Short Communication

Low incidence of human coronavirus among hospitalized children in Novosibirsk city, Russia during pre-pandemic period (2013–2020)

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Abstract We investigated the incidence of 15 respiratory viruses among 2991 children with acute respiratory infections in Novosibirsk city, Russia, prior to the COVID-19 pandemic (2013

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—2020). Viral infections were detected in 72.5% cases. The incidence of human coronavirus was 2% (*Alphacoronaviruses*, 63%; *Betacoronaviruses*, 37%).

The Coronaviridae family includes enveloped viruses with the largest positive-stranded RNA. These viruses may affect three classes of vertebrates: mammals, birds, and fishes. Viruses from the subfamily *Coronavirinae* (CoV) (alfa-, beta-, and gamma-CoV) may be transmitted via fomites or via aerogenic and/or fecal—oral routes. CoVs primarily target epithelial cells and are generally associated with respiratory and gastrointestinal infections that may be acute, mild, chronic, or asymptomatic. However, some CoVs can cause severe and even lethal diseases.[1] In December 2019, the novel β-coronavirus (SARS-CoV-2) caused pneumonia in Wuhan City, Hubei Province, China, which led to an epidemic and immediately spread worldwide. On March 11, 2020, the World Health Organization announced that the outbreak had become a pandemic. As of January 29, 2021, a total of 100 455 529 cases of SARS-CoV-2 infection have been globally confirmed, of which there have been 2 166 440 deaths.[2] In Russia, 3 793 810 cases were registered from March 02, 2020, to January 29, 2021.[3] Human-to-human transmission of SARS-CoV-2 occurs through droplets, contact, and fomites, similar that reported for previous outbreaks due to other coronaviruses (Middle East respiratory syndrome and severe acute respiratory syndrome). Genetic analysis of SARS-CoV-2 revealed that it was 70% similar to SARS-CoV-1.[4] MERS-CoV, SARS-CoV-1, and SARS-CoV-2 are associated with severe diseases in humans, with mortality rates of 34.4%, 9.5%, and 2.2%, respectively.[2] The other four seasonal human coronaviruses (hCoVs) NL63, 229E, OC43, and HKU1 mainly cause upper or lower respiratory tract infections, including pneumonia (mostly in children); currently, they also cocirculate with other respiratory viruses. HCoVs are globally distributed, and the predominant species may vary by region or year. Limited data exist regarding the epidemiology and clinical manifestations of hCoVs worldwide. We evaluated the incidence of hCoVs in hospitalized children with symptoms of acute respiratory infections (ARIs): fever, sore throat, cough, rhinorrhea, nasal congestion, sputum, shortness of breath, lung auscultation abnormalities, tachypnea, and chest pain. Nasopharyngeal swabs collected from children (0—15 years) with ARIs between 2013 and 2020 in the periods from October—November to March—April, according to the official information from the Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing, at the beginning of the epidemic season in Novosibirsk city were analyzed. The study included children who were hospitalized within 5 days of disease onset and had at least two of the abovementioned symptoms of ARIs. The samples were tested using real-time polymerase chain reaction (PCR) with the commercial kits AmpliSens® Influenza virus A/B-FRT and AmpliSens® ARVI-screen-FRT (Interlabservis, Russia) for the presence of respiratory viruses: RNA human influenza virus types A and B (hIfvs), human parainfluenza virus (hPiv) types 1—4, human respiratory syncytial virus (hRsv), human metapneumovirus (hMpv), four human coronaviruses (NL63, 229E, OC43, and HKU1), human rhinovirus (hRv), DNA human adenovirus (hAdv), and human bocavirus (hBov). For RNA viruses,

Table 1 Demographic characteristics of patients included in the study.

Characteristics of the population		Total number of samples (%)[a] N = 2991 (100%)	Infected (%)		
			Total infections N = 2169 (72.5%)[b]	Single infections N = 1813 (60.6%)[b]	Co-infections N = 356 (11.9%)[b]
Gender	Male	N = 1602 (53.6%)[a]	N = 1173 (73.2%)[c]	N = 967 (60.4%)[c]	N = 206 (12.8%)[c]
	Female	N = 1389 (46.4%)[a]	N = 996 (71.7%)[d]	N = 846 (60.9%)[d]	N = 150 (10.8%)[d]
Age groups	<1 year	N = 634 (21.2%)[a]	N = 467 (73.7%)[e]	N = 375 (59.2%)[e]	N = 92 (14.5%)[e]
	1—3 years	N = 1273 (42.6%)[a]	N = 1026 (80.6%)[f]	N = 833 (65.4%)[f]	N = 193 (15.2%)[f]
	4—6 years	N = 491 (16.4%)[a]	N = 364 (74.1%)[g]	N = 323 (65.8%)[g]	N = 41 (8.3%)[g]
	7—15 years	N = 593 (19.8%)[a]	N = 312 (52.6%)[h]	N = 282 (47.6%)[h]	N = 30 (5.0%)[h]

Note:
[a] - Proportion of each gender or age group in relation to the total sample size.
[b] - Proportion of virus-positive samples in relation to the total sample size.
[c] - Proportion of virus-positive samples in relation to the total amount of male.
[d] - Proportion of virus-positive samples in relation to the total amount of female.
[e] - Proportion of virus-positive samples relative to the total number of children in the age group under one year.
[f] — Proportion of virus-positive samples relative to the total number of children in the age group between one and three.
[g] — Proportion of virus-positive samples relative to the total number of children in the age group between four and six.
[h] — Proportion of virus-positive samples relative to the total number of children in the age group between seven and fifteen.
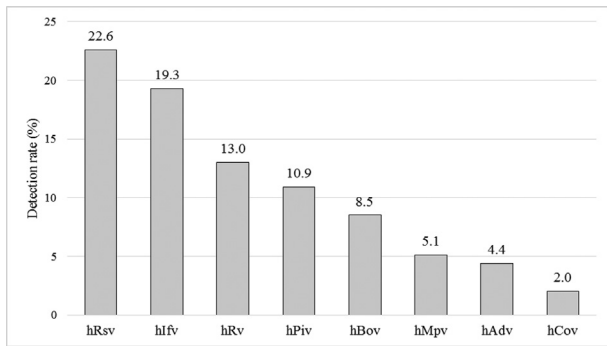
Figure 1. Detection rates of respiratory viruses in hospitalized children, Novosibirsk, Russia (2013—2020). Note: hRsv — human respiratory syncytial virus; hIfv — human influenza virus; hRv — human rhinovirus; hPiv — human parainfluenza virus; hBov — human bocavirus; hMpv - human metapneumovirus; hAdv — human adenovirus; hCov - four human coronaviruses.

before PCR, reverse transcription was performed using the AmpliSens® Reverta-L kit (Interlabservis, Russia)[5].

Results

A total of 2991 samples were analyzed: 1602 (53.6%) samples were obtained from boys and 1389 (46.4%) from girls. The study included patients aged 2 months to 15 years; 42.6% (1273/2991) of the samples were obtained from children aged 1—3 years. The demographic characteristics of the patients are shown in Table 1.

PCR analysis revealed that the genetic material of at least one of the studied viruses was detected in 72.5% (2169/2991) of the children, whereas viral coinfection was detected in 11.9% (356/2991) of the children. The highest level of respiratory virus detection (80.6%) was observed in the children aged 1—3 years, followed by a decrease in the

detection levels with increasing age of the examined children. The lowest percentage of virus detection (52.6%) was observed in school-aged children. The level of viral coinfection also decreased after 3 years of age, reaching the minimum value (5.0%) in the age group of >7 years.

The most common etiological agents in these children during the analysis period were hRsv (22.6%) and hIfv (19.3%) (Fig. 1).

Totally seasonal species of hCoVs (OC43, 229E, NL63, and HKU1) were detected in 2.0% of the examined children. The Alphacoronavirus lineages (NL63/229E) and Betacoronavirus lineage 2a was respectively accounted for 63% and 37% of the cases. In 53.3% of the cases, coronaviruses were detected in combination with other respiratory viruses. Of note, the coronavirus detection rate varied significantly in different epidemic seasons, ranging from 0% in 2017—2018 to 5.8% in 2018—2019 (Fig. 2). Simultaneously, there were no significant differences in the incidence of hCoVs according to sex and age (see Fig. 3).

Discussion

It is crucial to investigate other respiratory pathogens that may impact the epidemiological situation, both in terms of the pre-pandemic period and during the pandemic. The data we obtained in the pre-pandemic period and at the beginning of the pandemic will help track how the etiological structure of ARIs has changed.

This study aimed to describe the detection rates and seasonality of respiratory viruses (hIfvs A and B, hPiv types 1—4, hRsv, hMpv, four hCoVs, hRv, hAdv, and hBov) among children of different age groups hospitalized with ARIs. Samples were collected from October—November to March—April, according to the official beginning of the epidemic season in the study location. Moreover, because the rate of hospitalized children with ARIs is extremely low during the summer months, it was assumed that these cases would not have markedly impacted the number of identified incidents. The lowest incidence of respiratory
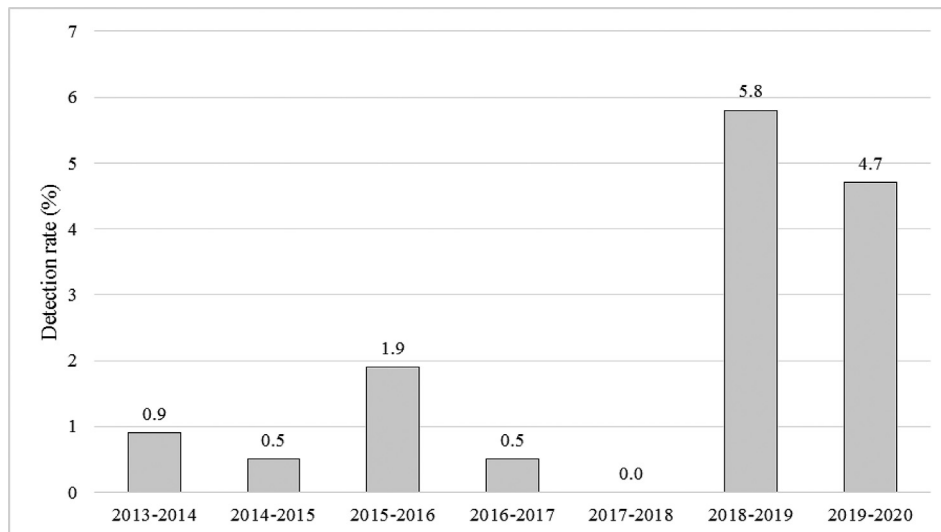

Figure 2. Detection rates of human coronavirus in hospitalized children in different seasons.
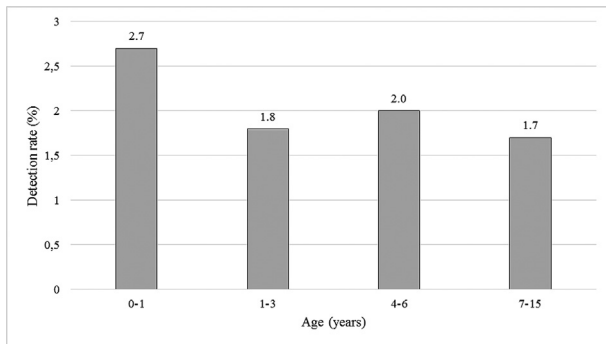
Figure 3. Detection rates of human coronavirus in different age groups.

viruses was noted in the children aged >7 years (52.6%), while in other aged groups the incidence of ARIs were higher (Table 1). The exact same highest level of respiratory virus detection (79.8%) among children aged 1—3 years was reported in a study conducted in Norway.[6] Moreover, we revealed a considerably lower incidence of ARIs in children aged >7—15 years (19.8%) and 4—6 years (16.4%).

In the present study, hRsv and hIfv were the most common agents for respiratory infection among infants and young children during the 8-year control period. HRsv was prevalent and detected in 22.6% of the cases. Similar results were reported by Shafik et al.[7] who detected hRsv infection in 23.8% of patients. The total percentage of hRsv detectability worldwide may vary from 4.4% to 59.2% for viruses causing ARIs.[7] In the present study, hIfv was detected in 19.3% cases. hIfv A was the most frequently identified. Based on the literature, hIfv A and hIfv B detection may vary from 0% to 5% and 1.1%—1.7%, respectively, among hospitalized children.[8]

In the present study, the general structure of respiratory agents also comprised a minor group of pathogens: hRv, 13.0%; hPiv, 10.9%; hBov, 8.5%; hMpv, 5.1%; and hAdv, 4.4%. The low percentage of these viruses was consistent with the data obtained from previous studies on acute respiratory diseases caused by different viruses among children aged <15years.[8]

Of particular interest is the circulation of endemic hCoVs (OC43, 229E, NL63, and HKU1) during the pre-pandemic period. According to our research, coronavirus infection accounts for 2% of all cases of ARIs, of which the majority (63%) were from the *Alphacoronavirus* lineage (NL63/229E) and a minority (37%) were from the *Betacoronavirus* lineage 2a (OC43/HKU1). Similar results were reported by Sergeeva et al.[9] who detected hCoV infection in 10% of all cases of ARIs in Russia in 2011—2012; the most significant etiological agents in children were reportedly *Alphacoronaviruses* (9%) and *Betacoronaviruses* (1%). Several studies have also reported the load of hCoVs in 2% of hospitalized children with respiratory tract infections.[6,8] We noted the highest hCoV detection rate in the group aged <1 year (2.7%) comprising with other aged groups, however, these differences were not statistically significant. Data obtained by Cimolai N[10] also revealed frequent occurrence of the hCoVs among very young pediatric patients.

According to the present study, the absence of hCoVs was registered in the 2017—2018 epidemic period (October—April). The reason for this may be related to dominance alternating with rhinovirus activity, which occurs for populations in both the northern and southern hemispheres.[10] Other researchers also didn't find any hCoVs in some years.[10] Coinfections were commonly noted in several samples collected from patients with hCoV. According to the literature, the frequency of seasonal hCoVs is mostly dominated by rhinovirus activity in populations worldwide.[10] In the present study, the most frequent combinations were hCoV + hRsv (13.3%), hCoV + hPiv (13.3%), and hCoV + hBov (11.7%).

In general, it can be noted that coronaviruses are definitely common respiratory viruses for the population of Novosibirsk and that they have considerable impacts. It is also noteworthy that the current pandemic was preceded by a relative increase in cases of children infected with coronavirus infection, which was not observed earlier since 2013 to the beginning of the study.

In this work, we investigated the incidence of 15 respiratory viruses among 2991 children with ARIs in Novosibirsk city, Russia, prior to the COVID-19 pandemic (2013—2020). Viral infections were detected in 72.5% cases. The incidence of hCoV was 2% (*Alphacoronaviruses*, 63%; *Betacoronaviruses*, 37%).

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Declaration of competing interest

All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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