ORIGINAL ARTICLE

CONTENTS

Clinical and epidemiological characteristics and risk factors for the development of recurrent respiratory diseases in children

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ABSTRACT

Aim: To investigate the influence of risk factors on the development of recurrent respiratory diseases, to analyze clinical and epidemiological components for the possibility of their prevention.

Materials and Methods: The research was conducted on the basis of the Uzhhorod Children Primary School. Children studied groups (n=118) aged 6–9 years with a diagnosis of "acute recurrent respiratory diseases" were formed.

Results: Childrens inflammatory episodes were most often observed, in particular: bacterial tonsillitis – 86 (72,89%), otitis – 56 (47,46%), pneumonia and sinusitis – 37 (31,36%) (identical indicators). In our study, respiratory infection caused by at least one pathogen was observed in 63,4±4,1% of patients. The proportion of viral infections was 48,34±3,6%, in particular, coinfections were identified in 36,4±2,9% of cases. The distribution of confirmed viruses is as follows: AdV (26,34±1,7%), SARS-CoV-2 (19,5±1,6%), RV (18,2%), RSV (17,8%), influenza A/B (11,4%) and others in minimal structural components (6.8%).

Conclusions: Recurrent respiratory tract infection is a multifactorial disease caused by a complex interaction of environmental and host factors. We suggest that an "additive effect," depending on the number of factors involved, most of which may be underestimated, may be a plausible explanation for the recurrence of respiratory tract infection in a significant proportion of healthy children with unexplained frequent respiratory symptoms.

KEYWORDS: recurrent respiratory diseases, acute respiratory viral infections, COVID-19, clinical and epidemiological characteristics, risk factors, children

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INTRODUCTION

There is currently no generally accepted consensus on the definition of recurrent respiratory diseases in children. When counting the number of episodes of respiratory diseases (to determine the recurrent nature), it is important to take into account their severity, duration and localization of the pathological process. Some authors propose the following definition of recurrent respiratory diseases: 8 or more respiratory diseases during the year in children under three years of age, and 6 or more in children over three years of age, with the prerequisite being the absence of any pathological conditions that could cause recurrent diseases [1, 2].

Some authors claim that the following number of mild cases of respiratory infectious diseases can be considered normal: in children under 4 years old – 11 episodes per year; in preschoolers (3–5 years old) – 8; in schoolchildren (6–12 years old) – 4 [3]. Other authors believe that 6–10 self-limiting viral infectious diseases, lasting 1–2 weeks, during the year are the norm [4].

Infectious rhinitis is considered recurrent if more than five episodes are recorded within a year; pharyngitis or tonsillitis – more than three episodes; otitis media – three episodes within six months, or four episodes within a year. Bronchitis and pneumonia are defined as recurrent if more than three episodes occur per year [5].

The most significant etiological agents of severe lower respiratory tract infections are bacteria such as Streptococcus pneumoniae and Haemophilus influenzae, as well as viruses such as SARS-CoV-2, influenza virus, and respiratory syncytial virus (RSV) [6]. A study conducted in Bulgaria during the COVID-19 pandemic showed that Haemophilus influenzae and RSV were the most common co-pathogens in patients testing positive for SARS-CoV-2 [5]. Our previous studies also found that the presence of an additional viral or bacterial co-pathogen is a risk factor for developing severe COVID-19. Respiratory infections are the most common reason for primary care visits among children. An increase in the number of episodes of recurrent infections is observed with the beginning of attending children's groups [6].

Acute respiratory viral infections are a global health problem, as they are the leading cause of morbidity and mortality in children worldwide [7, 8]. Respiratory infections are the most common pathology between the ages of 6 months and 6 years. There are two peaks in the incidence of recurrent respiratory infections in children. The first is observed between the ages of 6 months and one year. The reason is a decrease in the level of immunoglobulins inherited from the mother and the still insufficient production of its own immunoglobulins. The second – with the beginning of attending children's groups [9, 10].

Immunological immaturity is considered one of the main causes of recurrent respiratory infectious diseases in children. The development of the immune system in childhood occurs gradually. In the prenatal period, the immune system must be tolerant to maternal antigens. A baby is born with an immature immune system that gradually matures. Early protection against infections is provided by maternal antibodies, which are transmitted transplacentally and in milk. After breastfeeding ends, children become more susceptible to infections, but at this time the innate and adaptive immune systems are already better developed. Vaccination provides additional protection. As we age, the immune system's defenses increase, and young adults become sick much less frequently [11, 12].

AIM

The aim of the study was to investigate the influence of risk factors on the development of recurrent respiratory diseases, to analyze clinical and epidemiological components for the possibility of their prevention.

MATERIALS AND METHODS

The research was conducted on the basis of the Uzhhorod Primary School "Yalynka" of the Uzhhorod City Council of the Transcarpathian Region and the Municipal Non-Profit Enterprise "Transcarpathian Regional Children's Sanatorium «Malyatko»" of the Transcarpathian Regional Council. Three groups of children diagnosed with «acute recurrent respiratory diseases» were formed: group 1 – treatment with optimized therapy (n=62), group 2 – treatment with basic therapy (n=56). For comparative characteristics of the obtained data, group 3 was created – a control group of children identical in age and sex, without subjective and objective signs of acute recurrent respiratory diseases (n=26). The group of studied children (n=118) was characterized by the following parameters: age – 7,48 ± 0,68 years (min – 6 years; max – 9 years), weight – 28,41 ± 6,65 kg (min – 17,80 kg; max – 49,5 kg), height – 131,42 ± 8,22 cm (min – 114,5 cm; max – 156,5 cm). The diagnosis of recurrent respiratory tract infection is established if at least one of the following criteria is met: six or more episodes of acute respiratory infections per year, one or more cases of upper respiratory tract infection per month from September to April, or three or more episodes of lower respiratory tract infections per year [13, 14, 15]. All studies performed and treatment methods applied were carried out with the voluntary written consent of the patients, in compliance with all requirements for ensuring the anonymity and confidentiality of the results obtained. The methodology of scientific and practical monitoring was carried out in accordance with the criteria of the Helsinki Declaration of Human Rights of 1975 and its revision of 1983, the norms of the Council of Europe Convention on Human Rights and Biomedicine, as well as the current norms of Ukrainian legislation and the requirements of the local medical commission of the State Higher Educational Institution «Uzhhorod National University».

RESULTS

Respiratory tract infections (RTIs) are a common reason for specialist consultations and medication prescriptions [1]. RTIs are mostly caused by viruses and are usually self-limiting. It is estimated that a quarter of preschool children experience RTIs recurrences. Social factors such as kindergarten attendance, smoking, family size, sibling contact with kindergarten, and environmental pollution play an important role in the occurrence of RTIs in many children [16].

In the subgroup of children with recurrent RTIs, characterized by severe and frequent symptoms, primary immune defects, local anatomical factors, and genetic abnormalities play a leading role. It has been hypothesized that in children with recurrent RTIs, transient immunosuppression caused by the virus may predispose them to subsequent RTIs, creating a "vicious cycle" [16]. However, this hypothesis has never been proven. Other considerations, such as genetic susceptibility to infection, low levels of certain trace elements, and respiratory microbiota, may explain why some children develop RTIs and others do not. According to our research, an analysis of many factors that may have an impact on the development of pathology was conducted. In particular, among the children from the studied contingent, the consumption of vegetables and fruits in the diet was observed in 103 (87,29%) children, only fruits were consumed by 13 (11,02%) children, and neither fruits nor vegetables were consumed by 2 (1,69%) children. 114 (96,61%) children attended preschool education-

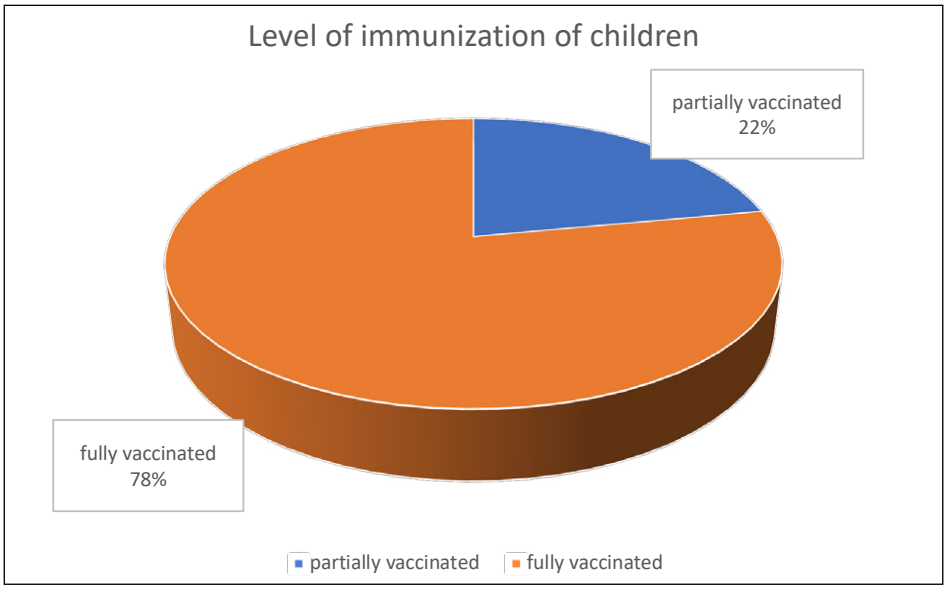

Fig. 1. Level of immunization of children
Picture taken by the authors

al institutions before starting primary school, and 4 (3,39%) children did not attend. In the autumn-winter period, children spent 101,61 ± 49,13 minutes outdoors (min – 30 minutes; max – 180 minutes). Sports activities were noted in 83 (70,34%) children, and the absence of sports activities was noted in 35 (29,66%) children. Iatrogenic factors, including the inappropriate use of antibiotics, nonsteroidal anti-inflammatory drugs, or glucocorticoids, can also contribute to the development of respiratory pathology. According to our data, the use of antibiotics was most often observed after 2 years of age – in 47 (39,83%) children, in the period from 12 to 24 months – in 32 (27,12%) children, from 6 to 12 months – in 14 (11,86%) children, and up to 6 months – in 25 (21,19%) children. Since 2013, the American Academy of Pediatrics (AAP) has encouraged the rational use of antibiotics for uncomplicated pediatric RTIs. However, while overall antibiotic prescribing rates for children have declined, unnecessary, overuse of antibiotics remains a devastating problem worldwide, leading to antibiotic resistance and contributing to rising healthcare costs and increased risk of side effects. An interesting report by Margolis et al. found a twofold increased risk of developing uncomplicated RTI in individuals who had received antibiotics for acne treatment within the previous 12 months. The intrinsic immunomodulatory effect of antibiotics has long been proven. Thus, overuse of antibiotics may impair the body's natural resistance to respiratory infections in several ways: by disrupting the respiratory microbiota and interfering with the innate immune response against viruses and bacteria [1, 17-20].

The study of the functional state of the respiratory tract revealed the following characteristics: chest circumference (inhalation) – 63,89 ± 2,89 cm (min – 53 cm; max – 78 cm); chest circumference (exhalation) – 61,49 ± 5,25 cm (min – 51 cm; max – 76 cm); chest circumference (pause) – 62,61 ± 5,18 cm (min – 52 cm; max – 77 cm); chest circumference (excursion) – 2,41 ± 0,81 cm (min – 2 cm; max – 4 cm).

Neonatal data are important. The following was found. Birth weight was 3357,03 ± 541,96 g (min – 2040 g; max – 4600 g). Duration of breastfeeding was, in particular:

- less than three months – 22 (18,64%) children;
- duration from 3 to 12 months – 36 (30,51%) children;
- duration 12 months and more – 25 (21,19%) children;
- duration up to two years – 33 (27,97%) children;
- artificial feeding – 2 (1,69%) children.

Therefore, the most common duration of breastfeeding was up to the age of three to twelve months (36 (30,51%) children), as well as up to two years (33 (27,97%) children). Despite the fact that among the children in the study group, artificial feeding occurred in only two children (1,69%), in a significant part of the children - 83 (70,34%), breastfeeding was completed by the age of twelve months. The average sleep duration of children was 8,71 ± 0,72 hours (min – 7 hours; max – 10 hours).

The Ruffier index characterizes the functional state of the cardiovascular system. According to our data, the following indicators ware observed:

- september 2021 – 8,15 ± 2,05 (min – 4; max – 15,2);
- september 2022 – 8,13 ± 2,11 (min – 4; max – 16,2);
- september 2023 – 8,23 ± 1,69 (min – 5,6; max – 12,8).

Number of days of illness with acute respiratory viral infections during the academic year:

- 2021–2022 – 8,85 ± 7,46 days;
- 2022–2023 – 20,64 ± 15,79 days;
- 2023–2024 – 11,28 ± 7,46 days.

Did children take vitamin D_3 in the autumn-winter period?
• yes – 48 (40,68%);
• no – 70 (59,32%).

We analyzed the level of immunization of the studied children (Fig. 1):
• fully – 92 (77,97%);
• partially – 26 (22,03%).

Let us consider the structural components of vaccination in children from the study group.
–Vaccination against tuberculosis:
• yes – 112 (94,92%);
• no – 6 (5,08%).
–Vaccination against diphtheria, pertussis, tetanus (vaccination 1):
• yes – 107 (90,68%);
• no – 11 (9,32%).
–Vaccination against diphtheria, pertussis, tetanus (vaccination 2):
• yes – 106 (89,83%);
• no – 12 (10,17%).
–Vaccination against diphtheria, pertussis, tetanus (vaccination 3):
• yes – 98 (83,05%);
• no – 20 (16,95%).
–Vaccination against diphtheria, pertussis, tetanus (revaccination 1):
• yes – 80 (67,79%);
• no – 38 (32,21%).
–Vaccination against diphtheria, tetanus (revaccination 2):
• yes – 34 (28,81%);
• no – 84 (71,19%).
–Vaccination against polio (vaccination 1):
• yes – 116 (98,31%);
• no – 2 (1,69%).
–Vaccination against polio (vaccination 2):
• yes – 113 (95,76%);
• no – 5 (4,24%).
–Vaccination against polio (vaccination 3):
• yes – 110 (93,22%);
• no – 8 (6,78%).
–Vaccination against polio (revaccination 1):
• yes – 109 (92,37%);
• no – 9 (7,63%).
–Vaccination against polio (revaccination 2):
• yes – 95 (80,51%);
• no – 23 (19,49%).
–Vaccination against measles, mumps, rubella (vaccination 1):
• yes – 117 (99,15%);
• no – 1 (0,85%).
–Vaccination against measles, mumps, rubella (vaccination 2):
• yes – 79 (66,95%);
• no – 39 (33,05%).

The vaccination rate in children is shown in Fig. 2.

The highest vaccination rate, according to our data, was for vaccination against measles, mumps, and rubella (vaccination 1) – 99,15%, and the lowest level was observed for vaccination against diphtheria, tetanus (revaccination 2) – 28,81%.

Environmental factors play a key role in the etiopathogenesis of respiratory infections. The most common environmental factors include biota diversity, winter season, overcrowding, nighttime crowding, household size (the smaller the house, the higher the risk), attendance at daycare, and attendance at daycare by siblings aged one to three years.

Of course, acute respiratory infections are also associated with maternal smoking during pregnancy and passive smoking. Exposure to harmful factors in children has been associated with several respiratory diseases, including lower respiratory tract infections, wheezing, and respiratory symptoms in the first year of life. This connection has been proven to be stronger in those whose mothers smoke heavily (more than one pack of cigarettes per day).

Among these environmental factors that increase the risk of wheezing and RTIs, several studies have shown that aerosolized cleaning chemicals (such as bleach) act as irritants, damaging the airway epithelium, maintaining inflammatory processes, and promoting infection by local flora [17, 18, 21-23].

We also examined the components of the respiratory tract disease group. Below are the results of the questionnaire and anamnestic data:
–Has the child had any cases of pneumonia?
• yes – 37 (31,36%)
–1 time in a lifetime – 34
–2 times in a lifetime – 1
–3 times in a lifetime – 2
• no – 81 (68,64%)
–Has the child had any cases of otitis media?
• yes – 56 (47,46%)
–1 time in a lifetime – 36
–2 times in a lifetime – 10
–3 times in a lifetime – 2
–4 times in a lifetime – 6
• no – 62 (52,54%)
–Has the child had any cases of acute bronchitis?
• yes – 37 (31,36%)
–1 time in a lifetime – 21
–2 times in a lifetime – 9
–3 times in a lifetime – 1
–4 times in a lifetime – 0
–5 times in a lifetime – 6

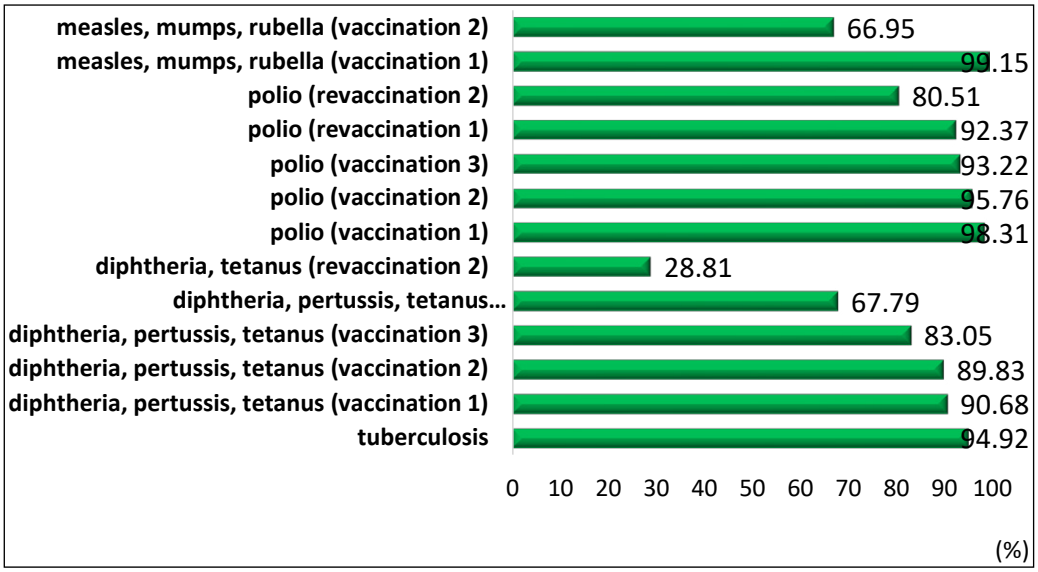

Fig. 2. Vaccination rate
Picture taken by the authors

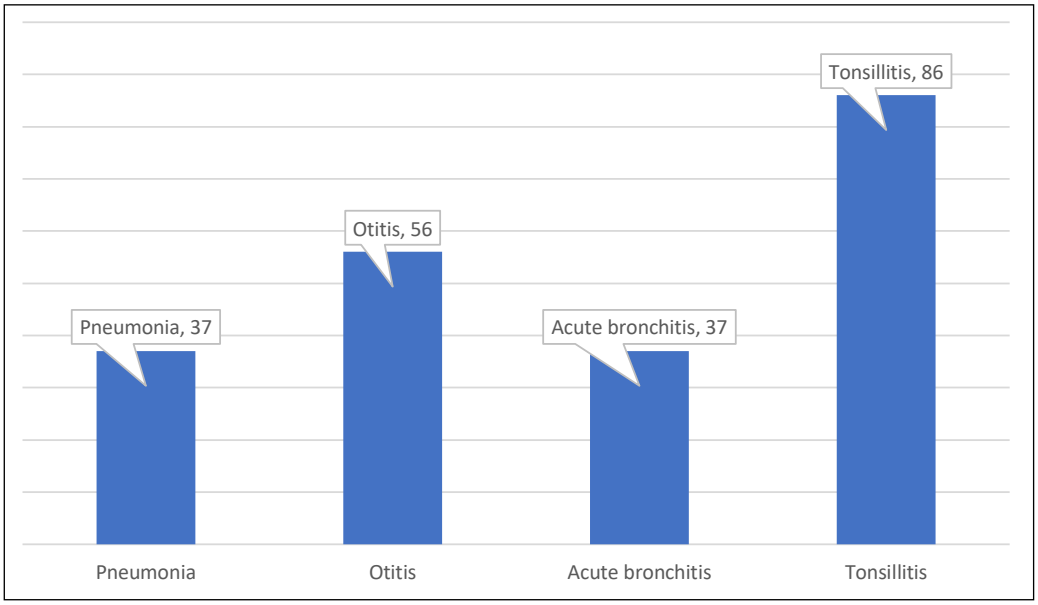

Fig. 3. Cases of recorded diseases during life
Picture taken by the authors

• no – 81 (68,64%)
–Has the child had any cases of tonsillitis?
• yes – 86 (72,89%)
–1 time in a lifetime – 32
–2 times in a lifetime – 30
–3 times in a lifetime – 14
–4 times in a lifetime – 3
–5 times in a lifetime – 7
• no – 32 (27,11%)

We present a graphical representation of the obtained data (Fig. 3).

So, the most frequent cases were acute tonsillitis (86 (72,89%)), otitis media (56 (47,46%)), and pneumonia and acute bronchitis with the same frequency – 37 (31,36%). We considered the data excluding children with a history of pneumonia. In our study, respiratory infection caused by at least one pathogen was observed in 63,4±4,1% of patients. The proportion of viral infections was 48,34±3,6%, in particular, coinfections were identified in 364±2,9% of cases.

The distribution of confirmed viruses is as follows: AdV (26,34±1,7%), SARS-CoV-2 (19,5±1,6%), RV (18,2%), RSV (17,8%), influenza A/B (11,4%) and others in minimal structural components (6,8%). It is important to note that atopy is an important additional risk factor for recurrent RTIs as it likely underlies immune dysfunction. Atopic disorders (allergic rhinitis, atopic dermatitis) are associated with pneumococcal infections in children almost twice as often as in healthy children in the control group. Furthermore, the duration of the disease in patients with atopy is longer than in patients without atopy. A defective innate immune response (e.g., associated with impaired interferon response) leads to more severe asthma exacerbations due to rhinovirus infection. In particular, early onset (up to two years) of severe RTIs correlates with an increased risk of later

Table 1. Results of psychodiagnostics of fluid intelligence (CF2A)

Parameters	IQF1	IQF2	IQF3	IQF4	General IQF
M ± m	101.51 ± 13.87	106.76 ± 11.59	103.71 ± 21.34	79.75 ± 26.23	90.49 ± 9.92

Source: compiled by the authors of this study

development of asthma/atopy, likely due to a Th1/Th2 shift in the cytokine milieu. In addition, atopic dermatitis is associated with increased fragility and permeability of the skin barrier to pathogens. This sensitivity may be explained by the insufficient synthesis of cutaneous antimicrobial peptides, such as cathelicidin (LL-37) and beta-defensin, which are involved in the innate immune response against bacterial and viral pathogens. Children with atopic dermatitis are at increased risk of sore throats, colds, bronchitis, flu, pneumonia, sinus infections, ear infections, chickenpox, and urinary tract infections. In particular, the combination of atopic dermatitis and other atopic conditions correlates with a higher number of infections than those who had only one of these conditions [23].

According to our research, negative impacts of mediated environmental factors were observed:

–Does anyone in the family smoke?
- yes – 44 (37,29%)
- no – 74 (62,71%)

–Is there a pet living at home?
- yes – 67 (59,78%): cat – 16; dog – 51
- no – 51 (40,22%)

–Does the child have any allergic diseases?
- yes – 5 (4,42%)
- no – 113 (95,76%)

–Are there any allergic diseases among relatives?
- yes – 15 (12,71%)
- no – 103 (87,29%)

Starting in the womb and throughout the "first 1000 days of life," harmful environmental factors on the development of the immune and respiratory systems can lead to a reduced ability to fight infections and an increased risk of allergic symptoms later in life. According to the authors, it has been proven that exposure to environmental tobacco smoke during pregnancy was associated with recurrent RTIs in children followed from birth to 4 years of age, as well as with early markers of atopic status (elevated total IgE or atopic dermatitis). Exposure to tobacco smoke has been shown to increase the duration and severity of RTIs symptoms by increasing bacterial adhesion or damage to the mucociliary apparatus of the respiratory tract and loss of local defenses [21].

Scientists have also identified a link between the presence of intracellular atypical pathogens (Mycoplasma pneumoniae and Chlamydia pneumoniae) and the development of recurrent RTIs, especially in preschool-aged patients (<5 years). Presumably, atypical bacteria cause both respiratory disorders and pathology of the nasopharyngeal area [21].

Overweight and obesity are also considered by scientists, along with other independent risk factors (exposure to cigarette smoke, allergies, history of chronic respiratory symptoms) and are significant risk factors for recurrent respiratory infections in children with pathological signs. There is a direct correlation between the frequency of RTI and body mass index (BMI). It has been reported that leptin deficiency in severely obese children may make them more sensitive to pro-inflammatory stimuli and infections [24].

Many studies highlight the immunomodulatory role of vitamin D_3, documenting an inverse relationship between 25(OH)D levels and the incidence of upper respiratory tract infections, with the risk depending on the degree of deficiency. On the other hand, there is some evidence that vitamin D_3 supplements help prevent acute pediatric RTIs. Hair zinc and selenium levels were lower in a cohort of pediatric patients with recurrent wheezing compared with healthy children. A higher incidence of recurrent infections has also been reported in patients with suboptimal antioxidant levels (β-carotene, retinol, α-tocopherol, ascorbic acid, glutathione). In addition, micronutrient supplementation during pregnancy apparently has a potential immunomodulatory effect on the offspring at the epigenetic level from the prenatal period [25].

A psychodiagnostics of fluid (potential) intelligence was also conducted using the "Culturally Free Intelligence Test (CF2A)" by R. B. Cattell and A. K. Cattell [26]. We present the results of four groups of psychodiagnostic subtests (Table 1).

According to the research, the general IQF corresponded to the range of the average level of social creativity of the individual.

The level of intelligence corresponded to the following gradation:
- good norm – 53 (44,92%);
- low – 32 (27,12%);
- borderline zone – 4 (3,38%);
- average – 29 (24,58%).

DISCUSSION

According to the World Health Organization (WHO), the largest number of acute respiratory diseases occurs at

the age of 6–18 months and 5–7 years, which can be explained by the expansion of children's contacts and the characterological features of the children's immune system [27, 13].

Proposals from pediatricians and family doctors regarding the unification of requirements for the frequency and nature of nosological forms that may indicate that a child belongs to the group of «frequently ill children» or recurrent respiratory diseases differ significantly in different countries.

Equally important is the study of the biological role of acute respiratory diseases in the development of a child. According to some researchers, cases of rhinitis, nasopharyngitis, and even bronchitis trigger the body's defenses [27, 28].

According to our data, repeated episodes of acute respiratory infections lasted 3–4 days and tended to recur after 3–4 weeks, during which no clinical symptoms were observed [14].

There was also a predominance of episodes of acute respiratory infections in winter and spring, while in summer episodes of acute respiratory diseases were almost not observed. The general condition of the children between exacerbations was satisfactory, and there were no complaints [27].

Scientific evidence suggests that children with recurrent RTIs (6–8 episodes of RTIs per year) have different health status than those with fewer such episodes. In particular, they are more likely to develop complications requiring hospitalization. The level of inpatient treatment depends on the season and the child's age [15, 29, 30].

CONCLUSIONS

1. According to our study, negative impacts of indirect environmental factors were observed: smoking in the family – in 44 (37,29%), presence of pets at home – in 67 (59,78%), of which cats (in 16 children) and dogs (in 51 children), 22 children (18,64%) were breastfed until three months of age, vitamin D intake was not carried out in 70 children (59,32%), 35 children (29,66%) did not attend sports clubs.
2. According to our research, the vaccination rate of children was not at the proper level. The highest vaccination rate, according to our data, was observed for vaccination against measles, mumps, and rubella (first vaccination) – 99,15%, and the lowest level was for vaccination against diphtheria and tetanus (second booster) – 28,81%.
3. Among the children in the study group, inflammatory episodes were most often observed, in particular: bacterial tonsillitis – 86 (72,89%), otitis – 56 (47,46%), pneumonia and sinusitis – 37 (31,36%) (identical indicators). 71 children (60,17%) had experience with antibiotic therapy under the age of two, 25 children (21,19%) were used antibiotics before the age of six months.
4. Respiratory infection caused by at least one pathogen was observed in 63,4±4,1% of patients. The proportion of viral infections was 48,34±3,6%, in particular, coinfections were identified in 36,4±2,9% of cases. The distribution of confirmed viruses is as follows: AdV (26,34±1,7%), SARS-CoV-2 (19,5±1,6%), RV (18,2%), RSV (17,8%), influenza A/B (11,4%) and others in minimal structural components (6,8%).
5. Recurrent RTI is a multifactorial disease caused by a complex interaction of environmental and host factors. We suggest that an "additive effect," depending on the number of factors involved, most of which may be underestimated, may be a plausible explanation for the recurrence of RRI in a significant proportion of healthy children with unexplained frequent respiratory symptoms.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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