmila N. Mazankova^{b,c}, Elmira R. Samitova^{b,c}, Ismail M. Osmanov^c, Natalya V. Gavelya^c, Viktor P. Volok^{a,d}, Ekaterina S. Kolpakova^{a,e}, Anna A. Shishova^{a,e}, Natalia A. Dracheva^b, Liubov I. Kozlovskaya^{a,e}, Galina G. Karganova^{a,d,e,*}, Aydar A. Ishmukhametov^{a,e}

^a Chumakov Federal Scientific Center for Research and Development of Immune-and-Biological Products of Russian Academy of Sciences, Moscow 108819, Russia

^b Russian Medical Academy of Continuous Professional Education of the Ministry of Healthcare of the Russian Federation, Moscow, 125993, Russia

^c Z.A. Bashlyayeva Children's Municipal Clinical Hospital, Moscow, 125373, Russia

^d Department of Biology, Lomonosov Moscow State University, Moscow, 119991, Russia

^e Institute of Translational Medicine and Biotechnology, Sechenov Moscow State Medical University, Moscow, 119991, Russia

ARTICLE INFO

Article history:

Received 19 October 2021

Revised 1 December 2021

Accepted 6 December 2021

Keywords:

COVID-19

Molecular diagnostics

Respiratory viruses

SARS-CoV-2

Obesity

Children

ABSTRACT

Objectives: This study aimed to estimate the impact of the COVID-19 pandemic on the circulation of non-SARS-CoV-2 respiratory viruses and the clinical characteristics of COVID-19 in hospitalized children.

Methods: A total of 226 and 864 children admitted to the Children's City Clinical Hospital with acute respiratory infection in September to November of 2018 and 2020 in Moscow were tested for respiratory viruses using multiplex polymerase chain reaction (PCR) and *Mycoplasma pneumoniae/Chlamydia pneumoniae* using enzyme-linked immunosorbent assay.

Results: The detection rate of non-SARS-CoV-2 viruses in 2020 was lower than in 2018, 16.9% versus 37.6%. An increase in the median age of children with respiratory viruses was observed during the pandemic (3 years vs 1 year). There was no significant difference in the frequency of intensive care unit (ICU) admission in children with SARS-CoV-2 and other respiratory virus infections (2.7% vs 2.9%). SARS-CoV-2 and human rhinoviruses, human metapneumoviruses, and human adenoviruses showed significantly lower than expected co-detection rates during co-circulation. An increase in body mass index (BMI) or bacterial coinfection leads to an increased risk of ICU admission and a longer duration of COVID-19 in children.

Conclusions: The COVID-19 pandemic led to significant changes in the epidemiological characteristics of non-SARS-CoV-2 respiratory viruses during the autumn peak of the 2020 pandemic, compared with the same period in 2018.

© 2021 The Author(s). Published by Elsevier Ltd on behalf of International Society for Infectious Diseases.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

* Corresponding author: prem. 8, k.17, pos. Institut Poliomyelita, poselenie Moskovskiy 108819 Moscow, Russia. +74958419327.

E-mail addresses: alex-montreal@yandex.ru (A.S. Yakovlev), belyaletdinova_i@mail.ru (I.K. Belyaletdinova), mazankova@list.ru (L.N. Mazankova), samitova_rudn@mail.ru (E.R. Samitova), osmanovim@zdrav.mos.ru (I.M. Osmanov), viktor.p.v@mail.ru (V.P. Volok), katerina.kolp@gmail.com (E.S. Kolpakova), a_shishova@list.ru (A.A. Shishova), lubov_i_k@mail.ru (L.I. Kozlovskaya), karganova@bk.ru (G.G. Karganova), ishmukhametov@chumakovs.su (A.A. Ishmukhametov).

Introduction

Acute respiratory infections (ARIs) are a serious public health problem and a leading cause of morbidity and mortality in children worldwide (Williams et al., 2002). ARIs are associated with a wide range of respiratory viruses such as a respiratory syncytial virus (RSV), human metapneumoviruses (hMPV), human adenoviruses (hAdV), human bocaviruses (hBoV), human rhinoviruses

(hRV), parainfluenza viruses (PIV), human coronaviruses (hCoV), and others.

On March 11, 2020, the World Health Organization (WHO) announced the start of the COVID-19 pandemic (World Health Organization W 2019). Several studies have shown that an influenza pandemic could affect the epidemiology of other respiratory viral infections (RVI). Therefore, the prevalence, age distribution, and other epidemiological characteristics of the virus circulation can change (Meningher et al., 2014; Pascalis et al., 2012; Thiberville et al., 2012).

Another important issue is the impact of coinfections with a pandemic virus on the severity of other RVI. The issue has not yet been sufficiently studied (Lai et al., 2020; Sarkar et al., 2021). Moreover, there are a limited amount of data on the effect of bacterial infections on the clinical course of COVID-19 (Oliva et al., 2020; Rawson et al., 2020). This is important for the prediction of the disease progression, prognosis, and treatment strategy, especially in a high-risk group such as young children.

In the present study, we analyzed data and specimens from children hospitalized with ARIs during the COVID-19 pandemic in Moscow, Russia (September to November 2020) and compared them with those obtained for the same period of 2018 to assess the impact of the COVID-19 pandemic on the distribution and clinical characteristics of non-influenza RVI and to assess the epidemiological and clinical features of the SARS-CoV-2 infection in Russia.

Methods

Study design and participants

The study was performed at the Children's City Clinical Hospital named after Z.A. Bashlyaeva, Moscow, Russia, which is the largest hub of infectious diseases in the city. The study included participants aged between 1 month and 18 years hospitalized with acute respiratory symptoms from September 27 to November 30 (226 patients in 2018 and 864 in 2020).

Nasopharyngeal swabs were taken from all patients within 24 hours of admission and tested using reverse transcription-polymerase chain reaction (RT-PCR) (AmpliSens ARVI-screen-Fl kit, InterlabService, Russia) for common respiratory viruses, including RSV, hMPV, hAdV, hBoV, hRV, PIV 1–4, alpha and beta-hCoV. Patients admitted in 2020 were also tested for SARS-CoV-2 (POLYVIR SARS-CoV-2, Lytech, Russia). Enzyme-linked immunosorbent assay was used to detect IgM/IgA antibodies to *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in the serum samples.

Ethics

This study was approved by the ethics committee of the Children's City Clinical Hospital named after Z.A. Bashlyaeva (#14 from August 13, 2020). All study participants or their representatives had provided written informed consent.

Statistical analysis

Data analysis was performed using GraphPad Prism 9.0.0 (GraphPad Software, LLC). Baseline characteristics of all positive viral detections were analyzed using appropriate descriptive statistics. Continuous data are presented as medians and interquartile ranges, and categorical data as numbers and percentages. Chi-square test or Mann-Whitney test were used for comparisons (significance threshold, $P < 0.05$).

Results

Prevalence of respiratory viruses

First, we compared the incidence of infections caused by respiratory viruses, including RSV, hMPV, hAdV, hRV, hBoV, PIV 1–4,

Table 1

Distribution of positive laboratory cases by virus species in 2018 and 2020

Virus	2018 (%)	2020 (%)
RSV	0	0.1
hMPV	0.4	3.0*
hAdV	9.3	3.7*
hBoV	2.2	0.7*
hRV	17.3	6.3*
PIV 1	0	0
PIV 2	0.4	0
PIV 3	5.3	0.2*
PIV 4	4.0	2.0
hCoV (NL63/229E)	0	0
hCoV (HKU-1/OC 43)	0.4	2.3
SARS-CoV-2	-	33.2
TOTAL n	226	864

* Differences between 2018 and 2020 are statistically significant (chi-square test, $P < 0.05$). - no data.

alpha, and beta-hCoV and SARS-CoV-2 in September to November of 2018 and 2020. The detection rate of RVI in 2018 was lower than that in 2020, 37.6% versus 49.3% (chi-square test, $P < 0.05$). However, when we excluded patients with SARS-CoV-2, the detection rate of RVI in 2018 became higher: 37.6% versus 16.9% in 2020 (chi-square test, $P < 0.05$). Then we compared the detection rates of individual non-SARS-CoV-2 RVI in the same periods in 2018 and 2020 (Table 1). Detection rates of hRV, hAdV, PIV 3, and hBoV were significantly higher in 2018 compared with 2020. However, the detection rate of hMPV was greater in 2020 (chi-square test, all $P < 0.05$). The incidence of bacterial-viral coinfections did not differ significantly between 2018 and 2020.

Age distribution of patients infected with non-SARS-CoV-2 respiratory viruses before and during the COVID-19 pandemic

We assessed the age distribution of patients hospitalized with ARI in 2018 and 2020. A significant increase in the age of children having RVI was observed during the SARS-CoV-2 pandemic (the median age was 1 year [IQR 0.75–2] in 2018 vs 3 years [IQR 1–5] in 2020) (Mann-Whitney test, $P < 0.001$).

We compared the prevalence of respiratory viruses in different age groups before and during the pandemic. Higher rates were observed in 2018 compared with 2020 in patients up to 3 years of age, but in patients older than 3 years, the rates were lower (chi-square test, $P < 0.0001$) (Table S1).

There was a significant increase in the proportion of children older than 3 years with an hRV infection in 2020 compared with 2018 (46.4% vs 12.9%) (chi-square test, $P < 0.01$). The group of infants made 14.3% of patients with hAdV infection in 2018, whereas, in 2020, most patients represented the group of 3–7 years of age, and there were no cases in infants. The same trend was observed in the case of PIV 4 and hBoV infections. In both cases, patients aged 1–3 years prevailed in 2018, and patients aged 3–7 years were seen more in 2020 (Fig. 1).

The prevalence of SARS-CoV-2 infection in children in the autumn of 2020

A total of 287 cases of SARS-CoV-2 infection were identified of 864 patients hospitalized with symptoms of ARIs. Bacterial coinfections, represented by *C. pneumoniae* or *M. pneumoniae*, were detected in 7.7% of cases of COVID-19. SARS-CoV-2 was co-detected with another respiratory virus in 3.1% of cases, whereas non-SARS-CoV-2 respiratory virus coinfections were detected in 6.5% (chi-square test, $P = 0.1082$). There were both viral and bacterial coinfection in 1 case of COVID-19.

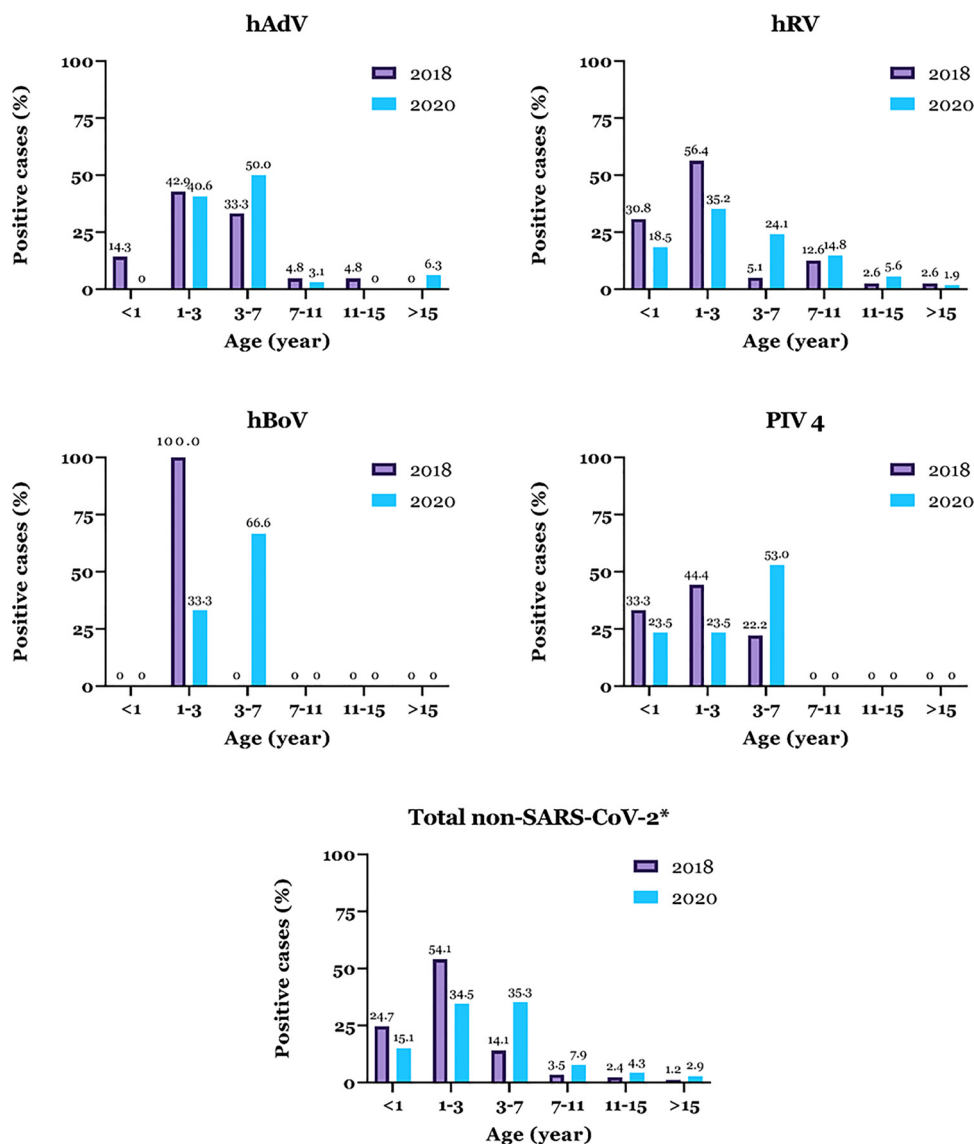


Figure 1. Age distribution of patients infected with non-SARS-CoV-2 respiratory viruses before and during the SARS-CoV-2 pandemic
 * Including all non-SARS-CoV-2 respiratory viruses (RSV, hMPV, hAdV, hBoV, hRV, PIV 1-4, hCoV [NL63/229E] hCoV [HKU-1/OC 43])

Age distribution of patients with SARS-CoV-2 infection

The age distribution of patients with SARS-CoV-2 infection was significantly different from other RVI registered in 2020. The median age of patients with non-SARS-CoV-2 RVI was 3 years [IQR 1-5] versus 10 years [IQR 2-15] in patients with SARS-CoV-2 (Mann-Whitney test, $P < 0.001$). Approximately 85% of patients infected with respiratory viruses were infants and children younger than 7 years (Table 2), whereas more than 66% of cases of SARS-CoV-2 infection occurred in children older than 7 years. Moreover, the number of detected infections increased with age (Fig. 2). It is worth noticing that SARS-CoV-2 accounted for 88.9% of the total number of viruses identified in children older than 7 years versus 43.3% in children younger 7 years (chi-square test, $P < 0.05$). More than 93% of cases of RVI were detected in children younger than 7 years in 2018.

Clinical characteristics of patients with SARS-CoV-2 infection

The most common symptoms of COVID-19 in children were fever, cough, runny nose, and fatigue (Fig. 3). Fever duration of

7 days or more was observed in 25.9% of cases. Anosmia was noted in 10.2% of cases, however, it is difficult for young children to present such complaints. Gastrointestinal manifestations were a common symptom of COVID-19 (overall 20.9%), vomiting was noted in 6.7%, diarrhea and abdominal pain in 7.1%. Upper respiratory tract symptoms were detected more often than lower respiratory tract symptoms (60.8% vs 31%) (chi-square test, $P < 0.0001$). The median duration of illness with SARS-CoV-2 was 14 days [IQR 10-18] versus 11 days [IQR 8-15] for non-SARS-CoV-2 RVI (Mann-Whitney test, $P < 0.001$).

There was no significant difference in the frequency of ICU admission in children with SARS-CoV-2 and other RVI (2.7% vs 2.9%). The median age in COVID-19 patients who required ICU admission was significantly higher than in patients with non-SARS-CoV-2 RVI (13 years [IQR 12; 16] versus 9 months [IQR 2;11]) (Mann-Whitney test, $P < 0.05$). Importantly, there was not a single case of severe SARS-CoV-2 infection in children younger than 8 years. All patients younger than 8 years who required ICU admission were tested positive for other RVI (hRV 75% and PIV 4 25%).

In this study, no significant differences were found when comparing complete blood count data from patients infected with

Table 2
The incidence of various respiratory virus infections in children younger than 7 years and older than 7 years in 2018 and 2020

Age	RSV (%) n=0	hMPV (%) n=1	hAdV (%) n=21	hBoV (%) n=5	hRV (%) n=39	PIV 3 (%) n=12	PIV 4 (%) n=9	hCoV HKU-1 / OC 43(%) n=1	PIV2 n=1	Total No. (%) n=89
<7	0.0	1.2	22.9	6.0	43.4	14.5	10.8	0.0	1.2	93.3
>7	0.0	0.0	33.3	0.0	50.0	0.0	0.0	16.7	0.0	6.9

Age	RSV (%) n=1	hMPV (%) n=26	hAdV (%) n=32	hBoV (%) n=6	hRV (%) n=54	PIV 3 (%) n=2	PIV 4 (%) n=17	hCoV HKU-1/OC 43(%) n=20	SARS-Cov-2 n=287 (%)	Total No. (%) n=445
<7	0.4	9.2	12.2	2.5	17.7	0.4	7.1	7.1	43.3	54.0
>7	0.0	1.9	1.5	0.0	5.8	0.5	0.0	1.5	88.9	46.0

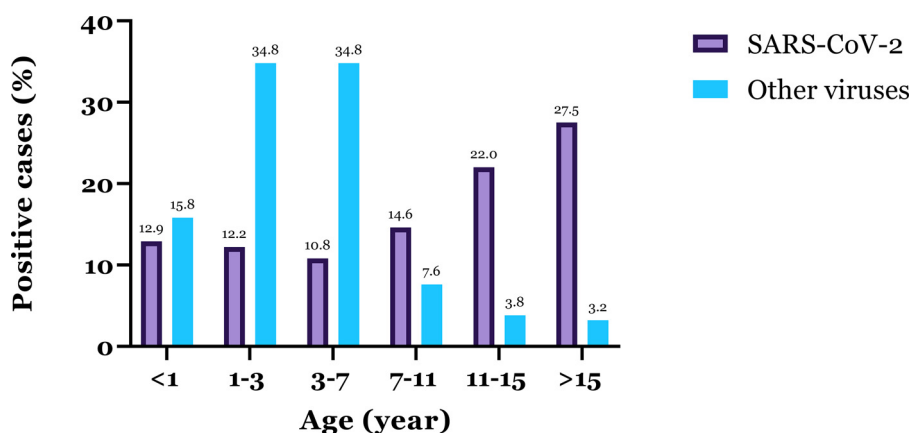


Figure 2. Age distribution of patients with SARS-CoV-2 and other respiratory virus infections in 2020

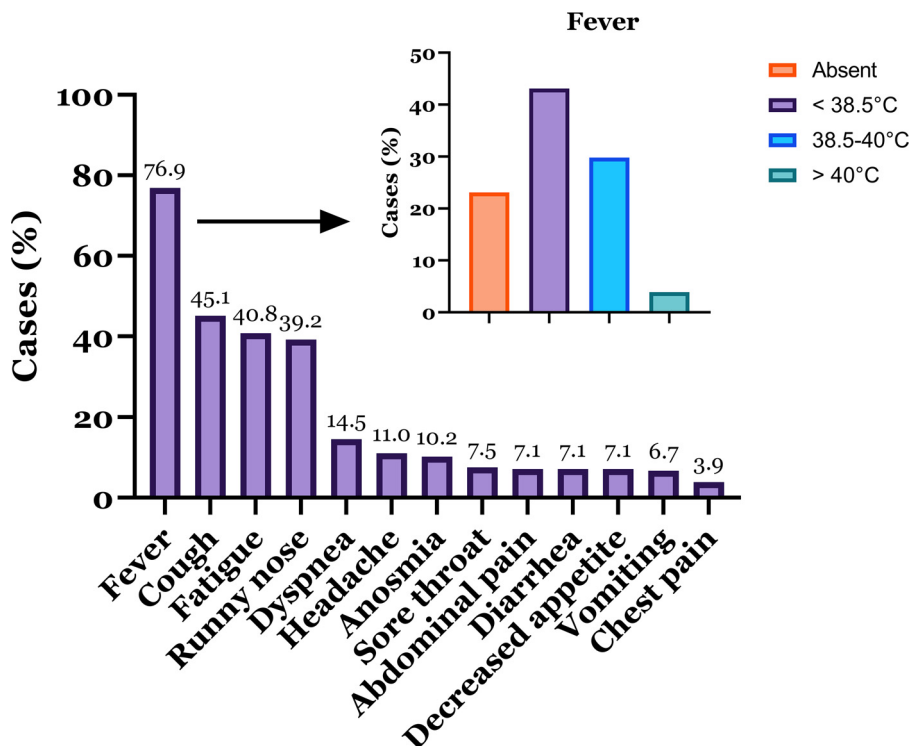


Figure 3. Clinical manifestations of SARS-CoV-2 infection

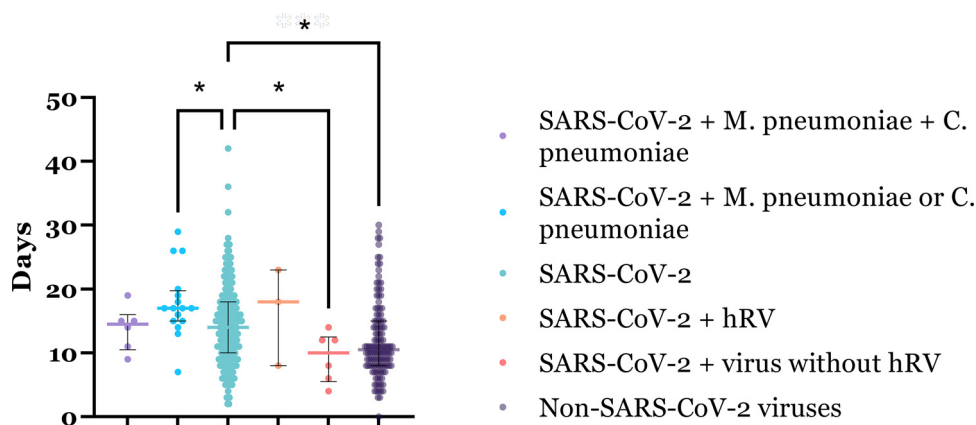


Figure 4. The duration of illness in COVID-19 patients with and without coinfections
* Statistically significant (Mann-Whitney test, $P < 0.05$)

SARS-CoV-2 and other respiratory viruses (Table S2). Lymphocytosis in 38.0% and neutropenia in 21.6% were most often observed in patients with COVID-19, which is typical for the clinical course of viral infections. Leukocytosis was observed in 12.5%, neutrophilia in 10.6%, and increased CRP levels were noted in 12.9% of patients with SARS-CoV-2 infection. We noted a low incidence of leukopenia 4.3% and lymphopenia 2.4%, which was significantly less than previously described (Ma et al., 2021).

Coinfections in patients with COVID-19

Bacterial or viral coinfections in patients with COVID-19 were detected in 32 cases (11.1%): 22 cases were represented by bacterial pathogens (7.7%), 9 cases were associated with one of the respiratory viruses (3.1%), and there was also 1 case of simultaneous bacterial and viral coinfection (0.3%). Respiratory virus coinfections comprised 6.5% of all non-SARS-CoV-2 RVI.

Viral coinfections with SARS-CoV-2 were represented by hRV (33.3%), hCoV (HKU-1/OC 43) (33.3%), hMPV, PIV 3 and PIV 4 (11.1% each). The median age of patients with viral coinfections was 1 year [IQR 0.7–2.5], whereas, in patients with only SARS-CoV-2, it was 11 years [IQR 3–15] (Mann-Whitney test, $P < 0.01$). Viral coinfections were not characterized by a more severe course of the COVID-19. There were no cases of ICU admission, and the duration of the illness, except for the case of coinfection with hRV, was lower than that in patients with only SARS-CoV-2: 10 [IQR 5.5–12.5] versus 14 [IQR 10–18] (Mann-Whitney test, $P < 0.05$) (Fig. 4). There was a tendency for a longer duration of the illness in coinfection with hRV compared with other viral coinfections. The median duration of illness in patients with SARS-CoV-2 and hRV coinfections was 18 days (IQR 8–23), whereas in patients with other viral coinfections the median was 10 days (IQR 5.5–12), respectively. However, this difference was not significant (Mann-Whitney test, $P = 0.1786$), probably owing to the small number of cases.

SARS-CoV-2 and hRV showed significantly lower than expected co-detection rates during co-circulation. In addition, a significant negative association was found between SARS-CoV-2 and hAdV, SARS-CoV-2, and hMPV (Table 3).

In patients with COVID-19 bacterial coinfections occurred in 22 cases overall: with *M. pneumoniae* (40.9%) and *C. pneumoniae* (31.8%), both pathogens occurred in 27.3% of cases. The median age of patients with bacterial coinfection was 12 years [IQR 7.5–15]. Cases of bacterial coinfection were associated with a more severe course of COVID-19. Patients with SARS-CoV-2 and antibody positivity for *M. pneumoniae* and/or *C. pneumoniae* had a longer median duration of illness than patients infected only with SARS-CoV-2 (*M. pneumoniae* 18 days [IQR 16–23], *C. pneumoniae* 16 days

Table 3

Expected versus observed co-detections with SARS-CoV-2, September 28, 2020, to November 25, 2020

Virus	Expected co-detections	Observed co-detections	Chi-square test, P value
hRV	18	4	0.0029*
hAdV	11	0	0.0009*
hMPV	9	1	0.0112*
hCoV HKU-1/OC 43	7	3	0.2046
PIV 4	6	1	0.0583
hBoV	2	0	0.1571
PIV 3	1	1	>0.9999

* Differences are statistically significant (chi-square test, $P < 0.05$). The expected number of coinfections was defined as the product of the prevalence of virus 1 and the prevalence of virus 2, multiplied by the total sample size. Then, we used the chi-square test (significance threshold, $P < 0.05$) to assess whether there was a significant difference between the actual and expected number of coinfections.

[IQR 14–17], both bacteria 14.5 days [IQR 10.5–16] vs 14 days [IQR 10–18] for SARS-CoV-2 mono-infection). Bacterial coinfection with COVID-19 led to ICU admission in 26% of cases (SARS-CoV-2 mono-infection 2.7% (chi-square test, $P < 0.0001$). The median age of patients with bacterial coinfections who required ICU admission was 15 years [IQR 12.5–15.2].

Asthma and COVID-19 severity in children

An association between the COVID-19 severity and the presence of bronchial asthma remains unknown. In our study, 8 patients infected with SARS-CoV-2 were diagnosed with bronchial asthma. The median duration of illness in patients with asthma was 14 days [IQR 11.25–18.75], the same as in patients with COVID-19 without asthma. The incidence of pneumonia also did not differ significantly from the group of patients without bronchial asthma. In addition, no cases required ICU admission in children with bronchial asthma. There were no cases of bronchial asthma in children with other respiratory viruses.

Association between obesity and COVID-19 severity in children

Body mass index (BMI) was classified according to the World Health Organization (WHO) centile tables into the following categories: underweight (from -1 SD to -3 SD), healthy weight (Normal), and overweight (from $+1$ SD to $+3$ SD) (World Health Organization (WHO), 2021).

There was a tendency for an increase in the median duration of illness depending on the BMI; with a normal BMI, the median duration of disease in COVID-19 patients was 14 days, whereas, in

Table 4
Association between obesity and COVID-19 severity in children

BMI	N	Median duration of illness (days) median [IQR]	% ICU ^a	% LRTD ^b
3 SD	8	20 [8.25–22.75]	25.0%*	37.5%
2 SD	17	16 [11.50–19.50]	0.0%	35.0%
1 SD	37	15 [10.00–16.50]	5.4%	37.8%
Normal	133	14 [10.00–17.50]	1.5%	26.3%
–1 SD	30	11.5 [7.00–19.50]	0.0%	26.6%
–2 SD	12	12.5 [11.00–17.00]	0.0%	41.6%
–3 SD	5	13 [10.50–15.50]	0.0%	40.0%

^a Intensive care unit

^b Lower respiratory tract diseases

* Statistically significant difference from normal BMI (Chi-square test, $P < 0.05$).

patients with increased BMI from +1 SD to +3 SD, it became 15, 16 and 20 days, respectively. The percentage of ICU admissions also increased from 1.5% at normal BMI to 5.4% at +1 SD and 25% at +3 SD. Lower respiratory tract diseases (LRTD) were also more common in overweight children 35–37.8% versus 26.3% than in children with normal body weight (Table 4).

The group of underweight children should be considered separately. The duration of the illness in all underweight groups was lower than that in the normal-weight group (11.5–13 days vs 14 days). In all cases of COVID-19 in underweight children, no cases were requiring ICU admission. However, the groups –2 SD and –3 SD BMI had the highest percentage of LRTD 40–41.6% versus 26.3% in the group of children with normal body weight.

Discussion

According to the health care authorities, the incidence of ARI in the population ranged from 19,505 to 21,664 per 100,000 people in Russia during the past 10 years (Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing. 2021:131 November 10, 2021). The ARI incidence in children was on average 2.8 times higher than the incidence in the total population. In 2020, owing to the COVID-19 pandemic, there was a significant increase in the incidence of ARI compared with the previous year (by 11.5%) and the long-term average incidence—by 8.8%. Our study, which was carried out at the Children's City Clinical Hospital in Moscow, where the overwhelming majority of children with ARI symptoms in the city were hospitalized, shows a similar increase in the ARI incidence in children.

Previous studies have shown that a respiratory virus pandemic can affect circulation, age distribution, and other properties of seasonal RVI (Meningher et al., 2014; Navarro-Mari et al., 2012), and several studies have provided evidence of respiratory virus interactions during circulation (Ånestad, 1987; Arden et al., 2020; Casalegno et al., 2010; Nickbakhsh et al., 2019; Wu et al., 2020). Our study demonstrates the impact of the SARS-CoV-2 infection pandemic on the prevalence of other RVI and age distribution of children hospitalized with ARIs and presents clinical features of COVID-19 in children in Moscow, Russia, during the autumn wave of the COVID-19 pandemic in 2020 (Fig. S1).

We noted a significant decrease in the frequency of detection of non-SARS-CoV-2 RVI in hospitalized children with symptoms of ARIs in the period from September 2020 to November 2020 compared with the same period of 2018 in Russia. This is consistent with the data presented in the United Kingdom (Poole et al., 2020). The main reason for the decrease in the detection rate of seasonal RVI was likely connected to the restrictive measures that were taken during the COVID-19 pandemic.

Another possible reason for the decreased detection of non-SARS-CoV-2 RVI could be the interactions between the respiratory viruses themselves. Previously, in some studies, it was shown that respiratory viruses could affect the spread of other viruses.

For example, it was shown that rhinoviruses delayed the circulation of the pandemic influenza A (H1N1) 2009 virus in France (Casalegno et al., 2010). Our research demonstrates that interference is possible between SARS-CoV-2 and hRV, hAdV, and hMPV. This conclusion is based on a comparison of actual and expected rates of co-detection of SARS-CoV-2 and other respiratory viruses. The exact mechanism of viral interference is not fully understood, but there are several proposed explanations for this phenomenon, including competition of viruses for the host cell entry receptors and resources and the induction of innate immune response by another virus (Agrawal, 2019; Pinky and Dobrovoly, 2016; Schultz-Cherry, 2015; Wu et al., 2020).

During the COVID-19 pandemic, we noted a change in the spectrum of seasonal RVI. There was a higher prevalence of hMPV in 2020, whereas hRV, PIV 3, hAdV, and hBoV prevailed in 2018. Interestingly, during the 2009 influenza A (H1N1) pandemic, there was also an increase in the prevalence of hMPV in young children (Meningher et al., 2014).

We have shown an increase in the age of children with RVI during the pandemic. If, in 2018, the median age of patients was 1 year, in 2020, it was 3 years. The changes were seen also in the distribution of seasonal RVI by age. There was a trend toward an increase in the age of children who had RVI during the COVID-19 pandemic compared with the previous period. There was a significant increase in the proportion of older children infected with hRV, hAdV, PIV 4, and hBoV.

SARS-CoV-2 prevailed in all RVI detected in 2020. The median age of patients with COVID-19 was significantly higher than that of patients with seasonal RVI. It was noted that most of the COVID-19 cases occurred in children older than 7 years, and, at the same time, the detection rate increased with age. Interestingly, SARS-CoV-2 made up 88.9% of the total number of viruses identified in children older than 7 years.

We observed a milder course of COVID-19 in children, compared with the disease severity seen in adult patients (Docherty et al., 2020; Poole et al., 2020; Richardson et al., 2020). In all patients with COVID-19, only 4.5% required ICU admission, and there were no lethal outcomes recorded. At the same time, it was noted that the severe clinical course of COVID-19 mainly occurred in children older than 11 years, and there was not a single case of requiring ICU admission in infants, which contradicted the previous review reporting more severe clinical courses in infants than in older children (Yasuhara et al., 2020). In the present study, a severe clinical course of ARI in infants has been associated with hRV and PIV 4. Diseases of the upper respiratory tract were detected more often than the diseases of the lower respiratory tract in children with SARS-CoV-2 infection. The main clinical manifestations were fever, cough, fatigue, and runny nose, which was consistent with other studies (Castagnoli et al., 2020; Mehta et al., 2020).

Bacterial and viral coinfections can have a serious impact on the severity of the disease. During the 2009 influenza A pandemic, there was a high percentage of bacterial coinfections in patients

who had a severe illness and died (Joseph et al., 2013). In addition, previous studies have shown that coinfection of SARS-CoV-2 with the influenza virus can lead to a significant increase in the severity of the disease and mortality (Lai et al., 2020; Sarkar et al., 2021). Currently, there are no reliable data on the increase of severity of the disease when SARS-CoV-2 is co-detected with non-influenza respiratory viruses. In our study, the frequency of detection of bacterial and viral coinfections in patients infected with SARS-CoV-2 was consistent with the data of the previous review (Lansbury et al., 2020). Viral coinfections occurred mainly in young children and the disease was mild. Moreover, we found that the duration of illness, except for the case of coinfection with hRV, was lower than in patients with only SARS-CoV-2. Bacterial coinfections with SARS-CoV-2 were more common in older children and were seen in 26% of cases with a severe clinical course requiring ICU admission.

Recent studies in adults have shown that the severity of the disease increases with increasing BMI in patients with COVID-19 (Kompaniyets et al., 2021; Simonnet et al., 2020). In our study, an association between increased BMI and ICU admission rate was observed in children with COVID-19, which was exemplified by the fact that 25% of +3SD BMI patients required ICU. In addition, obese children had a longer duration of the illness and more often had LRTD. The duration of illness in children with a BMI below normal was shorter than in children with a normal BMI, and there were no cases of severe COVID-19 requiring ICU admission. However, this group was characterized by the highest incidence of LRTD. However, a small number of patients did not allow this to be statistically confirmed.

According to some reports, asthma may increase the risk of a more severe clinical course of COVID-19 (asthma.org.uk. shielding advice high risk 2021 April 15, 2021; CDC, 2020; Hartmann-Boyce et al., 2021; Skevaki et al., 2020; Williamson et al., 2020). In our study, there was no difference in the severity of disease between patients with and without bronchial asthma. Duration of illness, frequency of ICU admission, and the incidence of pneumonia did not differ significantly between the groups. This may be due to the constant use of inhaled glucocorticosteroids, which is associated with a lower risk of severe COVID-19 in people with bronchial asthma (Bloom et al., 2021; Finney et al., 2021).

Conclusion

The COVID-19 pandemic led to a significant decrease in the detection rate of non-SARS-CoV-2 RVI and changed the age distribution of hospitalized children with ARIs during the autumn peak of the pandemic, compared with the same period of 2018. There was no significant difference in the frequency of ICU admission in children with SARS-CoV-2 and other RVI (2.7% vs 2.9%). There were no cases of the severe clinical course of COVID-19 in infants. The severe clinical course of ARI in infants has been associated only with hRV and PIV 4, thereby, physicians should be vigilant when these viruses are detected in samples from young children. The possibility of interference between SARS-CoV-2 and hRV, hAdV, and hMPV has been shown in this study. An increase in BMI and bacterial coinfections leads to an increased risk of ICU admission and a longer duration of COVID-19 in children.

Funding

This work was supported by the Ministry of Science and Higher Education of the Russian Federation (AAAA-A20-120081790043-5).

Declarations of interest

none

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2021.12.358.

References

- Agrawal B. Heterologous Immunity: Role in Natural and Vaccine-Induced Resistance to Infections. *Front Immunol* 2019;10. doi:10.3389/fimmu.2019.02631.
- Ånestad G. Surveillance of respiratory viral infections by rapid immunofluorescence diagnosis, with emphasis on virus interference. *Epidemiol Infect* 1987;99:523–31. doi:10.1017/S0950268800068023.
- Arden KE, Greer RM, Wang CYT, Mackay IM. Genotypic diversity, circulation patterns and co-detections among rhinoviruses in Queensland, 2001. *Access Microbiol* 2020;2(e000075). doi:10.1099/ACMI.0.000075.
- asthma.org.uk. shielding advice high risk 2021. Available at: <https://www.asthma.org.uk/advice/triggers/coronavirus-covid-19/shielding-advice-high-risk/>. (accessed April 15, 2021).
- Bloom CI, Drake TM, Docherty AB, Lipworth BJ, Johnston SL, Nguyen-Van-Tam JS, et al. Risk of adverse outcomes in patients with underlying respiratory conditions admitted to hospital with COVID-19: a national, multicentre prospective cohort study using the ISARIC WHO Clinical Characterisation Protocol UK. *Lancet Respir Med* 2021;9:699–711. doi:10.1016/S2213-2600(21)00013-8.
- Casalegno JS, Ottmann M, Bouscambert Duchamp M, Escuret V, Billaud G, Frobert E, et al. Rhinoviruses delayed the circulation of the pandemic influenza A (H1N1) 2009 virus in France. *Clin Microbiol Infect* 2010;16:326–9. doi:10.1111/j.1469-0691.2010.03167.x.
- Castagnoli R, Votto M, Licari A, Brambilla I, Bruno R, Perlini S, et al. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review. *JAMA Pediatr* 2020;174:882–9. doi:10.1001/JAMAPEDIATRICS.2020.1467.
- CDC. People with Moderate to Severe Asthma. Centers Dis Control Prev 2020;19:2019–21. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/asthma.html> (accessed April 24, 2021).
- Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: Prospective observational cohort study. *BMJ* 2020;369. doi:10.1136/bmj.m1985.
- Federal Service for Surveillance on Consumer Rights Protection and Human Well-being. 2021:131. https://www.rosпотребнадзор.ru/upload/iblock/5fa/gd-seb_02_06-_s-podpisyu_.pdf (accessed November 10, 2021).
- Finney LJ, Glanville N, Farne H, Anisenco J, Fenwick P, Kemp SV, et al. Inhaled corticosteroids downregulate the SARS-CoV-2 receptor ACE2 in COPD through suppression of type I interferon. *J Allergy Clin Immunol* 2021;147:510–19 e5. doi:10.1016/j.jaci.2020.09.034.
- Hartmann-Boyce J, Gunnell J, Drake J, Otunla A, Suklan J, Schofield E, et al. Asthma and COVID-19: Review of evidence on risks and management considerations. *BMJ Evidence-Based Med* 2021;26:195. doi:10.1136/bmjebm-2020-111506.
- Joseph C, Togawa Y, Shindo N. Bacterial and viral infections associated with influenza. *Influenza Other Respi Viruses* 2013;7:105. doi:10.1111/IRV.12089.
- Kompaniyets L, Goodman AB, Belay B, Freedman DS, Sucusky MS, Lange SJ, et al. Body Mass Index and Risk for COVID-19–Related Hospitalization, Intensive Care Unit Admission, Invasive Mechanical Ventilation, and Death – United States, March–December 2020. *MMWR Surveill Summ* 2021;70:355–61. doi:10.15585/mmwr.mm7010e4.
- Lai CC, Wang CY, Hsueh PR. Co-infections among patients with COVID-19: The need for combination therapy with non-anti-SARS-CoV-2 agents? *J Microbiol Immunol Infect* 2020;53:505–12. doi:10.1016/j.jmii.2020.05.013.
- Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. *J Infect* 2020;81:266–75. doi:10.1016/j.jinf.2020.05.046.
- Ma X, Liu S, Chen L, Zhuang L, Zhang J, Xin Y. The clinical characteristics of pediatric inpatients with SARS-CoV-2 infection: A meta-analysis and systematic review. *J Med Virol* 2021;93:234–40. doi:10.1002/jmv.26208.
- Mehta NS, Mytton OT, Mullins EWS, Fowler TA, Falconer CL, Murphy OB, et al. SARS-CoV-2 (COVID-19): What Do We Know about Children? A Systematic Review. *Clin Infect Dis* 2020;71:2469–79. doi:10.1093/cid/ciaa556.
- Meningher T, Hindiyeh M, Regev L, Sherbany H, Mendelson E, Mandelboim M. Relationships between A(H1N1)pdm09 influenza infection and infections with other respiratory viruses. *Influenza Other Respi Viruses* 2014;8:422–30. doi:10.1111/irv.12249.
- Navarro-Marí JM, Pérez-Ruiz M, JC Galán Montemayor, MÁ Marcos Maeso, Reina J, De Oña Navarro M, et al. Circulation of other respiratory viruses and viral coinfection during the 2009 pandemic influenza. *Enferm Infect Microbiol Clin* 2012;30:25–31. doi:10.1016/S0213-005X(12)70101-5.
- Nickbakhsh S, Mair C, Matthews L, Reeve R, Johnson PCD, Thorburn F, et al. Virus-virus interactions impact the population dynamics of influenza and the common cold. *Proc Natl Acad Sci U S A* 2019;116:27142. doi:10.1073/PNAS.1911083116.
- Oliva A, Siccardi G, Migliarini A, Cancelli F, Carnevalini M, D'Andria M, et al. Co-infection of SARS-CoV-2 with *Chlamydia* or *Mycoplasma pneumoniae*: a case series and review of the literature. *Infection* 2020;48:871–7. doi:10.1007/s15010-020-01483-8.

- Pascalis H, Temmam S, Turpin M, Rollot O, Flahault A, Carrat F, et al. Intense Co-Circulation of Non-Influenza Respiratory Viruses during the First Wave of Pandemic Influenza pH1N1/2009: A Cohort Study in Reunion Island. *PLoS One* 2012;7:e44755. doi:[10.1371/JOURNAL.PONE.0044755](https://doi.org/10.1371/JOURNAL.PONE.0044755).
- Pinky L, Dobrovolny HM. Coinfections of the respiratory tract: Viral competition for resources. *PLoS One* 2016;11. doi:[10.1371/journal.pone.0155589](https://doi.org/10.1371/journal.pone.0155589).
- Poole S, Brendish NJ, Clark TW. SARS-CoV-2 has displaced other seasonal respiratory viruses: Results from a prospective cohort study. *J Infect* 2020;81:966–72. doi:[10.1016/j.jinf.2020.11.010](https://doi.org/10.1016/j.jinf.2020.11.010).
- Rawson TM, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, et al. Bacterial and Fungal Coinfection in Individuals with Coronavirus: A Rapid Review to Support COVID-19 Antimicrobial Prescribing. *Clin Infect Dis* 2020;71:2459–68. doi:[10.1093/cid/ciaa530](https://doi.org/10.1093/cid/ciaa530).
- Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes among 5700 Patients Hospitalized with COVID-19 in the New York City Area. *JAMA - J Am Med Assoc* 2020;323:2052–9. doi:[10.1001/jama.2020.6775](https://doi.org/10.1001/jama.2020.6775).
- Sarkar S, Khanna P, Singh AK. Impact of COVID-19 in patients with concurrent coinfections: A systematic review and meta-analyses. *J Med Virol* 2021;93:2385–95. doi:[10.1002/jmv.26740](https://doi.org/10.1002/jmv.26740).
- Schultz-Cherry S. Viral Interference: The Case of Influenza Viruses. *J Infect Dis* 2015;212:1690–1. doi:[10.1093/infdis/jiv261](https://doi.org/10.1093/infdis/jiv261).
- Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, et al. High Prevalence of Obesity in Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Requiring Invasive Mechanical Ventilation. *Obesity* 2020;28:1195–9. doi:[10.1002/oby.22831](https://doi.org/10.1002/oby.22831).
- Skevaki C, Karsonova A, Karaulov A, Xie M, Renz H. Asthma-associated risk for COVID-19 development. *J Allergy Clin Immunol* 2020;146:1295–301. doi:[10.1016/j.jaci.2020.09.017](https://doi.org/10.1016/j.jaci.2020.09.017).
- Thiberville SD, Ninove L, Hai VV, Botelho-Nevers E, Gazin C, Thirion L, et al. The viral etiology of an influenza-like illness during the 2009 pandemic. *J Med Virol* 2012;84:1071–9. doi:[10.1002/jmv.23265](https://doi.org/10.1002/jmv.23265).
- Williams BG, Gouws E, Boschi-Pinto C, Bryce J, Dye C. Estimates of world-wide distribution of child deaths from acute respiratory infections. *Lancet Infect Dis* 2002;2:25–32. doi:[10.1016/S1473-3099\(01\)00170-0](https://doi.org/10.1016/S1473-3099(01)00170-0).
- Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020;584:430–6. doi:[10.1038/s41586-020-2521-4](https://doi.org/10.1038/s41586-020-2521-4).
- World Health Organization W. Coronavirus disease 2019 (COVID-2019). Situation Report - 51. Available at: https://www.who.int/docs/default-source/coronavirus/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57_10. World Heal Organ 2020;2019:2633. (accessed April 15, 2021).
- World Health Organization (WHO). WHO body mass index for age bmi for age Available at: <https://www.who.int/toolkits/child-growth-standards/standards/body-mass-index-for-age-bmi-for-age>. (accessed April 15, 2021).
- Wu A, Mihaylova VT, Landry ML, Foxman EF. Interference between rhinovirus and influenza A virus: a clinical data analysis and experimental infection study. *The Lancet Microbe* 2020;1:e254–62. doi:[10.1016/S2666-5247\(20\)30114-2](https://doi.org/10.1016/S2666-5247(20)30114-2).
- Yasuhara J, Kuno T, Takagi H, Sumitomo N. Clinical characteristics of COVID-19 in children: A systematic review. *Pediatr Pulmonol* 2020;55:2565–75. doi:[10.1002/ppul.24991](https://doi.org/10.1002/ppul.24991).