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Changes in the etiological structure of severe acute respiratory viral infections in children and adults under the influence of the COVID-19 pandemic

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Abstract

Introduction. The traditional surveillance system for influenza and ARVI provides a general description of epidemics, but does not provide information on the age-related characteristics of the etiology and clinical peculiarities of severe acute respiratory diseases (SARI) in hospitalized patients.

Aim. To monitor the etiology of SARI in hospitalized children and adults, assessing the impact of the COVID-19 pandemic on this process.

Materials and methods. Standardized clinical and laboratory monitoring of SARI among 18,458 hospitalized patients was carried out in hospitals in three cities of Russia with weekly PCR detection of 11 types of pathogens.

Results. According to the investigation of hospitalized patients with SARI for the period from 2018 to 2023, the viral etiology of respiratory diseases was deciphered in 58.3% of cases. Weekly monitoring showed a change in the etiological mosaic of SARI pathogens during the SARS-CoV-2 pandemic with a sharp decrease in the frequency of detection of influenza and respiratory syncytial virus (RSV) during the 2020–2021 season against the background of a significant increase of metapneumovirus and rhinovirus infections in children. During the 2022-2023 season an increase in the proportion of RSV infection in children under 6 years of age (up to 36.2%) was noted against the background of a significant decrease in the frequency of SARS-CoV-2. In the intensive care units (ICU), RSV infection was most often in children during the post-pandemic period (up to 30.1–53.6% of positive cases, $p < 0.001$); in adults, SARS-CoV-2 was mostly detected (76,5–100% of cases, $p < 0.001$).

Conclusion. Hospital surveillance data significantly complements the epidemiological information obtained in the traditional surveillance system. Monitoring of infections has shown a continuously changing etiological infrastructure of SARI, with the disappearance of influenza and RSV during the COVID-19 pandemic and their return to circulation in the post-pandemic period.

Keywords: *influenza, parainfluenza, SARS-CoV-2, COVID-19, respiratory syncytial virus, rhinoviruses, adenoviruses, metapneumovirus, etiology, surveillance, hospital*

Ethics approval. The study was conducted with the voluntary informed consent of the patients or their legal representatives. The study protocols were approved by the Ethics Committee of the Smorodintsev Research Institute of Influenza (protocols No. 194, dated December 12, 2022; No. 178, dated January 10, 2022; No. 161, dated December 14, 2020; No. 149, dated December 18, 2019; No. 136, dated December 21, 2018; No. 3120, dated December 18, 2017).

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Оригинальное исследование
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Изменения этиологической структуры тяжёлых острых респираторных вирусных инфекций у детей и взрослых под влиянием пандемии COVID-19

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Аннотация

Введение. Традиционная система надзора за гриппом и острыми респираторными вирусными инфекциями даёт общую характеристику эпидемий, но не обеспечивает получение информации по возрастным особенностям этиологии и клиники тяжёлых острых респираторных заболеваний (ТОРИ) у госпитализированных больных

Цель работы — провести мониторинг этиологии ТОРИ у госпитализированных детей и взрослых с оценкой влияния на этот процесс пандемии COVID-19.

Материалы и методы. Стандартизованный клинико-лабораторный мониторинг ТОРИ среди 18 458 госпитализированных больных проведён в стационарах 3 городов России с еженедельной детекцией 11 типов возбудителей с помощью полимеразной цепной реакции.

Результаты. По данным обследования госпитализированных больных с ТОРИ за 2018–2023 гг. вирусная этиология респираторных заболеваний была расшифрована в 58,3% случаев. Еженедельный мониторинг показал изменение этиологической мозаики возбудителей ТОРИ в период пандемии COVID-19 с резким снижением частоты детекции вирусов гриппа и респираторно-синцитиального вируса (РСВ) в сезон 2020–2021 гг. на фоне достоверного роста у детей метапневмовирусной и риновирусной инфекций. В сезон 2022–2023 гг. отмечен рост удельного веса РСВ-инфекции у детей в возрасте до 6 лет (до 36,2%) на фоне достоверного снижения частоты COVID-19. В отделениях реанимации и интенсивной терапии у детей в постпандемический период чаще всего (до 30,1–53,6% от числа положительных случаев, $p < 0,001$) выявляли РСВ-инфекцию, у взрослых — SARS-CoV-2 (76,5–100% случаев, $p < 0,001$).

Заключение. Данные Госпитального надзора существенно дополняют эпидемиологическую информацию, получаемую в традиционной системе надзора. Мониторинг инфекций показал непрерывно меняющуюся этиологическую инфраструктуру ТОРИ с исчезновением гриппа и РСВ в период пандемии COVID-19 и их возвращением в циркуляцию в постпандемический период.

Ключевые слова: *грипп, парагрипп, SARS-CoV-2, COVID-19, респираторно-синцитиальный вирус, риновирусы, аденовирусы, метапневмовирус, этиология, надзор, стационар*

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Introduction

Although progress has been made in influenza and acute respiratory disease surveillance and preparedness for the upcoming influenza pandemic through improved methods for specific detection and monitoring of acute respiratory viral infections (ARVI), vaccination of target populations, development and validation of platform technologies for rapid vaccine release, expansion of vaccine production capacity, and improved collaboration among countries in the World Health Organization (WHO) system with the development of the Global influenza strategy[1], many problems and unresolved issues remain in this area, specifically in the area of epidemiology and prevention. The existing system of traditional surveillance of influenza and acute respiratory infections has only statistical information on the total number of diseases and hospitalizations with these infections, as well as deciphering their etiology in general among the surveyed groups, but does not provide information on the clinical features and severity of diseases depending on their etiology, age of patients and other individual characteristics. At the same time, in recent years, new data on the role of co-morbidities in influenza, as well as the long-term consequences of severe acute respiratory infections (SARI) of different etiologies (heart attacks, strokes, exacerbations of chronic obstructive pulmonary disease, diabetes, etc.) have been emerging [1–3]. This determines the need for further improvement of surveillance of influenza and other acute respiratory infections.

The importance of personalized clinical and epidemiological surveillance became evident during the development of the latest influenza pandemic caused by the emergence of a new reassortant with the antigenic formula A(H1N1)pdm09 in 2009. To this end, in Russia, starting in 2010, a pilot project began to investigate the possibilities of Signal (sentinel) surveillance of SARI and influenza-like illnesses and acute respiratory infections [4], and since 2012 — in-depth Hospital Surveillance (HS) for influenza and other acute respiratory infections as part of the Global Influenza Hospital Surveillance Network [5–9]. This system, currently used for scientific purposes in more than 20 countries in the Northern and Southern Hemispheres, makes it possible to study the etiology of severe influenza, identify risk groups in need of priority protection, determine the age-specific etiology of SARI with the identification of dominant pathogens, dangerous combinations with comorbidities leading to hospitalization, and assess the severity of the epidemic/pandemic.

In the HS system, for each patient included in the study, an anonymized card is filled in, containing the hospital code, patient number, information on gender, age, chronic diseases, influenza and COVID-19 vaccination status, bad habits, previous hospitalizations, as well as criteria for the severity of the course of infection (need for oxygen support, hyperthermia, transfer to the intensive care unit (ICU), etc.), disease outcome and laboratory diagnosis data. It should be noted that all participants of the system use unified standardized case definitions and patient records, which allows comparing the features of SARI according to uniform criteria in different countries of the world. The main feature is diagnosis using polymerase chain reaction (PCR) for respiratory infectious agent viruses of all patients included in the study, and sequencing and antigenic analysis for a number of samples from patients. Analysis of the antigenic and genetic structure of influenza viruses

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[1] World Health Organization. Global influenza strategy 2019–2030. Geneva; 2019. URL: https://www.who.int/publications/i/item/9789241515320 (date of access: 16.04.2024).

can determine whether viruses circulating in a particular season match the strains included in the vaccine.

The spread of the COVID-19 pandemic has led to a marked shift in the pattern of circulating influenza and acute respiratory viruses among hospitalized patients of different age groups with SARI. Therefore, the aim of the study was to monitor the etiology of SARI in hospitalized children and adults, assessing the impact of the COVID-19 pandemic on this process.

Materials and methods

Study design

Clinical and laboratory monitoring of influenza, COVID-19 and other acute respiratory viral infections among hospitalized patients in the HS was conducted in 9 hospitals in St. Petersburg, Novosibirsk and Yekaterinburg in accordance with the Standard Protocols for Children Under 5 Years of Age and for Patients 5 Years of Age and Older used in the HS. In addition to the basic parameters (sex, age, hospitalization period, etiology according to PCR data, vaccination history, diagnosis at admission and discharge, concomitant pathology, smoking, disease outcome, etc.), physicians assessed the severity of the disease. The study was conducted according to the principles of Good Clinical Practice after approval by the Local Ethics Committees. Throughout all 5 seasons (from 2018–2019 to 2022–2023), the screening survey started from week 40 and the main HS surveys started on the week when the first 3 laboratory-confirmed cases of influenza were detected by PCR in the city hospitals. Surveys were completed at the end of the influenza epidemic season, usually in week 18-20, when no more cases of SARI with laboratory-confirmed influenza were identified in the wards of all hospitals included in the study. The duration of the study averaged 6-7 months. The results of the examination of patients were submitted by physicians into Individual patient charts and sent via the Internet to the Electronic Database at the A.A. Smorodintsev Research Institute of Influenza, where they (after control of completeness and accuracy of filling) were stored throughout the period of work with the possibility of automated output of the requested data.

To be included in the study, patients had to have a combination of the following symptoms: 1 or more of 4 systemic symptoms: fever, weakness, headache, myalgia, and 1 or more of 3 respiratory symptoms: cough, sore throat, rapid breathing. The duration of the disease at the time of inclusion in the study should have been no more than 7 days from the onset of registration of symptoms, the duration of hospitalization — no more than 48 h. The study was conducted with the voluntary informed consent of the patients or their legal representatives. The study protocols were approved by the Ethics Committee of the Smorodintsev Research Institute of Influenza (protocols No. 194, dated December 12, 2022; No. 178, dated January 10, 2022; No. 161, dated December 14, 2020; No. 149, dated December 18, 2019; No. 136, dated December 21, 2018; No. 3120, dated December 18, 2017).

Criteria for exclusion from the study: the patient is not a resident of the city, duration of illness more than 7 days, duration of hospitalization less than 24 hours, patient's belonging to a specialized medical or social institution, lack of patient's consent to participate in the study, inability to communicate with the patient.

Collection and statistical analysis of data

Data collection, their subsequent correction, systematization of initial information and analysis of the obtained results were carried out by specialists of the A.A. Smorodintsev Research Institute of Influenza using the Individual patient records entered by physicians in the Electronic Database of HS.

Statistical processing of the results was carried out using the Statistica v. 10 program: descriptive statistics, nonparametric criteria. When assessing quantitative indicators, the median was counted as the center of distribution, and the first (Q_1) and third (Q_3) quartiles were counted as variation indicators. The results of qualitative traits were expressed in absolute numbers with indicating percentages. Comparison of nominal data between groups was performed using Pearson's χ^2 test. When the number of expected observations in any cell of the quadratic table was less than 10, Fisher's exact test was used to assess the significance level of differences. Differences were considered statistically significant at $p \leq 0.05$.

PCR diagnostics

For laboratory diagnosis, nasopharyngeal and oropharyngeal swabs were taken from each patient aged ≥ 14 years, and nasal and pharyngeal swabs were taken from children younger than 14 years. Laboratory testing for influenza viruses and other ARI pathogens was performed by PCR within the first 48 h of hospitalization. For clinical specimens, velour swabs (Copan) were used, which were immersed in universal transport medium UTM-330C (Copan) for mycoplasmas, chlamydia and viruses. RNA was isolated from clinical samples using AmpliSens RIBO-prep (InterLabService) or QIAGEN RNeasy Mini (Qiagen) kits. RNA reverse transcription was performed with the Reverta-L kit (InterLabService) or QIAGEN OneStep RT-PCR (Qiagen). AmpliSens Influenza virus A/B-FL kits (InterLabservice) were used to test for influenza A and B; influenza A-positive samples were used to subtype influenza viruses A(H1N1)pdm09 and A(H3N2) using AmpliSense Influenza virus A/H1-swine-FL kits (InterLabservice) and AmpliSens Influenza A subtyping-FL kit (InterLabservice). All samples were also tested for the presence of other ARVI pathogens (human respiratory syncytial virus, metapneumovirus, parainfluenza virus types 1–4, coronavirus, rhinovirus, adenoviruses, bocavirus) and examined using the AmpliSens ARVI-screen-FL kit (InterLabservice). Specific sequences of influenza B virus of the Yamagata or Victoria lineages were determined in all influenza B-positive samples using the QIAGEN OneStep RT-PCR Kit (Qiagen) with WHO-recommended primers and probes. Real-time PCR was performed on a Rotor-Gene 6000 (Corbett Research) or the CFX96 Touch™ Real-Time PCR Detection System (Bio-Rad).

Results

Age distribution of patients

Over a 5-year period, starting from the 2018–2019 season, 18,458 patients hospitalized in ARVI wards with primary diagnoses of influenza, acute respiratory viral infection, pneumonia, acute bronchitis, and other manifestations of acute respiratory infections of varying severity were examined in 3 infectious diseases hospitals for adults and 6 multidisciplinary hospitals for children in St. Petersburg, Novosibirsk and Yekaterinburg. Analysis of the age distribution of the hospitalized (on average) showed a significant proportion of children (73.8%), including those aged ≤ 2 years (39.7%), 3–6 years (18.5%), 7–14 years (15.6%). The frequency of hospitalization of patients aged 15–64 years averaged 19.7% for the whole period, including patients aged 65 years and older — 6.5% (**Table 1**).

Table 1. Age distribution of the admitted patients included in the study

Age, years	Number of patients	Median age, years (Q_1; Q_3)
0–2	7321	11* (5; 23)
3–6	3418	4,25 (3,5; 5,33)
7–17	2880	10,33 (8,42; 12,5)
18–64	3645	31,66 (21,5; 45,8)
≥ 65	1194	75,75 (70,0; 83,7)
Total	18458	4,75 (1,5; 21,7)

Note. *For children of group 0–2 years, age indicated in months.

The frequency of hospitalization of children of the 0–2 years age group was significantly higher ($p < 0.001$) than patients of all other age groups in general during the study period, and also significantly higher in 2018–2019 and 2020–2023. In the period from October 2019 to September 2020, when the first wave of the pandemic developed in Russia, the age distribution of patients hospitalized in wards with acute respiratory infections changed: the frequency of hospitalization in the group 15–64 years increased to 37% against the background of a decrease in hospitalization of children aged ≤ 2 years to 29.3% ($p < 0.001$). In 2021–2022, there was an increase in the frequency of hospitalization of patients aged 65 years and older compared with the frequency of hospitalization in other years ($p < 0.000$; **Figure 1**).

Etiology of ARVI

The viral etiology of diseases was deciphered in 58.3% of cases on average over the entire period (57.8–59.1%; $p = 0.95$). In our observations, the frequency of cumulative detection of non-influenza acute respiratory infections during the entire period and in the last 3 seasons was significantly higher ($p < 0.0001$) than cases of laboratory-confirmed influenza and SARS-CoV-2. Interestingly, the ratio of patients hospitalized with laboratory-confirmed influenza and other acute respiratory infections was similar before the pandemic in 2018–2019 and 2019–2020 (0.95 and 1.2, respectively; $p = 0.275$), but changed dramatically in the following 3 years due to the spread of SARS-CoV-2. Thus, in 2020–2021, influenza virus was practically eliminated from circulation and was detected in the HS system in only 0.1% of cases, although other SARI pathogens

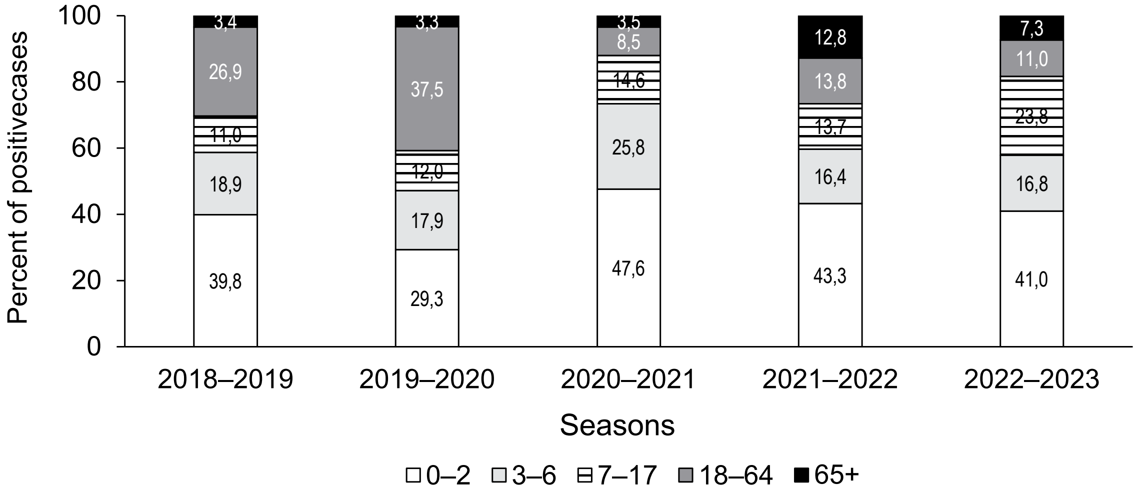

Fig. 1. Age distribution of patients with influenza, COVID-19 and other acute respiratory infections included in the study.

(excluding RSV) were detected with the same, or even higher frequency (89.0%).

In the post-pandemic period, the detection rate of influenza viruses among hospitalized persons began to increase (to 11.7–22.3%), but never reached the pre-pandemic level and remained significantly lower ($p < 0.001$) compared to ARVI (4.3 and 2.9 times in the 2021–2022 and 2022–2023 seasons). The frequency of SARS-CoV-2 detection peaked (38.4%) in the 2021–2022 season with a decrease to 11.4% in the latter season (**Figure 2**).

Analysis of diseases caused by different types/subtypes of influenza virus

In the 2018–2019 and 2019–2020 seasons, influenza A(H1N1)pdm09 virus was the main etiologic agent, causing 53.2% and 44.0% of influenza illnesses, respectively, and co-circulating with influenza A(H3N2) virus (45.1%) in 2018-2019 and with influenza B Victoria virus (48.6%) in 2019–2020. Few cases of Yamagata influenza B lineage were reported at the end of the 2018–2019 (9 cases) and 2019–2020 (2 cases) seasons, while the remaining influenza B cases were detected only with Victoria lineage viruses. In the 2020–2021 season, with the start of the active phase of the COVID-19 pandemic in Russia, no influenza cases were registered among hospitalized patients, except for 2 cases in Yekaterinburg, when trace amounts of influenza B virus RNA were detected in patients, which did not allow its subtyping to be performed.

The 2021–2022 season was characterized by an unusually early onset of influenza A(H3N2) virus circulation: the first influenza cases among hospitalized patients were detected as early as week 41 of 2021, and the number of influenza cases peaked in week 48. The epidemic was mono-ethiologic (97.0%) and was caused by influenza A(H3N2) virus. Only at the end of the season, sporadic cases of influenza B were detected. Against the background of the increased number of hospitalizations with COVID-19, the total number of influenza cases among hospitalized patients became significantly lower ($p < 0.001$) by 4.0 and 5.5 times

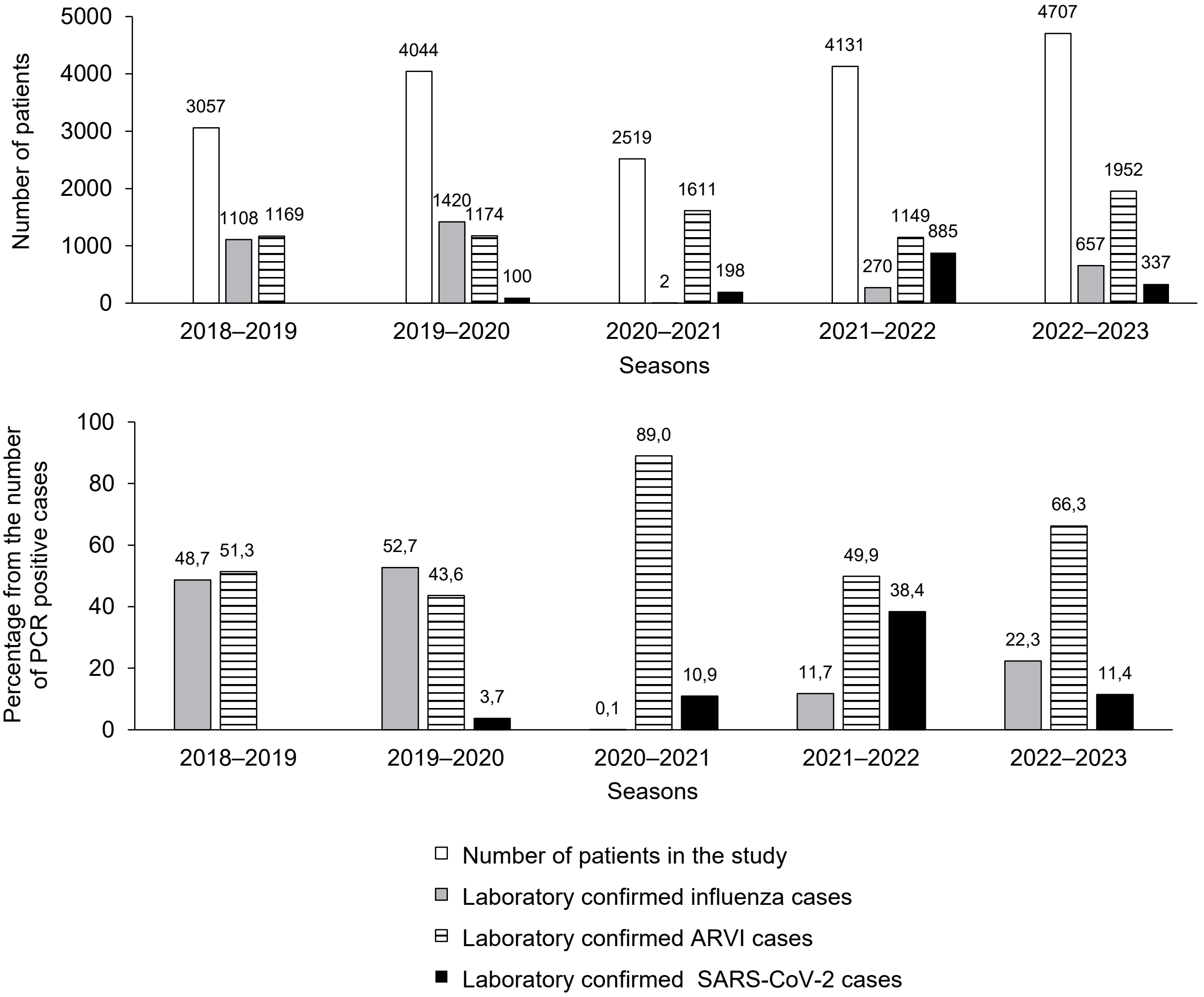

Fig. 2. Changes in the frequency of laboratory-confirmed cases of influenza, ARVI (total) and COVID-19 among hospitalized patients over a 5-year period.

compared to the 2018–2019 and 2019–2020 seasons, respectively. The last influenza epidemic season was characterized by a cardinal change of the pathogen with the return of influenza virus subtype A(H1N1) pdm09 and influenza B viruses of the Victoria lineage (**Table 2**, **Fig. 3**).

Thus, a feature of the last 2 epidemics was an earlier onset of influenza virus circulation (by 6–9 weeks compared with the epidemics of the pre-pandemic period) with peak PCR detection of viruses in hospitalized patients as early as the 48th and 50th weeks of the year (compared with 5–7 weeks of the following year in the pre-pandemic seasons) (**Fig. 3**).

Monitoring the etiology of non-influenza acute respiratory diseases

A study of the structure of respiratory morbidity of non-influenza etiology, whose incidence among hospitalized patients was significantly higher than that of influenza (38.2% vs. 21.7% of the number of patients examined; $p < 0.0001$), showed that in the pre-pandemic period the most significant ($p < 0.0001$) pathogen was RSV, which caused the greatest number of hospitalizations (up to 26.8% in children aged ≤ 2 years). Rhinoviruses were the next most important (up to 16.6% in this age group). The role of the other pathogens was generally relatively minor.

The emerging COVID-19 pandemic has fundamentally changed the etiologic picture: in the 2020-2021 season, RSV (as well as influenza viruses) practically disappeared from circulation, and only isolated cases of this infection were registered among hospitalized patients. Of particular interest is the sharply increased (6–12 times) importance of metapneumovirus infection ($p < 0.000$), the pathogen of which belongs to the same family as RSV (Pneumoviridae). In the next season (2021–2022), there were practically no cases of metapneumovirus infection, but RSV reappeared in the circulation, which became even more active in the 2022–2023 season, reaching the indicators characteristic of the pre-pandemic period (**Fig. 4**).

Age-specific etiologies of the most important respiratory infections

Analysis of the total annual data on the role of the main pathogens in the hospitalization of patients depending on age showed that in all these years, except for two seasons of active spread of SARS-CoV-2, RSV affected predominantly children of younger age groups 0–2 and 3–6 years (up to 16.5–26.8% of patients), but was rarely registered in age groups 7 years and older ($p < 0.0001$). The age range for rhinovirus infection was significantly wider, covering all pediatric age groups. The frequency of rhinovirus detection in hospitalized children in the 0–2 year age group ranged from 10.1 to 16.6% and was significantly higher than in adult patients aged 18–64 and ≥ 65 years in all years ($p < 0.001$). Differences between rhinovirus detection rates in hospitalized children aged 0–2 and 3–6 years were not significant. Interestingly, in the 2020–2021 season, when RSV circulation decreased dramatically, there was a significant increase in the frequency of rhinovirus detection compared to the previous two seasons ($p < 0.001$). In the last season compared to 2021–2022, there was a trend of increasing frequency of RSV ($p < 0.001$) and rhinovirus infection ($p < 0.001$) against the background of decreasing significance of COVID-19 ($p < 0.001$).

In contrast to RSV and rhinovirus infection, COVID-19 as a cause of hospitalization was reported significantly less frequently in children than in adults ($p < 0.001$). At the beginning of the pandemic (2019–2020 season), no COVID-19 cases were reported among hospitalized children under 17 years of age; in the following season, the detection rate of the virus in children across age groups was also low, ranging from 0.8% to 2.4% of those examined in this age group (with a detection rate of 52.1–66.7% in adults). In the 2021–2022 season, the detection rate of SARS-CoV-2 among hospitalized children increased to 6.8–13.6%. These differences became less pronounced in the latter season due to a decrease in SARS-CoV-2 detection among both children and adults. The detection rate of SARS-

Table 2. The role of influenza viruses A(H1N1)pdm09, A(H3N2) and B) in the development of acute respiratory diseases requiring hospitalization over 5 consecutive seasons

Season	Number of patients	Influenza cases		Percentage of PCR-positive influenza cases by type/subtype			
		number	%	A(H1N1) pdm09	A(H3N2)	A not subtyped	B
2018–2019	3057	1108	36,2	53,2	45,1	0,4	1,3
2019–2020	4044	1420	35,1	44,0	5,4	2,0	48,6
2020–2021	2519	2	0,1	0,0	0,0	0,0	–
2021–2022	4131	270	6,5	0,0	97,0	0,4	2,6
2022–2023	4707	657	14,0	42,8	0,3	18,7	38,2
Total	18458	3457	18,7	43,3	24,3	4,5	27,9

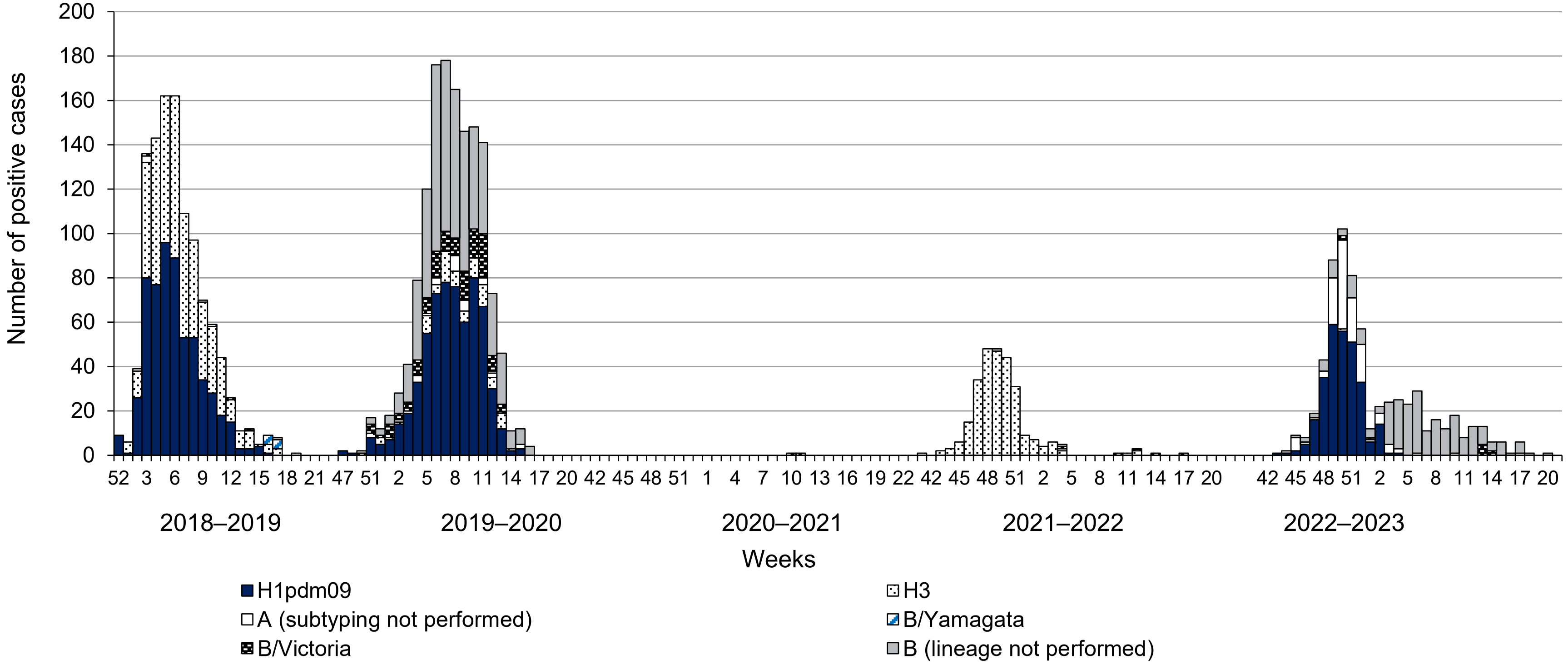

Fig. 3. Monitoring of PCR-detection of influenza A(H1N1)pdm09, A(H3N2) and B viruses among hospitalized patients for 5 consecutive seasons in the hospital surveillance system.

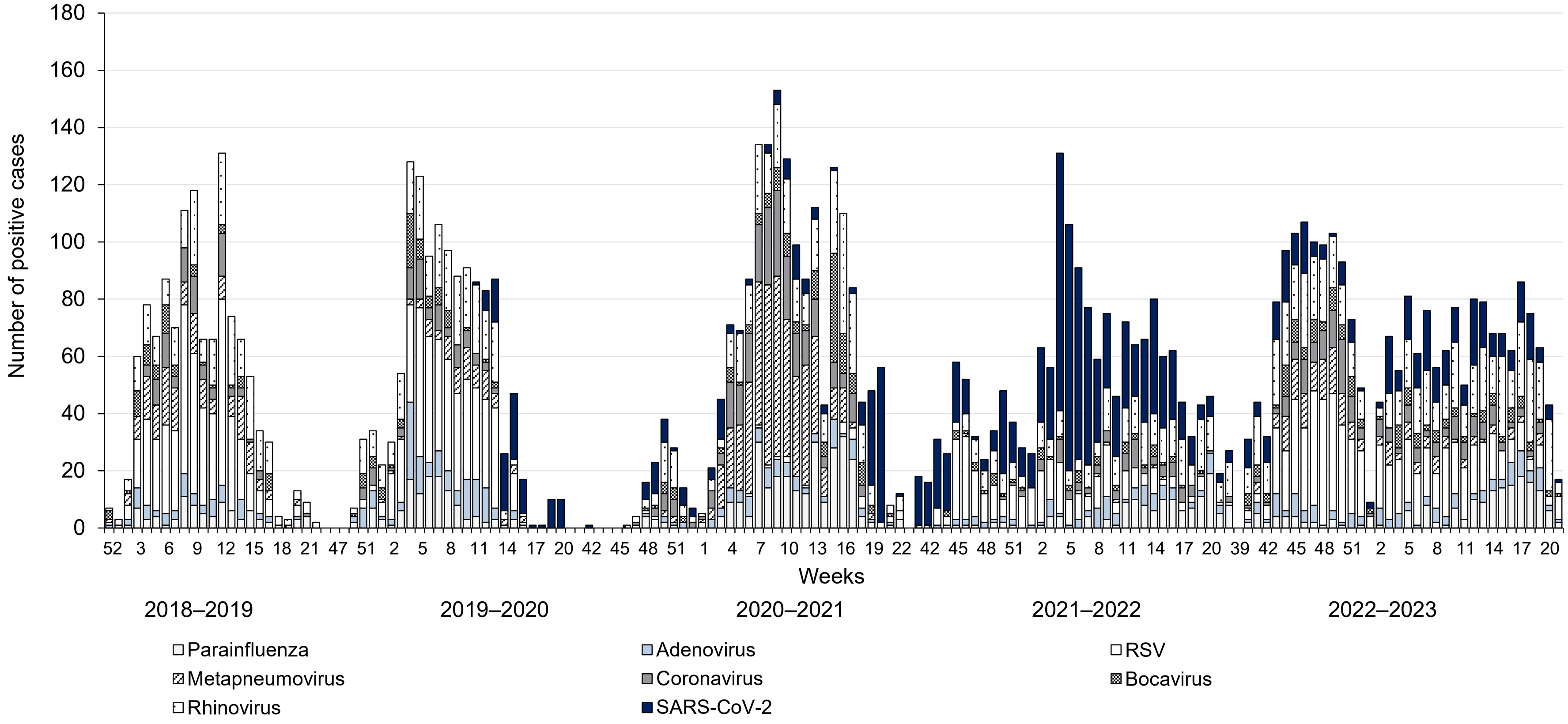

Fig. 4. Changes in the etiological mosaic of the distribution of ARVI pathogens in the development of severe forms of diseases requiring hospitalization due to the development of the COVID-19 pandemic.

CoV-2 in adult patients aged 18–64 and ≥65 years was significantly higher compared with other age groups in all seasons ($p < 0.001$), but the differences between the detection rates of SARS-CoV-2 in the 18–64 and ≥ 65 age groups were only significant in the 2022–2023 season, when the percentage of hospitalizations among adults aged 18–64 years decreased 3.5-fold ($p < 0.001$; **Figure 5**).

Etiology of respiratory disease in intensive care units

During the entire period, 1112 (6.0%) of the total 18,458 hospitalized patients included in the study were referred to the ICU. Influenza viruses, SARS-CoV-2 or other ARI pathogens were detected in 668 patients. Children under 6 years of age were most frequently hospitalized in ICU in 517 (77.4%) cases during the whole period, children aged 7–17 years in 86 (12.9%) cases, and adults were the least frequently hospitalized in ICU in 65 cases (9.7% of the total number of patients in ICU (the differences are significant, $p < 0.001$).

In young children (0–6 years of age), RSV infection was most frequently diagnosed in all seasons except 2020–2021, when SARS-CoV-2 spread widely (28.9–47.7% of all PCR-positive cases in the ICU). In the 2020–2021 season, the RSV detection rate dropped to 3.6% against the background of a 2–5-fold increased role compared with previous years of metapneumovirus infection (up to 28.4%), seasonal coronavirus infection (up to 14.2%), bocaviruses (up to 11.2%), and rhinoviruses (up to 20.9%) ($p < 0.001$). In the next 2 seasons, the incidence of RSV and rhinoviruses increased to 28.9–41.7% and 45.4–18.7%, respectively, while COVID-19 was diagnosed in only 0.5–7.2% of cases in this group. The role of influenza viruses varied by season: during the pre-pandemic period, influenza A(H1N1)pdm09 virus was more frequently reported in children aged ≤ 6 years (11.9–16.4% of cases), influenza A(H3N2) virus was detected in 0.9–7.3%, and influenza B virus in up to 9.2% of cases. In the 2020–2021 season, diseases of influenza etiology among children were not registered in ICU, and their detection rate in the postpandemic period in ICU did not exceed 4.1%.

In school-aged children 7–17 years of age, the leading causes of hospitalization in the ICU were influenza A(H1N1)pdm09 viruses, 66.7 and 25.0% in the 2018–2019 and 2022–2023 seasons, influenza A(H3N2) viruses, 12.5 and 30.0% in the 2019–2020 and 2021–2022 seasons, and influenza B viruses, 50.0 and 19.4% in the 2018–2019 and 2019–2020 seasons, while metapneumovirus (24.0%), seasonal coronavirus (14.0%), and rhinoviruses (30.2%) were most frequent-

Table 3. Age-related peculiarities of the etiology of the most significant respiratory infections

Season	Age, years				
	0–2	3–6	7–17	18–64	65+
RSV					
2018–2019	26,8	16,5	4,8	2,2	4,9
2019–2020	25,7	13,6	3,3	1,0	2,3
2020–2021	1,7	1,2	0,3	0,0	0,0
2021–2022	13,4	6,9	3,6	1,2	1,3
2022–2023	24,1	12,1	3,8	1,3	2,3
Rhinovirus					
2018–2019	10,1	11,3	7,4	4,3	2,9
2019–2020	10,2	8,3	5,1	3,8	1,5
2020–2021	16,6	14,6	14,6	2,3	1,1
2021–2022	13,8	13	6,5	2,6	0,8
2022–2023	14,2	13,7	12,2	5,2	2,9
SARS-CoV-2					
2018–2019	0,0	0,0	0,0	0,0	0,0
2019–2020	0,0	0,0	0,0	5,3	15,2
2020–2021	1,2	0,8	2,4	52,1	66,7
2021–2022	10,6	6,8	13,6	50,7	53,6
2022–2023	4,7	1,5	4,0	13,5	34,6

ly detected in the 2020–2021 season. COVID-19 cases were most frequently (32.0%) detected in schoolchildren in the 2021–2022 season, with a decrease to 8.4% in the following season due to the increased role of influenza and RSV viruses.

A different picture was observed in adult patients. If in the pre-pandemic period, influenza B viruses were the main cause of hospitalization in SARI, then, starting from the season 2019–2020, SARS-CoV-2 virus became the main cause of hospitalization in ICU (60–100% of cases). The role of other pathogens in the development of SARI in adults was insignificant.

A comparative analysis of disease etiology in patients admitted on general acute respiratory (GAR) and ICU wards showed that young children had the highest incidence of RSV diagnoses in ICU in all seasons except pandemic season 2020–2021, exceeding diagnosis incidence in GAR by 8.1–13.2%. In the 2021–2022 season, an excess of rhinovirus infection diagnosis was observed in ICU compared to GAR. In children 7–17 years of age, during the seasons of active circulation of influenza A(H1N1)pdm09 virus (2018–2019 and 2022–2023), this pathogen was diagnosed more frequently in ICU compared to GAR. In adult patients, the main differences concerned SARS-CoV-2, the detection rate of which was distinctly higher in ICU than in GAR. Differences in other infections were insignificant (**Fig. 6**).

Discussion

Over a 5-year period, all 18,458 patients hospitalized in infectious diseases hospitals in 3 major Russian cities (St. Petersburg, Novosibirsk, and Yekaterinburg) were examined by PCR to determine the role of influenza viruses A(H1N1)pdm09, A(H3N2), Victoria and Yamagata B lineages, SARS-CoV-2, as well as other pathogens such as RSV, rhinoviruses, metapneumoviruses, coronaviruses, adenoviruses, parainfluenza viruses, bocaviruses, in the development of SARI requiring hospitalization, and to determine age-specific etiology of disease. Weekly monitoring of influenza cases among the examined patients showed an alternation of dominant pathogens: A(H1N1)pdm09 and A(H3N2) in the 2018–2019 season, A(H1N1)pdm09 and B in the 2019–2020 season, A(H3N2) in the 2021–2022 season, A(H1N1)pdm09 and B in the 2022–2023 season. Among influenza B viruses, strains of the Victoria lineage predominated in all seasons. The last cases of influenza B lineage Yamagata in our study among hospitalized patients were reported at the end of 2019–2020 season. In 2020–2021 season (developed SARS-CoV-2 pandemic), there were almost no cases of influenza A and B among the hospitalized patients studied. In the 2022–2023 season, the data obtained on the monitoring of influenza etiology among hospitalized patients clearly correlated with the results of traditional surveillance in Russia [10], while in North America and Western Europe, influenza A(H3N2) viruses were most prevalent [11, 12]. Such differences determine the necessity to formulate its own strategy of strain selection for vaccines in Russia (taking into account WHO recommendations) in order to improve the effectiveness of vaccine prophylaxis, as it is carried out at the national level in other highly developed countries, for example, the National Immunization Advisory Committee Technical Working Group in China [13].

Table 4. Comparison of the etiology of SARI in children 0–6 years old hospitalized in general wards for ARVI and in intensive care units (ICU) over a 5-year observation period

Сезон Season	A(H1N1) pdm09	A(H3N2)	B	Para-influenza	Adeno-virus	RSV	Metapneumo-virus	Corona-virus	Boca-virus	Rhino-virus	SARS-CoV-2
All patients											
2018–2019	23,1	13,5	0,4	3,9	3,3	27,1	8,9	4,1	3,6	12,1	0,0
2019–2020	22,7	2,0	15,2	5,5	5,7	26,2	3,7	3,3	3,8	11,8	0,0
2020–2021	0,0	0,0	0,1	16,9	5,3	2,0	29,8	14,8	9,0	20,7	1,3
2021–2022	0,0	11,4	0,3	12,3	6,9	20,1	0,4	4,6	3,7	23,5	16,6
2022–2023	9,1	0,1	6,3	7,2	4,4	28,5	6,1	7,1	6,6	19,5	5,2
ICU patients											
2018–2019	16,4	7,3	1,8	9,1	3,6	38,2	5,5	3,6	7,3	7,3	0,0
2019–2020	11,9	0,9	9,2	2,8	0,9	47,7	5,5	3,7	4,6	12,8	0,0
2020–2021	0,0	0,0	0,0	11,2	6,0	3,0	28,4	14,2	11,2	20,9	5,2
2021–2022	0,0	4,1	0,0	3,1	3,1	28,9	0,0	5,2	3,1	45,4	7,2
2022–2023	2,7	0,0	3,2	9,1	3,7	41,7	7,0	5,9	7,5	18,7	0,5

Table 5. Comparison of the etiology of SARI in children 7–7 years old hospitalized in general wards for ARVI and in intensive care units (ICU) over a 5-year observation period

Season	A(H1N1) pdm09	A(H3N2)	B	Para-influenza	Adeno-virus	RSV	Metapneumo-virus	Corona-virus	Boca-virus	Rhino-virus	SARS-CoV-2
All patients											
2018–2019	35,3	28,4	1,0	2,5	2,0	7,8	4,9	4,4	1,5	12,3	0,0
2019–2020	21,8	5,9	45,7	3,1	5,9	5,5	2,4	0,0	1,0	8,7	0,0
2020–2021	0,0	0,0	0,0	14,5	5,6	0,6	24,0	14,0	6,1	30,2	5,0
2021–2022	0,0	34,9	0,8	5,4	3,3	5,0	0,0	2,9	0,4	15,4	32,0
2022–2023	15,4	0,2	21,2	3,9	5,8	8,1	6,0	5,1	0,4	25,7	8,4
ICU patients											
2018–2019	66,7	0,0	0,0	0,0	0,0	11,1	0,0	11,1	0,0	11,1	0,0
2019–2020	12,5	12,5	50,0	0,0	12,5	0,0	0,0	0,0	0,0	12,5	0,0
2020–2021	0,0	0,0	0,0	5,9	5,9	0,0	23,5	29,4	0,0	35,3	0,0
2021–2022	0,0	30,0	0,0	5,0	0,0	10,0	0,0	10,0	0,0	20,0	25,0
2022–2023	25,0	0,0	19,4	0,0	5,6	13,9	8,3	2,8	2,8	19,4	2,8

Table 6. Comparison of the etiology of SARI in patients 18+ years hospitalized in general wards for ARVI and in intensive care units (ICU) over a 5-year observation period

Season	A(H1N1) pdm09	A(H3N2)	B	Para-influenza	Adeno-virus	RSV	Metapneumo-virus	Corona-virus	Boca-virus	Rhino-virus	SARS-CoV-2
All patients											
2018–2019	31,0	45,2	1,2	3,3	1,6	4,5	2,7	3,1	0,0	7,4	0,0
2019–2020	25,3	3,4	38,6	3,3	3,3	2,1	1,3	3,2	0,4	7,0	11,9
2020–2021	0,0	0,0	0,0	4,7	0,5	0,0	5,7	5,2	0,5	2,8	80,6
2021–2022	0,0	2,5	0,2	0,3	0,3	2,2	0,9	1,2	0,3	3,0	89,1
2022–2023	5,9	0,0	4,7	3,7	2,5	4,7	5,0	3,1	0,0	11,5	58,9
ICU patients											
2018–2019	0,0	0,0	50,0	50,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0
2019–2020	10,0	0,0	20,0	0,0	0,0	0,0	10,0	0,0	0,0	0,0	60,0
2020–2021	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	100,0
2021–2022	0,0	0,0	0,0	0,0	4,2	4,2	0,0	0,0	0,0	0,0	91,7
2022–2023	0,0	0,0	0,0	0,0	0,0	0,0	6,3	0,0	0,0	12,5	81,3

Interesting data were obtained by monitoring the expanded etiologic infrastructure of respiratory infections. It is generally believed that the sharp decline in the activity of influenza and RSV viruses in the early years of the pandemic caused by SARS-CoV-2 was due to the wide implementation of anti-epidemic measures [14]. Without denying this, it should be noted that according to our more extensive studies, against the background of suppression of these infections in the season 2020-2021, the role of such pathogens as seasonal coronaviruses, parainfluenza viruses and, especially, metapneumoviruses in the development of SARI increased significantly, despite the anti-epidemic measures. In the following seasons, the frequency of RSV and influenza virus detections began to recover, and the importance of metapneumovirus infection in the hospitalization of patients decreased to the usually reported rates. These data support the earlier assumption that there is interference between individual pathogen species at the population level [15], which was previously observed only during the development of influenza pandemics. Thus, it is known that the subtype of seasonal influenza A(H1N1) in 2009–2010 was completely displaced by the newly emerged reassortant of human, swine and avian influenza viruses — variant A(H1N1)pdm09, in 1957–1958 the A(H1N1) subtype was displaced by the "Asian" influenza A(H2N2) virus, and in the 1968–1969 season, the A(H2N2) influenza virus subtype was completely displaced by the newly emerged pandemic A(H3N2) strain of the "Hong Kong influenza" virus. The mechanisms of this phenomenon need to be further investigated. Obviously, the results of the HS significantly complement the data of the existing traditional surveillance system, allowing to analyze the etiology of SARI requiring hospitalization, which is not only of theoretical interest, but also important for practically significant calculations of socio-economic damage from costly hospitalization of patients. It is known that the system of traditional surveillance allows determining the start/end of the epidemic on the basis of comparison of the actual level of morbidity with threshold values (base lines) calculated from archival materials of non-epidemic morbidity for the previous 5 seasons. Furthermore, these data allow estimating the intensity of the epidemic based on the average statistical data for the previous years [16–20]. At the same time, the WHO guidelines have recently set new tasks: they point out the need to define such indicators "as the severity of the disease". It is stated that "the severity of the disease depends on the host organism, such as the presence of concomitant medical conditions that predispose the individual to develop severe disease, history of preventive vaccination (e.g., influenza and pneumococcal disease), the age of the individual, and the availability of medical care". HS opens up new possibilities for defining these indicators, which will be reflected in the following publications.

Summary

Peculiarities of etiology of severe acute respiratory infections in children and adults were determined with assessment of the impact of the COVID-19 pandemic on the etiologic infrastructure of diseases.

Weekly monitoring showed a change in the etiologic mosaic of SARI pathogens during the COVID-19 pandemic, with a sharp decrease in the detection rate of influenza and RSV viruses and its gradual recovery in the post-pandemic period.

Age-specific etiologic features of SARI in ICU have been established. Severe forms of diseases in children in ICU in the post-pandemic period were most often associated with respiratory syncytial infection, while in adults the main pathogen of SARI was SARS-CoV-2.

Conclusion

HS data significantly complement epidemiologic information obtained in the traditional surveillance system, which determines the feasibility of its introduction into clinical and epidemiologic practice. Monitoring of infections showed a continuously changing etiologic infrastructure of SARI, with the disappearance of influenza and RSV during the COVID-19 pandemic and their return to circulation in the post-pandemic period.

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