Characterisation of frequency of norovirus infection among hospitalised patients of Children's clinical university hospital in 2021

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Abstract. *Objective*. To characterize the frequency of norovirus infection depending on where infection was acquired, age, sex, department profile, presence of other pathogens and socio-demographic factors among hospitalized patients of "Children's Clinical University Hospital" in 2021.Materials and Methods. Data was taken from the Children's Clinical University Hospital internal information system *Andromeda* and the laboratory information system *DIALAB* about hospitalized patients in 2021 with a diagnosis of acute gastroenteropathy caused by norovirus (A08.1). A total number of included cases in the data analysis were 266 children aged 17 years and younger. For statistical data analysis descriptive statistical methods and single-factor, multi-factor binary logistic regression was used. *Results.* The incidence of healthcare-associated norovirus infection (NoV-HAI) was 4.14 cases per 1000 hospitalized children per year. There were no statistically significant differences between socio-demographic factors, the presence of other pathogens and place where infection was acquired. The chances of becoming infected with NoV in the hospital`s therapeutic profile departments were 3.99 (CI 2.07-7.69) times higher than in the departments of infectious diseases. Children with chronic illnesses and norovirus (NoV) infection were only in the NoV-HAI group (n = 10). In the NoV group acquired in the society, children were 5.24 times more likely (CI 2.71-10.13) to suffer from dehydration than in the NoV-HAI group. *Conclusions*. The chances of hospitalized children to obtain NoV-HAI are related to compliance with infection control measures in departments of different profiles, not to the child's socio-demographic factors.

Key words: norovirus, children's hospital, healthcare associated norovirus infection.

1 Introduction

Norovirus or Norwalk virus (NoV) infection is the main cause of viral acute gastroenteritis (GE) worldwide and is an important cause of hospitalization in children under five years

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old. The virus causes widespread outbreaks in health care facilities, placing a burden on both the hospital and the health care system [1-5].

The infection is characterized by sudden, watery diarrhoea (lasting more than 12 hours) and vomiting, with or without fever, abdominal pain, and nausea. The incubation period of the disease can be from 10 hours to four days, but most often symptoms appear 24 to 48 hours after infection. Spontaneous vomiting is the most characteristic primary symptom in children with NoV [6-9]. The listed symptoms increase the body's fluid release - this can lead to severe dehydration, which is dangerous for infants, young children, and people with weakened immunity [3, 9], as it can result in seizures. Children with compromised immune systems or chronic diseases may have a more severe disease course and longer duration of treatment [5, 6].

NoV is resistant to the effects of the external environment, so it can survive on various surfaces for a long time. In addition, new strains of NoV develop every two to three years, causing outbreaks. The virus is transmitted mainly through contact. The most common way is through direct contact from an infected person to another person, but it is also possible to get infected through contaminated objects or surfaces, as well as food and water. The course of NoV disease and virus shedding in immune-compromised patients is longer than in other patients [3, 5, 8-9].

In Europe, there are 0.5 to two episodes of diarrhoea per child under the age of five each year. The most common cause of acute GE was rotavirus, but with increased coverage of the rotavirus vaccine in recent years, NoV has become the leading cause of hospitalization for acute GE. According to research data, it is estimated that in the countries of the European Union (EU) all children under the age of five have experienced at least one episode of NoV infection and every seventh has needed a doctor's consultation, while every 98th child has been treated in a hospital. It should be emphasized that there is currently no NoV vaccine available [2, 6].

In Latvia, the diagnosis of the international statistical classification of diseases and health problems, 10th edition (SSK-10) - acute gastroenteropathy (GE) proposed by NoV (A08.1) is subject to the registration of infectious diseases [10]. Statistical data show that starting from 2019, the number of intestinal infections caused by NoV (1263 cases) in children aged zero to 17 years exceeds the number of intestinal infections caused by rotavirus (1046 cases). With the start of the Covid-19 pandemic in 2020, the number of infections in children decreased significantly, but the number of intestinal infections caused by NoV (175 cases) continued to exceed the number of intestinal infections caused by rotavirus (165 cases) [11-12]. In the study conducted by the EU, NoV is the second most frequent cause of outbreaks of contaminated food in 2019 - 8.8% (n = 457). Of all NoV infectious disease cases, 2.5% (n = 279) were hospitalized [13]. This shows that the number of NoV infectious disease cases and outbreaks in Europe is relatively high.

A healthcare-associated infection (HAI) is defined if the symptoms of the disease appear at least 48 hours after hospitalization and if there was no incubation period of the infection during that time. Or, during re-hospitalization, the patient is diagnosed with an infection, if no more than 48 hours have passed since the previous acute care in the hospital. The definition of a case of healthcare-associated norovirus infection (NoV-HAI) states that the patient has the following clinical symptoms: watery diarrhoea (more than 12 hours) with vomiting and/or fever (at least 38.0 C) without known cause and with at least two of the following symptoms – abdominal pain, fever, and headache. As well, there is a laboratory confirmation of NoV antigen in the analysis sample [1, 3, 5, 14].

Worldwide, the most common causes of HAI in paediatrics are rotavirus and norovirus. NoV-HAI increases patient suffering, length of hospital stays, hospital costs, the possibility of re-hospitalization, as well as the need to introduce patient isolation measures and prolong the sick leave for the patient's parents [3-4]. The risk of infection is related to age – as the

child's age increases, the risk decreases. In the first year of life, the risk of NoV-HAI is 26-48% higher than in older children. A second risk of NoV-HAI is related to length of hospital stay – the risk increases significantly if the length of hospital stay exceeds six days [6].

Currently, there are no public health guidelines in force, but it is possible to familiarize yourself with the draft guidelines "Public Health Guidelines for 2021-2027". Admittedly, it emphasizes other infectious diseases, but it is recognized that the number of outbreaks of acute intestinal infections in collectives, especially those related to the catering industry, has increased in recent years. It is noted that society lacks proper hand hygiene skills and understanding of its necessity. The main goals of the draft guidelines are to reduce the risks of the spread of infections and improve epidemiological surveillance [15].

In EU countries, the burden of NoV on health care has been little studied, possibly because NoV-HAI is specific to departments with a paediatric profile. European data show that 10% of all paediatric HAIs are directly caused by viruses in GE, but in adults by *Clostridium difficile* [16], therefore more research is investigating HAIs directly related to this bacterium. More research on NoV infection and its effects is needed to improve the vaccine development and research process.

The study found out in which sections of the profile NoV-HAI is more common, how often the presence of other pathogens is also detected, as well as the socio-demographic factors that influence them. The study obtained information on the frequency of NoV-HAI and community-acquired NoV infection, which allowed conclusions and recommendations to be made, which patient groups are most exposed to this infection and which profile departments should focus on improving infection control. The study data provided additional information that may be useful for defining new hypotheses and for further research to reduce the prevalence of NoV-HAI. The results made it possible to target groups of patients who need new interventions to improve personal hygiene.

Study objective was to characterize the frequency of NoV infection depending on where infection was acquired, age, sex, department profile, presence of other pathogens and socio-demographic factors among hospitalized patients of "Children's Clinical University Hospital" in 2021. Study hypotheses – 1) Socio-demographic factors of hospital-acquired and community-acquired NoV infections do not differ; 2) Children with chronic diseases more frequently have NoV-HAI; 3) The risk of NoV-HAI varies between departments.

2 Material and methods

The study used structured data without personal identification (anonymous) available in the internal information system of "Children's Clinical University Hospital" *Andromeda*, manually retrieved data from unstructured fields of the electronic medical history of patients, as well as data from the laboratory information system *DIALAB*, integrated into the system, about laboratory examinations. The following available data were used: date of hospitalization, diagnosis, department/s where the patient was treated, age of the patient, gender, residence, educational institution, date of discharge from the hospital, and date of sampling selected by NoV antigen - positive, rotavirus and adenovirus antigen (positive/negative). The researchers marked also the date of specimen collection, culture for *Shigella*, *Salmonella*, *Campylobacter jejuni*, *Yersinia enterocolitica* (positive/negative) and medical history, and/or daily physician records with information about the symptoms of the disease and the date of their appearance.

Participants with the following criteria were included in the study – 1) Children aged from their first birthday to 17 years (inclusive) who have been treated at the Children's Clinical University Hospital in 2021 with laboratory-confirmation of NoV. 2) With at least one of the following clinical symptoms: watery diarrhoea (lasting more than 12 hours),

vomiting, fever (at least 38.0 C) without known cause, or with at least two of the following clinical symptoms: abdominal pain, fever (at least 38.0 C), headache, nausea.

2.1 Definitions

NoV-HAI was defined if the hospitalized patient had norovirus GE symptoms, at least 48 hours after admission to the hospital and no incubation period of the disease was described in the anamnesis and laboratory confirmed NoV (analysis in the sample taken at least 48 hours after the patient's admission to the hospital). Also, if the patient repeatedly, less than 48 hours after the previous discharge from the hospital, had referred to the hospital with signs of GE caused by NoV and laboratory confirmed NoV in the analysis sample.

Community-acquired NoV infection was defined if the hospitalized patient had norovirus GE symptoms in the hospital, at the time of admission, or the history data described the incubation period of the infection at the time of admission and laboratory-confirmed NoV analysis in the specimen.

2.2 Database preparation

Structured patient data was extracted with the business intelligence tool *Qlik*, which was further exported to Microsoft Office Excel. Missing data fields were filled in manually using electronic patient records in *Andromeda* and *DIALAB*. After sampling and symptom onset dates, it was determined whether NoV infection was community acquired or NoV-HAIand was noted in a separate field.

Hospitalization and discharge diagnoses were divided into four groups based on SSK-10 diagnosis codes – acute gastroenteropathy caused by norovirus (A08.1); other infectious diseases, non-infectious diseases and congenital malformations, deformities, and chromosomal abnormalities (Q00-Q99) [17]. Hospital wards were grouped into three profiles - therapeutic profile departments, infectious disease profile departments and departments of other profiles. The presence of other pathogens, mainly considering the sample size, was examined - NoV and other pathogens, NoV only. Signs of dehydration were defined when the patient had at least one of the following symptoms – lethargy, drowsiness, convulsions, acute urination.

Socio-demographic characteristics were divided into gender groups (male, female), four age groups: newborns and infants (up to the first year of life), early preschool children (from one to three years), late preschool children (from four to six years) and school-aged children (from seven to 17 years, inclusive). The educational institution was separated into two groups: attending or not attending, excluding children younger than two years of age from the analysis.

2.3 Data processing methods

Descriptive statistical methods were used in the data analysis - cross-tabulation method, frequency analysis, absolute and relative frequencies, univariate and multivariate models of binary logistic regression were calculated. In all calculations, the determined confidence interval (hereinafter - CI) is 95%, the level of significance (hereinafter - p) is 0.05. It is assumed that if the *p*-value is less than 0.05, then obtained result is statistically significant, if it is higher, then obtained result is not statistically significant. Data statistical processing was performed with the computer program IBM SPSS Statistic 27.0 for Windows. Microsoft Office Excel was used to represent the results graphically.

3 Results

In total, 266 children aged zero to 17 years (inclusive) were hospitalized with laboratory confirmed NoV infectious disease in 2021 at "Children's Clinical University Hospital". Of all hospitalized children, 56.8% (*n* = 151; CI 0.51-0.63) were men and 43.2% (*n* = 115; CI 0.37-0.49) were women. Describing the frequency in each age group, the results show that the largest proportion of cases in the group of early preschool children, respectively, 65.8% (*n* = 175; CI 0.60-0.71) (see Fig. 1).

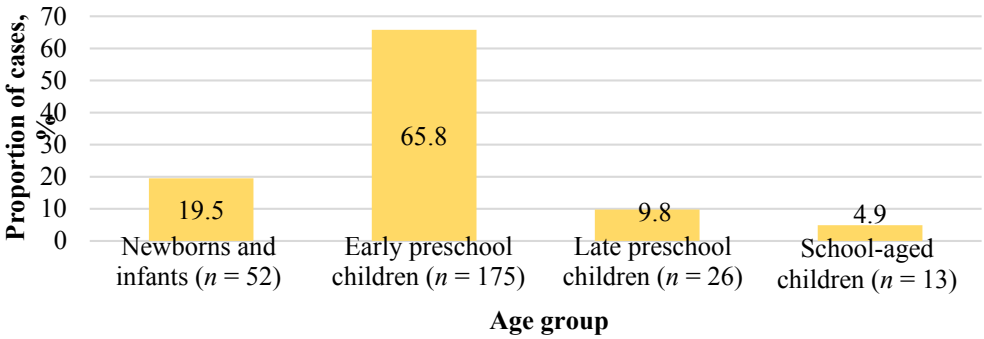

Figure 1. Distribution of hospitalized patients with acute gastroenteritis caused by norovirus (*n* = 266) in age groups, Children's Clinical University Hospital in 2021.

Looking at the place of residence of hospitalized children, 51.5% (*n* = 137; CI 0.46-0.57) live in Riga, 29.7% (*n* = 79; CI 0.25-0.35) live in Pieriga region, but in other regions living 18.8% (*n* = 50; CI 0.15-0.24). When describing attendance of an educational institution, there were a total of 124 children aged two to 17 years, of whom 83.1% (*n* = 103; CI 0.75-0.89) attended an educational institution and 16.9% (*n* = 21; CI 0.11-0.25) did not attend.

68.0% (*n* = 181; CI 0.62-0.73) of children were hospitalized with community-acquired NoV infection, while NoV-HAI was detected in 32.0% (*n* = 85; CI 0.27-0.38) or NoV-HAI associated with existing hospitalization was 25.9% (*n* = 69; CI 0.72-0.88) of cases, but with re-hospitalization in 6.0% (*n* = 16; CI 0.12-0, 28).

The total number of hospitalized patients was 20,696 children. The cumulative incidence (IC) of NoV, regardless of the site of infection, was 12.85 cases per 1000 hospitalized children per year. The highest incidence was reached in the month of December with 37.72 cases per 1000 hospitalized patients per year. Calculating the incidence by site of infection, the cumulative incidence of community-acquired NoV in 2021 was 8.75 cases per 1000 hospitalized children. When calculating the incidence of NoV-HAI in the total number of hospitalized patients, 181 cases were not considered, who were no longer exposed to the risk of NoV infection, respectively the incidence was calculated against 20515 hospitalized children. Obtaining that NoV-HAI incidence was 4.14 cases per 1000 hospitalized children per year. Looking at the frequency of NoV infection in age groups, the highest incidence was calculated for children of early age, namely 43.98 cases per 1000 hospitalized children per year. It is followed by newborns and infants with 20.74 cases, late preschool children with 6.96 cases and school-aged children with 1.24 cases per 1000 hospitalized children per year.

Dehydration signs were found in 38.0% (*n* = 101; CI 0.32-0.44). The proportion of dehydration signs was significantly higher in the community-acquired NoV group, reaching almost 50% (48.6%; *n* = 88; CI 0 .38-0.52).

In both groups, the proportion of age distribution is similar, but it should be emphasized that the infection was more often observed in children of early preschool age - in the community-acquired infection group 66.3% (n = 120; CI: 0.59-0.73) of cases and in the NoV-HAI group 64 .7% (n = 55; CI: 0.54-0.74) of cases. No statistically significant differences were found between socio-demographic groups and site of infection ($p > 0.05$). Of all children hospitalized with NoV-induced GE, only positive NoV antigen in feces was detected in 91.4% (n = 243; CI 0.87-0.94) of cases, and simultaneous positive NoV antigen and another pathogen in 8.6 % (n = 23; CI 0.06-0.13) of cases.

In total, 71.0% (n = 189; CI 0.65-0.76) were treated in the infectious diseases profile, 19.5% (n = 52; CI 0.15-0.25) in therapeutic profile departments, 9 in other profile departments .4% (n = 25; CI 0.06-0.14). On univariate binary logistic regression analysis, the odds of being infected with NoV in hospital therapeutic profile wards are four times higher than in infectious disease wards (OR = 4.11; CI: 2.14-7.88, $p < 0.001$). The results of multivariate logistic regression analysis show that the odds did not change significantly and remained statistically significant (s2OR = 3.99; CI: 2.07-7.69, $p < 0.001$). Although the chances of obtaining NoV-HAI are much higher in the profile of other departments (OR = 30.13; CI 8.56-106.06; $p < 0.001$), but the CI is too wide to draw correct conclusions (see Table 1).

Table 1. Odds of hospital-acquired norovirus in relation to sociodemographic factors and hospital wards.

	OR (95% CI)	s^2OR (95% CI)
Gender		
Male	0.74 (0.44-1.25)	0.69 (0.38-1.26)
Female (ref.)	--	--
Age group		
Newborns and infants	0.85 (0.24-2.97)	0.55 (0.14-2.15)
Early preschool children	0.73 (0.23-2.34)	0.67 (0.20-2.26)
Late preschool children	0.59 (0.14-2.42)	0.67 (0.15-3.03)
School-aged children (ref.)	--	--
Place of residence		
Pieriga region	0.87 (0.46-1.59)	0.86 (0.43-1.70)
Other region	1.19 (0.60-2.35)	0.87 (0.39-196)
Riga (ref.)	--	--
Hospital wards		
Therapeutic	**4.11** (2.14-7.88)***	**3.99** (2.07-7.69)***
Other	**30.13** (8.56-106.06)***	**33.81** (9.29-123.03)***
Infectious disease (ref.)	--	--

Odds ratios (OR – unproportioned; s2OR – prorated by the second model) with 95% CI characterize NoV-HAI cases relative to community-acquired NoV infection. No statistically significant difference at $p > 0.05$. Statistically significant differences where the 95% CI does not include the number 1.00 and $p < 0.05$ (*), $p < 0.01$ (**), $p < 0.001$(***).

Looking at the association of groups of hospitalization diagnoses with the site of infection, statistically significant differences were observed (x2 = 68.64; df = 3; $p < 0.001$). In the NoV-HAI group, the most frequent hospitalization diagnosis was other non-infectious diseases – 55.3% (n = 47; CI: 0.45-0.65). It should be emphasized that in the diagnosis group - with congenital deformities, deformations, and chromosomal anomalies (Q00 - Q99) all 10 cases were in the NoV-HAI group.

4 Discussion

Analyzing the proportion of children by age group, the largest proportion of hospitalized patients (65.8%) was for children of early preschool age. The incidence in this age group was 45.98 cases per 1000 hospitalized children per year. The second most frequently hospitalized age group was newborns and infants (19.5%), in which the incidence was 20.74 cases per 1000 hospitalized children per year. Compared to other studies, the results obtained are similar, emphasizing that the risk group for NoV-induced GE is children under five years of age [6, 18, 19]. Although a study in Israel emphasizes that NoV is the most common cause of acute GE associated with low hospitalization rates in children, it is neonates and infants (up to 11 months) who are defined as the risk group for GE due to NoV (59.1%) [20]. Similar results are found in a US study, where 70% of all recorded NoV-induced GE were in the age group of six months to one year [21].

Out of 124 children who were older than two years, 83.1% attended an educational institution. It can be concluded that children who attend an educational institution are more likely to be infected with NoV, which is also described in the scientific literature [6].

Basing on the fact that NoV infection cases were examined in only one children's hospital, the incidence of NoV infection is calculated per 1000 hospitalized patients. The incidence of acute GE caused by NoV was 12.85 cases per 1000 hospitalized children in 2021 at "Children's Clinical University Hospital". Looking at the incidence rate in calendar months, an increase in the frequency of infection can be observed from January to May and from October to December, reaching a peak in December - 37.72 cases per 1000 hospitalized children. Similar results can be found in the literature, emphasizing that the seasonality of NoV is elevated in the winter months, but peaks at the end of the spring months [9, 11-12, 22-23].

The frequency of NoV infection in the calendar months of 2021 also reflects the impact of the Covid-19 pandemic on the frequency of NoV infection, which has been described in other studies. Namely, a rapid increase in NoV infection was observed in July, with the incidence reaching less than 19 cases per 1000 hospitalized children. Several authors suggest that the Covid-19 restrictions reduced the incidence of NoV infection, but once the restrictions were eased, similar to the current study, the incidence of NoV infection was five times higher in the summer months than in previous years [24-27]. The cumulative incidence of NoV-HAI reached 4.14 cases per 1000 hospitalized patients. In the data of other studies, the incidence is calculated against the total population of children in age groups and not against the total number of hospitalized children in the hospital, so it is not possible to compare the obtained results with other studies. The data of the most similar study show that the incidence of GE hospitalization caused by NoV is 1.3 children per 1000 children, using the number of children up to five years of age in the adjacent area of the specific hospital as the denominator [20].

The first hypothesis – the socio-demographic factors of hospital-acquired and community-acquired NoV infections do not differ – was confirmed. The results show that there is no statistically significant relationship between the place of infection and socio-demographic factors. A study by other authors also found no statistically significant differences between genders and site of infection [22]. It should be emphasized that socio-economic factors may influence the course of NoV-induced GE [6], but the study data do not provide information on the severity or course of disease symptoms. It should be emphasized that in the community-acquired virus group, the highest proportion of NoV-induced acute GE cases was in males (59.1%), in females it was 40.9%. There are similar results in the studies of other authors, but the change in the proportion of cases was observed only in the group of high school students, namely in the group of men 69.2% [28]. In infection control practice, this means that every hospitalized child is exposed to a similar

risk of infection, and the frequency of outbreaks in certain structural units is not related to the patient, but to the observance of general precautions in the department. Prevention of NoV-HAI cases requires education of all patient groups and parents about precautions.

It should be emphasized that, in the hospital, health care specialists regularly monitor the health condition of children. Therefore, there is regularity between the signs of dehydration and the place of infection. Respectively, community-acquired children are five times more likely to suffer from dehydration than hospital-acquired children do due to timely rehydration therapy in the hospital [6, 19].

The second hypothesis – chronic diseases are more often observed in children with NoV-HAI – was confirmed. In the study, the group of ISK-10 diagnoses – congenital malformations, deformations, and chromosomal anomalies (Q00 – Q99) was considered a chronic illness. Ten children were hospitalized with this hospitalization diagnosis and subsequently acquired NoV-HAI in the hospital. A similar relationship has also been described in the literature that patients with immunodeficiency and chronic diseases are at higher risk of acquiring NoV-HAI [6, 7]. In addition, children with a non-infectious hospitalization diagnosis are three times more likely to have NoV-HAI than children with other infectious diseases (excluding A08.1). Similar results have been described in a study by other authors, where respiratory and gastrointestinal disease patients and neonates are at higher risk of acquiring NoV-HAI [22]. It is important to note that the study sample was too small to identify more cases with chronic diseases. With the existing data, it is not possible to characterize the severity and duration of symptoms of NoV infection in chronic patients.

The third hypothesis, that the risk of hospital-acquired NoV infections differs in different departments, was confirmed. Regarding paediatric ward profile and site of infection, the results show that children treated in therapeutic profile wards are almost four times more likely to acquire NoV-HAI than children treated in an infectious diseases ward. After adjusting for sex, age, place of residence, the odds did not change significantly, which proves that socio-demographic factors have no influence on a child's risk of acquiring NoV-HAI. Although the odds of NoV-HAI are 34 times higher in the profile of other departments, the TI is too broad to interpret this result accurately. The results of other authors' studies are similar, the risk of NoV-HAI is higher in those departments where NoV dominant genotypes circulate - patients of neonatal, pulmonology, gastroenterology, surgery, neurology departments [3-5, 22], as well as in patients of other wards who are long-term inpatients or suffer from chronic diseases [3, 6, 29].

The main preventive measures to emphasize to parents and children while in a health care facility are proper hand washing with soap and water after using the restroom or changing diapers and using common areas, toys, before eating [27, 30]. On the other hand, healthcare workers should be educated about the importance of hand hygiene in the spread of NoV infection, especially emphasizing that hands should be washed primarily with antibacterial soap and water before and after visiting a patient. The second most important infection control measure is cleaning the premises after a NoV positive patient. It is necessary to make sure that the cleaning agents used by the health care facility destroy NoV from all surfaces and that the cleaning is done thoroughly [27, 31-34].

More research is needed specifically on the incidence of NoV-induced acute GE in paediatric healthcare settings, focusing on NoV-HAI cases, especially the reasons for clustered cases. To prepare for other emergent situations, it would be important to find out the frequency of NoV infection over a period of several years and compare how the Covid-19 pandemic changed the frequency of NoV infection in children's health care facilities. It would be important to clarify the disease course and severity of NoV infection in chronic and immune-suppressed patients, as well as how long these patients can transmit and infect other patients and healthcare personnel.

5 Conclusions

In total, 266 children had acute GE caused by NoV, of which 68% had acquired the virus in the community and 32% in the hospital. Socio-demographic factors in the community-acquired NoV group and the NoV-HAI group did not differ. Children who acquired NoV infection in the community attended an educational institution in most cases (83.1%). The largest proportion of hospitalized patients (65.8%) was for children of early preschool age, reaching 45.98 cases per 1000 hospitalized children in 2021.

The total incidence of NoV infection was 12.85 cases per 1000 hospitalized children, while the frequency of NoV-HAI reached 4.14 cases per 1000 hospitalized patients. Children infected with NoV in the community with NoV are 5 times more likely to suffer from dehydration than children infected in hospital.

NoV-induced GE in patients with chronic diseases (congenital malformations, deformities, and chromosomal abnormalities) was observed only in the NoV-HAI group. Children treated in the therapeutic profile departments have almost 4 times higher chances of getting NoV-HAI than children who were treated in the department of infectious diseases, which is also proven by the fact that children with a non-infectious hospitalization diagnosis have 3 times higher chances of getting NoV-HAI, than children with other infectious diseases.

The increase in the frequency of NoV infection in 2021 was from January to May and from October to December, reaching a peak in December, but to determine the exact seasonal trends of NoV, it is necessary to analyze the data of several years. The presence of other pathogens was observed relatively rarely, so it could not be described in different sections. No international methodology has been developed to compare the frequency of NoV-HAI and community-acquired NoV between different hospitals.

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