Original article
https://doi.org/10.36233/0372-9311-513

Detection and type identification of non-polio enteroviruses in children against the background of acute intestinal infections of various etiologies: 2018–2023

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Abstract

Introduction. Enteroviruses (EV) are characterized by: species and type diversity, polymorphism of clinical manifestations, a tendency to epidemic spread, and are often the cause of disease outbreaks, which determines the relevance of monitoring EV strains in various clinical forms of infection, including in conditions of anti-epidemic measures.

The **aim** of the study: to characterize the prevalence and diversity of non-polio enteroviruses (NPEV) types in children with acute intestinal infection (AII) in the period 2018–2023, including the COVID-19 pandemic.

Materials and methods. The RT-PCR method was used to study 7302 samples of feces from children hospitalized with a diagnosis of AII in the infectious diseases hospital of Nizhny Novgorod. Genotyping of EV strains was carried out using fragment Sanger sequencing of the genome region encoding capsid protein 1 (VP1) and the online resource BLAST.

Results. EVs were found in 5.0 ± 0.3% (1.7–7.8%), both in mono- and mixed infections with other enteric viruses. The long-term dynamics of the frequency of EV detection and the incidence of EV infection in children in the Nizhny Novgorod region was characterized by a sharp decrease in indicators in 2020 against the backdrop of the introduction of anti-epidemic measures. When genotyping 299 strains, 41 types of NPEV of 4 species were identified. The spectrum included the main pathogens of exanthema and neuroinfections and rare types found in "minor" or intestinal forms of infection. During the study period, a redistribution of NPEV species was established. Before the pandemic, the ratio of *Enterovirus A : Enterovirus B : Enterovirus C* species was as follows — 41.0 : 46.7 : 12.3%; during the 2020 pandemic season the ratio was 0.0 : 37.5 : 62.5%; after the lifting of restrictive measures — 47 : 29 : 23%, which may be due to the different effectiveness of the restrictive measures on the mechanisms of transmission of EVs of different types.

Conclusion. The genetic diversity of NPEVs detected in children with AII complements information on the typical composition of the territorial enterovirus population. In children with AII, when the airborne transmission of SARS-CoV-2 was blocked, there was a decrease in the frequency of detection of viruses of the *Enterovirus B* type, the absence of detection of *Enterovirus A* and the constant presence of *Enterovirus C*.

Keywords: *Non-polio enteroviruses, genotyping, AII*

Ethics approval. The protocol of the study was approved by the local Ethics Committee of the Academician I.N. Blokhina Nizhny Novgorod Research Institute of Epidemiology and Microbiology (protocol No. 5, March 24, 2020). Voluntary informed consent was obtained from all patients included in the study or their legal representatives for the use of laboratory test data for scientific purposes.

Acknowledgement. The authors express their gratitude to L.N. Golitsyna for consultative assistance in writing the article.

Funding source. The authors declare that there was no external funding for the study.

Conflict of interest. The authors declare no apparent or potential conflicts of interest related to the publication of this article.

For citation: Selivanova S.G., Zverev V.V., Ponomareva N.V., Leonov A.V., Kashnikov A.Yu., Epifanova N.V., Polyanina A.V., Novikova N.A. Detection and type identification of non-polio enteroviruses in children against the background of acute intestinal infections of various etiologies: 2018–2023. *Journal of microbiology, epidemiology and immunobiology = Zhurnal mikrobiologii, èpidemiologii i immunobiologii.* 2024;101(3):351–361.
DOI: https://doi.org/10.36233/0372-9311-513
EDN: https://www.elibrary.ru/izgdty

Оригинальная статья
https://doi.org/10.36233/0372-9311-513

Обнаружение и типовая идентификация неполиомиелитных энтеровирусов у детей на фоне острых кишечных инфекций различной этиологии: 2018–2023 гг.

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Аннотация

Введение. Энтеровирусы (ЭВ) характеризуются видовым и типовым разнообразием, полиморфизмом клинических проявлений, склонностью к эпидемическому распространению, часто являются причиной вспышек заболеваний, что определяет актуальность мониторинга штаммов ЭВ при разных клинических формах инфекции, в том числе в условиях проведения противоэпидемических мероприятий.

Цель исследования — характеристика распространённости и типового разнообразия неполиомиелитных ЭВ (НПЭВ) у детей с острой кишечной инфекцией (ОКИ) в период 2018–2023 гг., включающий пандемию COVID-19.

Материалы и методы. Методом ОТ-ПЦР исследовано 7302 образца фекалий детей, госпитализированных с диагнозом ОКИ в инфекционный стационар Нижнего Новгорода. Генотипирование штаммов ЭВ проводили методом фрагментного секвенирования по Сэнгеру области генома, кодирующей капсидный белок 1 (VP1), и онлайн-ресурса BLAST.

Результаты. ЭВ обнаружены в 5,0 ± 0,3% (1,7–7,8%) случаев как в моноинфекции, так и в сочетании с вирусами кишечной группы. Многолетняя динамика частоты обнаружения ЭВ и заболеваемости ЭВ-инфекцией детей в Нижегородской области характеризовалась резким снижением показателей в 2020 г. на фоне введения противоэпидемических мероприятий. При генотипировании 299 штаммов идентифицирован 41 тип НПЭВ 4 видов. Спектр включал основных возбудителей экзантемных и нейроинфекций и редкие типы, встречающиеся при «малой» или кишечной формах инфекции. В изучаемый период установлено перераспределение видов НПЭВ. До пандемии соотношение видов *Enterovirus A* : *Enterovirus B* : *Enterovirus C* было следующим — 41,0 : 46,7 : 12,3%; в сезон пандемии 2020 г. — 0,0 : 37,5 : 62,5%; после снятия ограничительных мер — 47 : 29 : 23%, что может быть связано с различной эффективностью влияния ограничительных мероприятий на механизмы передачи ЭВ разных видов.

Заключение. Генетическое разнообразие НПЭВ, выявляемых у детей с ОКИ, дополняет информацию о типовом составе территориальной ЭВ-популяции. У детей с ОКИ в условиях блокировки аспирационного механизма передачи SARS-CoV-2 наблюдалось снижение частоты обнаружения вирусов вида *Enterovirus B,* отсутствие выявления *Enterovirus A* и постоянное присутствие *Enterovirus C.*

Ключевые слова: *неполиомиелитные энтеровирусы, генотипирование, острая кишечная инфекция*

Этическое утверждение. Протокол исследования одобрен Комитетом по этике при Нижегородском научно-исследовательском институте им. академика И.Н. Блохиной (протокол № 5 от 24.03.2020). У всех пациентов, включённых в исследование, или их законных представителей было получено добровольное информированное согласие на использование данных лабораторных анализов в научных целях.

Благодарность. Авторы выражают признательность Л.Н. Голицыной за консультативную помощь при написании статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Для цитирования: Селиванова С.Г., Зверев В.В., Пономарева Н.В., Леонов А.В., Кашников А.Ю., Епифанова Н.В., Полянина А.В., Новикова Н.А. Обнаружение и типовая идентификация неполиомиелитных энтеровирусов у детей на фоне острых кишечных инфекций различной этиологии: 2018–2023 гг. *Журнал микробиологии, эпидемиологии и иммунобиологии.* 2024;101(3):351–361.
DOI: https://doi.org/10.36233/0372-9311-513
EDN: https://www.elibrary.ru/izgdty

Introduction

Enteroviruses (*Picornavirales*: *Picornaviridae*: Enterovirus; EVs) are small in size (30 nm diameter), non-enveloped, icosahedral (pseudo T = 3) capsid (+) RNA-containing viruses. An important role in human infectious pathology is played by non-polio EVs (NPEVs), represented by more than 100 types belonging to 4 species: *Enterovirus A*, *Enterovirus B*, *Enterovirus C*, *Enterovirus D*[1]. In most cases, infection with NPEV is asymptomatic, but these viral agents can also be associated with central nervous system damage, myocarditis, neonatal sepsis, and other serious diseases [1–4]. It is important to note that NPEVs of different species and types can cause the same clinical syndromes, and the intestinal form of EV infection (EVI) can accompany infection with any type of EV [5].

EVs play an important role in the epidemic upsurges and outbreaks that have been reported in many countries. For example, a large-scale outbreak of EV-D68-respiratory disease with neurologic syndrome was recorded in 2014 in the United States and Europe [6, 7]; furthermore, periodic outbreaks of oral and extremity exanthema (EB-A71 infection) in the Asia-Pacific region [8] and serous meningitis (EVM) in Europe, the United States and Russia (CMV3, ESNO30) are also registered [9–11].

The diversity of clinical symptoms of varying severity, the risk of emergence and wide spread of epidemic variants of the virus among the population determine the relevance of worldwide studies aimed at molecular genetic monitoring of circulating EV strains[2] [12]. In Russia, monitoring the circulation of NPEV is an integral part of epidemiologic surveillance of EVI[3], which allows predicting epidemic outbreaks and the formation of foci of infection, and making timely management decisions.

Previously, we have shown the importance of examination of children with acute intestinal infection (AII) for molecular monitoring of EV circulation. Annual detection and a diverse type landscape of NPEVs, including not only *Enterovirus A* and *Enterovirus B* (pathogens of herpangina, exanthema, serous meningitis, etc.), but also latently circulating Enterovirus C NPEVs (mainly minor forms of infection, acute respiratory viral infections, AII), allow us to additionally obtain data expanding information on the specifics of circulation of EVs of different species [13, 14].

In 2019, a disease (COVID-19) caused by a novel coronavirus (SARS-CoV-2) was reported in Wuhan, China, which spread very rapidly around the world. In March 2020, WHO declared a pandemic of the disease and the need to introduce anti-epidemic measures aimed at reducing the activity of spread of the virus transmitted by airborne and household contact[4]. The widespread introduction of the emergency regime has affected the incidence not only of COVID-19, but also of other infectious diseases, mainly viral in nature. For example, in Oslo (Norway) in 2020–2021, the number of hospitalizations of children with acute bronchiolitis, viral pneumonia, gastroenteritis and viral infections of the central nervous system decreased by 90, 89, 74 and 78%, respectively, compared to previous years [15]. Japanese researchers reported that the number of patients with influenza, respiratory syncytial virus, human metapneumovirus and Mycoplasma pneumoniae with respiratory symptoms decreased dramatically by more than 98% during the restrictive measures [16]. Other studies have also reported a decrease in the incidence of various infections of viral etiology in children during the COVID-19 pandemic, including a decrease in the detection rate of enteric viruses (rotaviruses by 87% and noroviruses by 40%) [17].

In Russia during the year 2020, against the background of unprecedented anti-epidemic and preventive measures aimed at combating the COVID-19 pandemic, a significant decrease in the incidence of EVI/EVM was observed. In 2021 and 2022, there was a gradual increase in incidence and the rates returned to the average annual level before the pandemic (2010–2019) [18].

The aim of this study is to characterize the prevalence and type diversity of NPEV in children with AII in the period of 2018–2023, which includes the COVID-19 pandemic.

Materials and methods

In this study, 7302 fecal samples of children aged 0–17 years hospitalized with a diagnosis of AII (A08.4 — viral intestinal infection unspecified, ICD-10) in a pediatric infectious disease hospital in Nizhny Novgorod in 2018-2023 were examined for the presence of EV and viruses — causative agents of acute gastroenteritis (rotaviruses, noroviruses, adenoviruses, astroviruses).

Voluntary informed consent was obtained from all participants or their legal representatives. The study protocol was approved by the local Ethical Committee of the Academician I.N. Blokhina Nizhniy Novgorod Scientific Research Institute of Epidemiology and Microbiology (protocol No. 5 of 24.03.2020).

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[1] Picornaviridae Home Page. URL: https://picornaviridae.com/ensavirinae/enterovirus/enterovirus.htm (date of access: 13.03.2024).

[2] WHO. Enterovirus Surveillance Guidelines — guidelines for enterovirus surveillance in support of the polio eradication. Regional Office for Europe: World Health Organization. 2015. URL: https://iris.who.int/handle/10665/344375 (date of access: 13.03.2024).

[3] "Epidemiological surveillance and prevention of enterovirus (nepolio) infection for 2023-2027" Program. URL: https://fcgie.ru/page,3,koord_tsentr.html (date of access: 13.03.2024).

[4] WHO. Transmission of SARS-CoV-2: implications for infection prevention precautions. URL: https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions (date of access: 13.03.2024).

JOURNAL OF MICROBIOLOGY, EPIDEMIOLOGY AND IMMUNOBIOLOGY. 2024; 101(3)
DOI: https://doi.org/10.36233/0372-9311-513
ORIGINAL RESEARCHES

RNA of entero-, rota-, noro-, astroviruses and DNA of adenoviruses from fecal samples were isolated using the RIBO-prep reagent kit, for reverse transcription we used the REVERTA-L kit (Central Research Institute of Epidemiology). Detection of RNA of EV and enteric viruses was performed using AmpliSens Enterovirus-FL and AmpliSens Viro-Screen-FL test systems (Central Research Institute of Epidemiology) according to the manufacturer's instructions.

Samples containing EV RNA were used to determine the virus type. For the same purpose, 123 EV-containing fecal samples of children with AII provided by the CDC in the Nizhny Novgorod region in 2018–2023 were additionally investigated.

The EV type was determined by partial sequencing of the gene encoding capsid protein 1 (VP1). The 375 bp fragments of the EV genome were amplified according to the recommendations [19]. The nucleotide sequences of cDNA fragments were determined in automatic analyzers GenomeLab™ GeXP (Beckman Coulter) and Nanofor-05 (Institute of Analytical Instrumentation, Russian Academy of Sciences) using DTCS Quick Start Kit (Beckman Coulter) and GenSek (Syntol) reagent kits.

To identify closely related EV strains, the nucleotide sequences of VP1 gene fragments were analyzed using the online resource BLAST[5].

Statistical processing of the results was carried out using the generally accepted method of calculating the mean error (m) and Student's mean and probability (t) using an online calculator[6].

The multi-year dynamics of the incidence of EVI in children under the age of 17 in the Nizhny Novgorod region was analyzed on the basis of official statistics (Form No. 1 of statistical reporting "Information on infectious and parasitic diseases") for the years 2018–2023.

Results

Detection of enteroviruses in children with acute intestinal infection

A total of 7302 children hospitalized with a diagnosis of AII in 2018–2023 were examined for the presence of EV RNA in feces. The detection of EVs was performed as part of the etiologic interpretation of the disease. Enteric viruses (rotaviruses, noroviruses, astroviruses, and group F adenoviruses) and EVs combined were detected in 46.9% of cases (3424/7302), with EVs detected both as mono-infection (2.7%; 195/7302) and in combination with viruses that were pathogens of acute gastroenteritis (2.3%; 169/7302).

EVs were detected in 364 (5.0 ± 0.3%) cases. In different years of the observed period, the frequency of EV detection in children with AII ranged from 1.7-7.8%. In the period before the COVID-19 pandemic, EVs were significantly more frequently detected in 2018 (7.5 ± 0.7%; 120/1607; p = 0.009). Their detection rate decreased in 2019 and reached a minimum in 2020 (1.7 ± 0.3%, 24/1427; p = 0.0000001), when pandemic-related restrictive anti-epidemic measures were implemented. In 2021, after the partial lifting of the lockdown and when the mask regime was relaxed, the rate of EV detection in children with AII increased significantly (4.1 ± 0.5%; 58/1417; p = 0.00004) and peaked in 2022 (7.8 ± 0.9%; 65/832; p = 0.002136). **Fig. 1** shows that the dynamics of the frequency of EV detection until 2023 repeats the dynamics of the incidence of all forms of EVI in children in the Nizhny Novgorod region. Both dynamics have a pronounced decrease in rates in 2020 and an increase in 2021–2022. However, in 2023, the increase in the incidence of EVI continued, and the frequency of EV detection in children with AII significantly decreased (3.7 ± 0.9%; 18/493; p = 0.000001) compared to 2022. Comparison of the incidence rates of EVI and EVM in the analyzed time period revealed that the increase in the incidence rate in 2023 was due to non-meningeal forms of infection (in 2022 — 31.82‰; in 2023 — 42.38‰). The incidence of EVM remained approximately the same (in 2022, 13.52‰; in 2023, 12.42‰).

The monthly frequency of EV detection in different age groups of children with AII in 2018–2022 was analyzed. It was found that in 2018 and 2019 the dynamics of changes in the frequency of EV detection was homogeneous. A similar pattern was observed

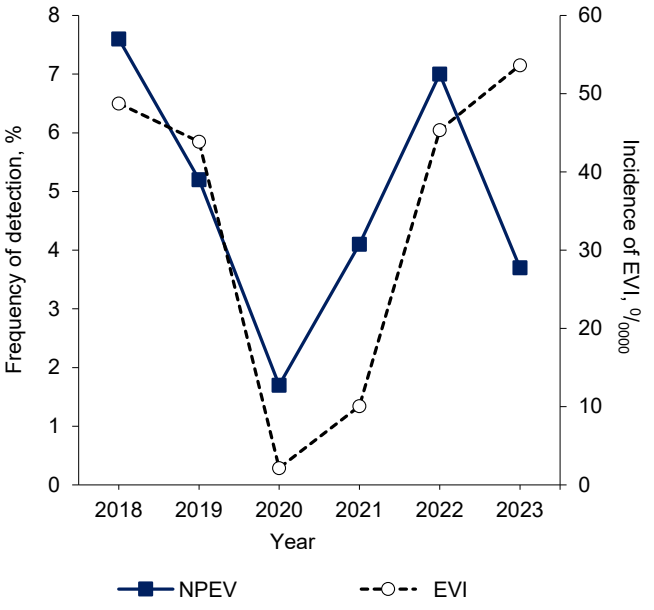

Fig. 1. Dynamics of the frequency of detection of NPEV (%) and incidence of EVI (per 100 thousand children under the age of 17 years) in the Nizhny Novgorod region in the period 2018–2023.

[5] BLAST. URL: https://blast.ncbi.nlm.nih.gov/Blast.cgi (date of access: 13.03.2024).

[6] Medical statistics. URL: https://medstatistic.ru/calculators/averagestudent.html (дата обращения 13.03.2024).

when comparing the seasons of 2021 and 2022, which made it possible to single out the combined seasons of 2018–2019 (pre-pandemic) and 2021–2022 (pandemic, cancellation of the lockdown) for comparison. The analysis showed that before the pandemic, EVs were detected in children with intestinal infection year-round, starting in April and ending in January–February of the following year. Peaks were recorded in May (10.0%; 22/221) and September (15.8%; 38/241). In 2020, EV detection peaked in September (5.7%; 7/123). During the 2021–2022 pandemic season, after phasing out restrictive measures, EVs in children with AII were detected from June through December, with a peak detection rate in July (10.8%; 34/315). In the 2023 season, EVs were more frequently detected in August (8.2%; 6/73) (**Fig. 2**).

Children of all ages are susceptible to NPEV infection. At the same time, the frequency of EV detection in patients with AII differed in different age groups during the study period (**Fig. 3**). Thus, prior to the COVID-19 pandemic, EVs were significantly more frequently detected in children under 3 years of age (7.3 ± 0.6%; 120/1644; $p = 0.006739$), whereas in 2021-2022, EVs were most frequently detected in children aged 3-7 years (6.8 ± 0.9%; 53/778; $p = 0.044991$) compared to children older than 7 years. In 2020 and 2023, against a background of low detection rates of EVs in children with AII, no significant group differences were found, with no EVs detected in children over 7 years of age in the 2023 season, despite the fact that the number of children aged 7-17 years examined in 2022 and 2023 differed little (169 and 118, respectively).

It was of scientific and practical interest to study the peculiarities of the type composition of EVs found in children with AII before the COVID-19 pandemic, during the pandemic and after its end.

Analysis of the diversity of NPEV types in children with AII

In order to study the diversity of EV types detected in hospitalized children diagnosed with AII, 299 typed strains were analyzed. All strains were identified as NPEVs.

A total of 41 types of NPEV identified in 2018-2023 were defined. **Fig. 4,** *a* shows that a number of NPEV types were identified in a single or small number of cases ($n = 64$: KA3, KA7, KA8, EV-A76, EV-A90, KV1, KV2, KV3, KV4, E1, E2, E3, E6, E7, E13, E14, E18, E21, E24, E25, KA19, KA20, KA21, KA24, EV-C99, EV-C116, EV-D68), while other types were detected relatively frequently ($n = 135$: KA2, KA5, KA10, EVA71, KA9, KV5, E9, E11, E30, KA22), 4 viruses were prevalent ($n = 100$: KA4, KA6, KA16, KA1). The detected viruses belonged to 4 species: *Enterovirus A* (44.5%; 133/299), *Enterovirus B* (35.1%; 105/299); *Enterovirus C* (20.1%; 60/299); *Enterovirus D* (0.3%; 1/299).

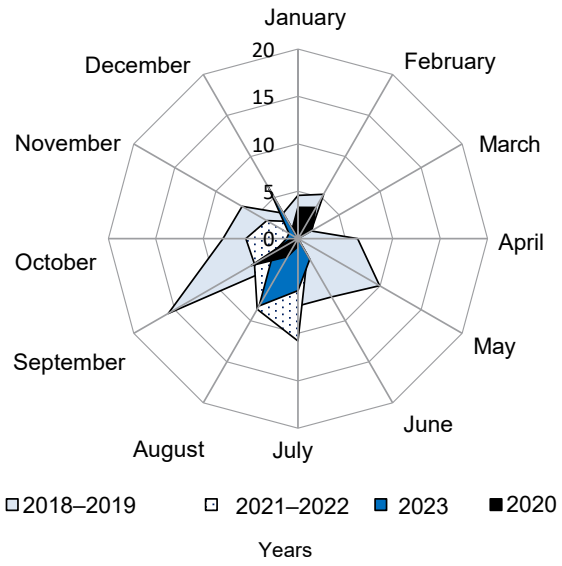

Fig. 2. Monthly frequency of detection of NPEV in children with AII during the period before the COVID-19 pandemic and after the lifting of the lockdown, %.

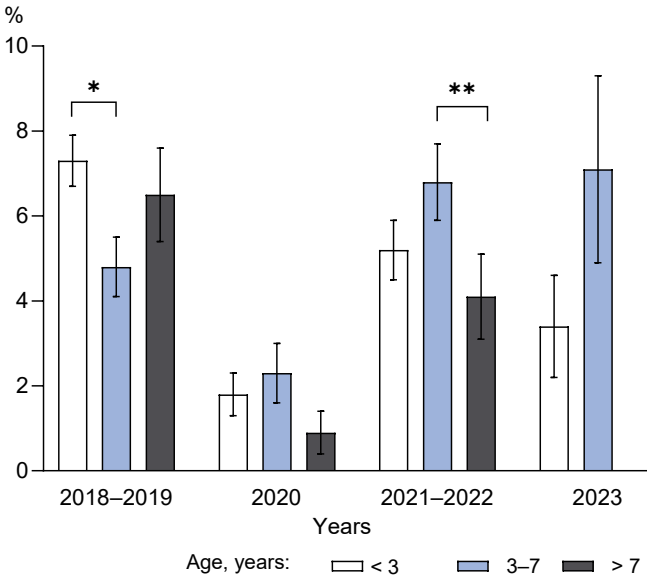

Fig. 3. Frequency of detection of EVs in different age groups of children with AII in the periods before the pandemic, during and after the COVID-19 pandemic.
*$p = 0.006739$; **$p = 0.044991$.

Twelve types of *Enterovirus A* species were identified among the NPEVs, with KA4 (18.8%; 25/133), KA6 (14.3%; 19/133), and KA16 (15%; 20/133) viruses being detected more frequently. *Enterovirus B* species included 20 types of NPEVs, dominated by viruses KA9 (11.4%; 12/105), KV5 (15.2%; 16/105), E11 (14.3%; 15/105), and E30 (13.3%; 14/105). Eight types of *Enterovirus C* NPEVs were identified, with KA1 virus being the most frequently detected (60%; 36/60). RNA of EV-D68 was detected in feces in one case.

The spectrum of NPEV types in different seasons of the study period was analyzed (Fig. 4, *b*). Thus,

before the COVID-19 pandemic, *Enterovirus A* was dominated by EV-A71 (13.3%; 14/105), which was subsequently undetected, and was replaced by virus KA16 (13.6%; 18/132). In 2023, KA4 (16.7%; 9/54) and KA10 (20.4%; 11/54) viruses were dominant. KA2, KA5 and KA6 viruses were detected relatively frequently. It is indicative that in 2020, in the conditions of strict anti-epidemic measures, representatives of *Enterovirus A* were not identified.

In 2018–2019, among *Enterovirus B*, KV5 (10.5%; 11/105), E30 (9.5%; 10/105) and E9 (5.7%; 6/105) viruses were detected more frequently than others; in the 2020 season, E9, E14 and E24 viruses were detected in single cases, whereas after the partial lifting of restrictive measures, KA9 (6.8%; 9/132) and E11 (10.6%; 14/132) viruses were detected. In 2023, KV5 virus (9.3%; 5/54) resumed circulation and E30 virus (5.6%; 3/54) was detected, while other EVM pathogens (E6 and E11 viruses) were not detected in the feces of children with AII.

Among *Enterovirus C* EVs, KA1 virus dominated both before the pandemic and during the pandemic (during the restrictive measures and after the lockdown was lifted). It is worth noting that in 2021–2022, its share in the type structure of NPEVs detected in children with AII amounted to 16% (21/132).

We analyzed the distribution of NPEV types in different seasons of the study period. **Fig. 5** shows that before the COVID-19 pandemic, *Enterovirus A* (41.0 ± 4.8%; 43/105) and *Enterovirus B* (46.7 ± 4.9%; 49/105) were detected in approximately equal proportions and statistically significantly predominated over *Enterovi-*

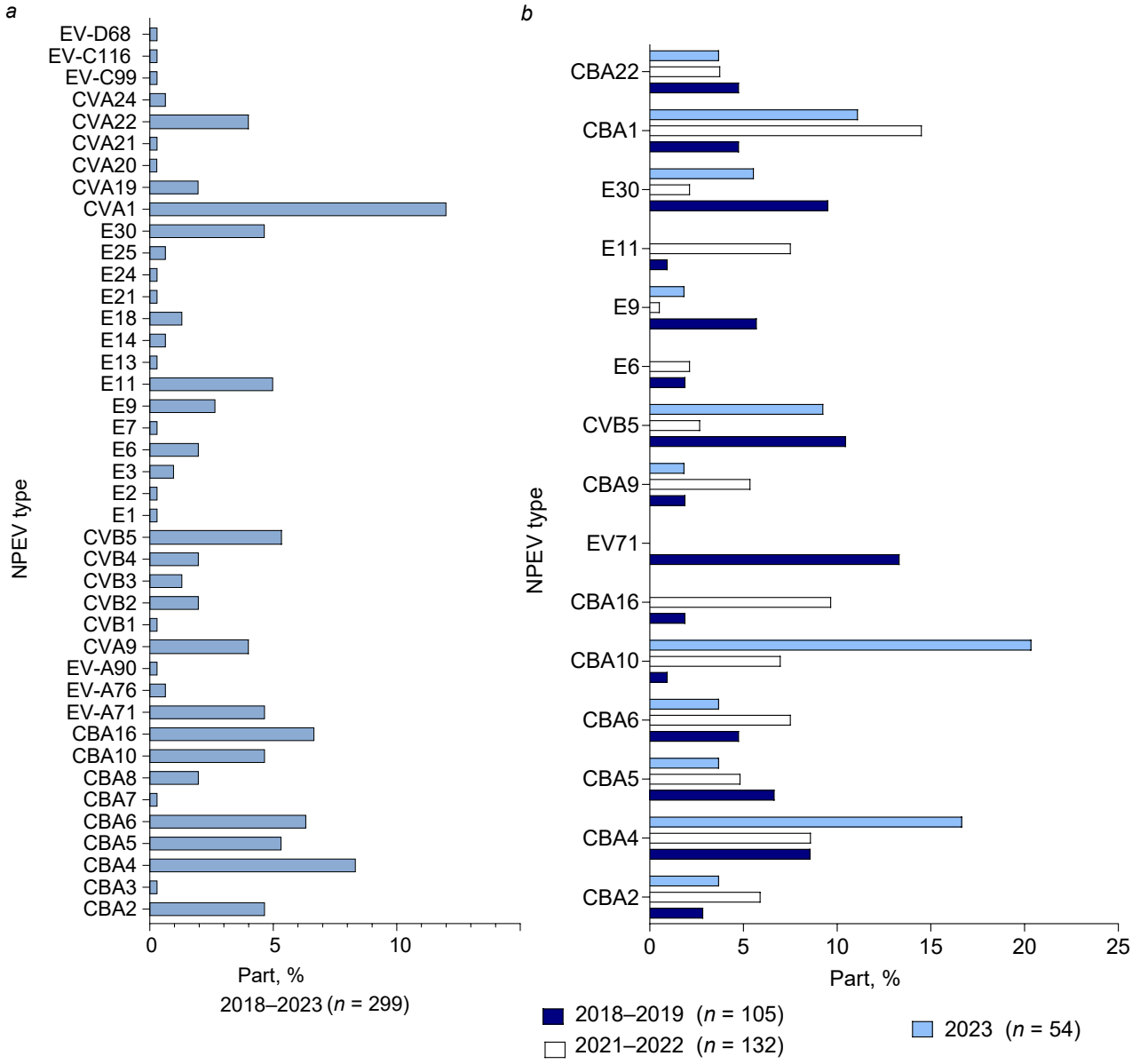

Fig. 4. Diversity of NPEV types identified in children with AII in 2018–2023 (*a*), before the pandemic (2018–2019), during the pandemic (2021–2022) and after its end (2023) (*b*).

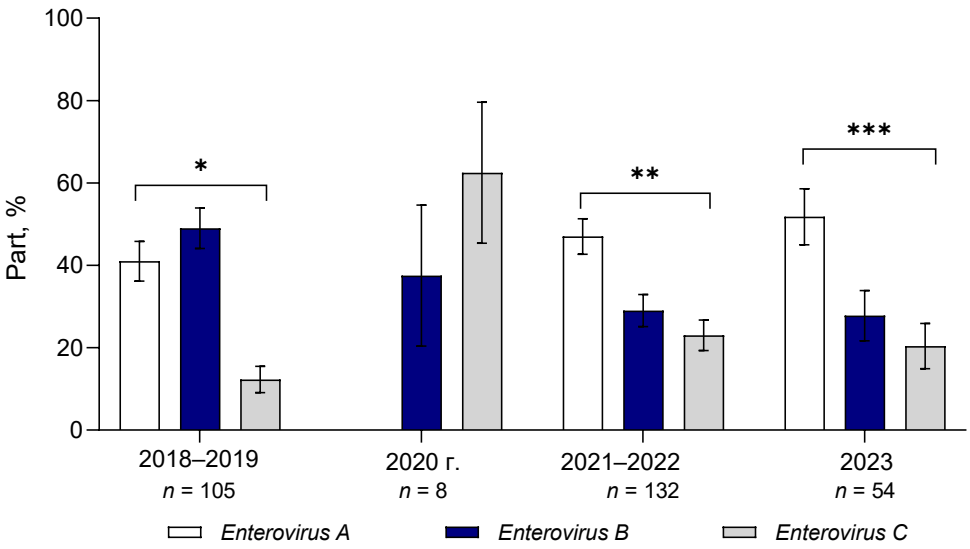

Fig. 5. Species distribution of NPEV isolated from children with AII in 2018–2023.
*p = 0.000001; **$p \leq 0.002142$; ***$p \leq 0.009897$.

rus C (12.3 ± 3.2%; 13/105; $p = 0.000001$), while after the lockdown was lifted (2021–2022), *Enterovirus A* (47.0 ± 4.3%; 62/132; $p \leq 0.002142$) was more frequently detected. During the period of the severe restrictive measures due the pandemic (2020), no EVs of *Enterovirus A* species were detected, and the major proportion among identified NPEVs belonged to *Enterovirus C* species (62.5 ± 17.1%; 5/8). In 2023, the distribution of NPEV species did not differ significantly from that in 2021–2022 and was characterized by a significant predominance of *Enterovirus A.*

Thus, during the period under study, children with AII showed a change in the frequency of detection of different types of NPEVs due to the change of the dominant type: before the pandemic — *Enterovirus B* (46.7%), *Enterovirus A* (41.0%), *Enterovirus C* (12.3%); during the pandemic season, during the period of strict restrictions (2020), *Enterovirus C* (62.5%) and *Enterovirus B* (37.5%) were detected; after the lockdown was lifted, *Enterovirus A* (47.0%), *Enterovirus B* (28.8%), *Enterovirus C* (23.5%), *Enterovirus D* (0.7%); in 2023, *Enterovirus A* (51.8%), *Enterovirus B* (27.8%), and *Enterovirus C* (20.4%) were detected.

Discussion

Many types of EVs are prone to epidemic spread, which determines the need to monitor their circulation. For this purpose, detection and type identification of NPEVs are performed in patients with different clinical presentation of the disease. In the present study, detection and type identification of EVs were performed in children hospitalized with AII in one of the infectious diseases hospitals of Nizhny Novgorod, as part of the etiological deciphering of the disease during the period including the time of the COVID-19 pandemic.

In 2018–2023, EVs both in mono-infection and in combination with other enteric viruses were detected in an average of 5.0% of cases. At the same time, before the pandemic (2018–2019), the frequency of EV detection was 6.4%, which is comparable to the data for 2006–2011, when in children hospitalized with AII in the same infectious disease hospital in Nizhny Novgorod, NPEVs were detected in 7.6 ± 0.3% of cases [14]. According to the data of foreign authors, EVs in children with AII before the COVID-19 pandemic were detected in the range of 3.3–11.0% [20–22].

The analysis of the incidence of all forms of EVI in the Nizhny Novgorod region and the frequency of EV detection in children diagnosed with AII showed that in 2018–2022 the dynamics of the frequency of EV detection repeated the dynamics of EVI incidence, and in 2020 in both cases a sharp decline in the studied indicators was observed. The incidence of EVI in children under 17 years of age in the Nizhny Novgorod region decreased by 22.7 times (according to official statistics), the frequency of EV detection — by 4.5 times. In 2020, in connection with the COVID-19 pandemic, anti-epidemic measures (mask regime, ban on mass events, self-isolation regime, quarantine, hygiene awareness, movement restrictions) were introduced in the Nizhny Novgorod region, as well as in the country as a whole, aimed at preventing the spread of SARS-CoV-2 due to the airborne transmission. At this time, the incidence of EVI in children under 17 years of age in the Nizhny Novgorod region decreased to 2.16 per 100,000, and the frequency of NPEV detection in children with AII reached a minimum (1.7%). These data indicate an effect of restrictive anti-epidemic measures on the activity of EV circulation, which can be transmitted via different mechanisms and routes, and, accordingly, the impact on the EVI incidence.

DOI: https://doi.org/10.36233/0372-9311-513

In 2021–2022, against the background of a marked increase in the incidence of all forms of EVI, the frequency of EV detection in children with AII increased, averaging 5.5% (4.1–7.8%). The gradual increase in the detection rate correlates with the results of a study conducted in the Republic of Belarus in 2020–2022, where NPEVs in children with AII were identified in a total of 3% of cases, and the annual detection rate also tended to increase (1.1–3.7%) [23]. However, after the pandemic in 2023, against the background of an increase in the incidence of all forms of EVI, the frequency of EV detection in children with the symptoms of AII significantly decreased by 2.1 times (7.8-3.7%).

EVs were detected in fecal samples during the seasonal summer-autumn rise in the incidence of EVI in all age groups of children hospitalized with AII. However, the peak months and the dominant age group of their detection varied in different years of the study period. Before the pandemic, the highest EV detection rates were recorded in May and September, predominantly in the age group of children under 3 years of age, while after the cancellation of the lockdown — in July, in the age group of 3–7 years (organized preschool children). It is noteworthy that in 2023 there were no cases of EV detection in children with AII in the age group older than 7 years, which is characterized by a high incidence of EV causing neurological forms of infection (KV5, E6, E30) [24]. The decrease in the frequency of EV detection in children hospitalized with AII in 2023 and the absence of cases of their detection in the age group older than 7 years may be associated, among other things, with the emergence in the general EV population of new epidemically significant EV variants causing specific clinical forms of EVI.

During 2018–2023, we identified 41 types of NPEV in children with a clinic of AII. The spectrum of EB types included widespread pathogens of exanthemal forms of infection and neuroinfections (in 2018 — KV5, E9, E30, EV-A71; in 2019 — KA6, KA4, EV-A71, E6; in 2021 — KA6, KA9, E11; in 2022 — KA6, KA5, KA16, KA9, E11; in 2023 — KA6, KA10, E30), which reflects the type composition of the Nizhny Novgorod EV population. Thus, in the Volga Federal District, including the Nizhny Novgorod region, during the pre-pandemic period, viruses E6, E30, KA6, EV-A71 circulated widely [25]; in 2021, KA6 was dominant, KA10 and KA9 were identified[7].

In addition to EVs, which are the etiologic cause of various symptomatic diseases, the types found, as a rule, in minor or intestinal forms of infection (KA3, E1, E2, E3, KA20, KA21, KA22, KA24, EV-C116) and types rarely detected in Russia (EV-A76, EV-A90, EV-C99) were identified in children with AII. The identification of rarely occurring types of NPEV in fecal samples of children with intestinal infection has completed the characterization of the type composition of the EV population in Nizhny Novgorod. The importance of screening of children with AII to detect rare types of NPEVs is also indicated by the results of a study conducted in Mozambique in 2014–2018 [26].

EVs detected in children with AII were of 4 types: *Enterovirus A* (44.5%), *Enterovirus B* (35.1%), *Enterovirus C* (20.1%), *Enterovirus D* (0.3%). Meanwhile, 27 types were identified before the COVID-19 pandemic, 5 types were identified during the 2020 pandemic, 24 after the lifting of restrictive measures during the pandemic, and 20 after the pandemic. The number of NPEV types detected in children with diarrheal disease at different time periods in different territories can vary considerably. In our previous study, 22 types of *Enterovirus A* (38.6%), *Enterovirus B* (38.6%), and *Enterovirus C* (20.8%) were identified during the typing of EVs detected in children with AII in 2006–2011 [14]. According to the data of foreign authors, in children examined in cases of AII, *Enterovirus B* and *Enterovirus C* types of NPEVs were detected more often. Thus, in India, 23 types of EVs, mainly of *Enterovirus B* species (73.68%; 28/38), were identified during the examination of 305 children with AII in 2011–2012 [27]. In Northern Brazil, in 2010–2011, 19 types of EV were identified in 175 children with symptoms of acute gastroenteritis, with 11 types (61.1%; 22/36) belonging to the *Enterovirus B* species [28]. In contrast, in North America in 2012, only 8 types of *Enterovirus A* and *Enterovirus B* were identified in children with acute gastroenteritis, and *Enterovirus C* was not detected in children with AII [21].

Analysis of the relative species distribution of NPEVs identified in children with AII in 2018–2023 showed that the ratio of EV species changed over time. For example, prior to the COVID-19 pandemic, *Enterovirus A* and *Enterovirus B* species EVs were predominantly identified, in approximately equal proportions. During the pandemic (2020), during the period of strict restrictive anti-epidemic measures, *Enterovirus C* EVs were predominantly identified (Coxsackie A1 predominated), *Enterovirus B* in isolated cases, and none of the *Enterovirus A* types were identified. The latter resumed their circulation after the relaxation of restrictive measures and the end of the pandemic and dominated the spectrum of viruses detected. A significant decrease in the incidence of oral and extremity exanthema and herpangina, the main pathogens of which are EV-A71 and CA16, during the pandemic was observed in studies conducted in China [29, 30], which, according to the authors, indicates the prevention of EV transmission by aspiration and contact mechanisms due to the application of anti-epidemic measures. Our study shows differences in the effectiveness of restrictive measures aimed at blocking the airborne transmission of SARS-CoV-2 on the frequency of detection of different types of

[7] Informative electronic bulletin. 2022. № 9. С 3–16. URL: https://nniiem.ru/file/publicat/2022/nniiem-inf-byulleten-evi-za-2021-n9.pdf (date of access: 27.02.2024).

EVs in children with acute respiratory tract infections, which, most likely, is a consequence of their realization of different transmission mechanisms.

Conclusion

The data of 6-year monitoring of NPEVs in children with AII demonstrate their genetic diversity, represented by at least 41 virus types of *Enterovirus A–D* species. The spectrum of types includes the main causative agents of serous meningitis, oral and extremity exanthema, herpangina, exanthema, myocarditis and rare types occurring in minor or intestinal forms of infection, which complements the characterization of the territorial EV-population.

The results of the study demonstrate a pronounced effect of the influence of the complex of anti-epidemic measures carried out during the COVID-19 pandemic on the incidence of EVI and the activity of circulation of NPEV of different types. In children with AII under the conditions of blocking the aspiration mechanism of SARS-CoV-2 transmission, there was a decrease in the frequency of detection of *Enterovirus B*, absence of *Enterovirus A* and constant presence of *Enterovirus C* in feces.

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The article was submitted 19.03.2024;
accepted for publication 22.05.2024;
published 29.06.2024

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Статья поступила в редакцию 19.03.2024;
принята к публикации 22.05.2024;
опубликована 20.06.2024