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# Influenza among Children Admitted to the Emergency Department of Children's Hospital in Vilnius: Two Seasons, Two Viruses

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**Summary**

***Background.*** No specific clinical signs of influenza are defined, although type A is thought to dominate and be responsible for more severe cases of influenza diseases.

Our study aimed to determine the value of clinical signs and routine laboratory results on influenza diagnose among children, reveal possible differences among different influenza subtypes.

***Methods.*** A retrospective study was conducted at Vilnius University Hospital Santaros Klinikos during two influenza seasons (2016/2017 and 2017/2018 year). Basic demographic, clinical data, vaccination for influenza status and results of laboratory testing, were collected.

***Results.*** Data of 655 influenza cases were analysed. Among them 355 (54.2%) were boys. Influenza A cases from 2016/2017 season and influenza B cases from 2017/2018 season were compared. Average age of influenza patients was 6.25±2.1 years: in influenza A group – 5.5±4.5 years, and in influenza B – 7.2±4.3 years. The main symptoms were fever 647 (98.8%), cough 387 (59.1%) and rhinitis 302 (46.1%). Diarrhoea, stomach ache, muscle pain, headache were more prominent in influenza B group. Complications were found more common in influenza A group (82 (55.4%)) and among children above 12 years of age (28/112 (25%)). Overall 159 (24.3%) children were hospitalized (influenza A dominated (56.6%)).

***Conclusions.*** The incidence of influenza B is increasing in children under 12 years of age and the incidence of influenza A is decreasing with increasing age of children (p=0.00). No significant statistical difference was found in clinical signs, complications and hospitalisation rate among two influenza virus types.

**Keywords:** influenza, children, influenza virus types, influenza clinical manifestation.

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## BACKGROUND

Influenza virus is one of the most significant causes of acute respiratory infection worldwide. Every year 5–10% of adults and 20–30% of children are affected by this seasonal infection characterized by respiratory and gastrointestinal symptoms as well as head, muscle, and eye pain [1, 2]. During the 2016–2017 influenza season in Lithuania – 30 958 cases of influenza

were registered and in 13 153 cases patients were between 0–17 years of age [3]. According various clinical studies 1 out of 3 children infected with influenza virus is at risk of experiencing severe influenza complications [4]. This risk is even higher for children with chronic diseases such as asthma or diabetes, neurological or neuromuscular pathology and children under the age of 5 years. As per data from the United States, during the past eight years the number of hospitalisations due to influenza-related illnesses among children under the age of five has increased from 7,000 to 26,000 cases per year [5]. Influenza is a major public health problem worldwide and its rapid diagnostics is an effective tool in early diagnosing of this infectious disease. The Polymerase Chain Reaction (PCR) and rapid antigen detection test are considered to be a gold standard in the diagnostics of influenza in clinical practice, but due to the limited availability of PCR in the primary health care, the diagnosis of influenza is usually based on clinical findings and routine laboratory parameters. Unfortunately, no specific clinical signs of influenza are defined, although type A is thought to dominate and be responsible for more severe cases of influenza disease [6].

## THE AIM

The aim of our study was to determine the value of clinical signs and routine laboratory results on influenza diagnose, reveal possible differences among different influenza subtypes on clinical signs and outcome of the disease. Importance of the study – it may be informative in improving diagnostic and prognostic skills in clinical practice.

## METHODS

A retrospective study was conducted at Children's Hospital, Affiliate of Vilnius University Hospital Santaros Klinikos (further – CH) during two influenza seasons (2016/2017 and 2017/2018 year). The patients, who were admitted to the Emergency Department of CH for suspected influenza according clinical signs, were included in the study. Only those who had rapid influenza antigen (nasopharyngeal swabs, rapid immunochromatographic test, Veda Lab, France) confirmed influenza infection were included to the further analysis.

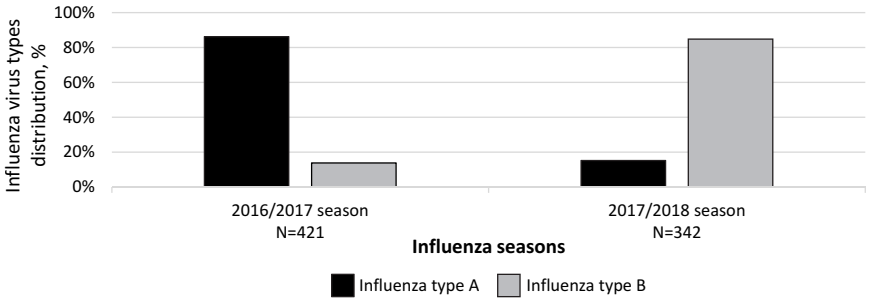



Fig. 1. **Distribution of influenza virus types during two influenza seasons**

Basic demographic, vaccination for influenza status, time from the onset of symptoms clinical data on admission and results of laboratory tests were collected. Type of influenza virus was verified by testing of nasopharyngeal swabs using rapid immunochromatographic test (Veda Lab, France) and in sub-cohort of influenza patients was confirmed by real-time RT-PCR assay (RT-PCR Influenza CDC Protocol from WHO Influenza Cooperation Centre CDC Atlanta, USA. The primers and probes set used was designed for universal detection of type A/B influenza viruses H1, H3, H1PDM09, H5, H7, Victoria, Yamagata).

Statistical analysis was performed using Microsoft Excel and SPSS v23.00. Categorical variables were expressed as number and percentages and continuous variables values as median and range or as average and standard deviation. Comparison of proportions between the groups was done by the $^2$ test. Statistical significance was set at a p value of less than 0.05.

The study was approved by the Regional Biomedical Ethics Committee (No. 158200-18/4-1025-525) and the State Data Protection Inspectorate (No. 2R-3369). As the study was retrospective, a special permission was given by Regional Biomedical Ethics Committee to perform the study without informed consent from the patients or their parents.

## RESULTS

In total 2066 nasopharyngeal swabs were taken from the patients with suspected influenza during two influenza seasons. Using rapid antigen detection test influenza infection was detected in 763 cases, of which influenza A virus was proven in 416 (54.5%) cases, as all the rest was influenza B virus – 347 (45.5%).

Influenza A virus was more prevalent during 2016/2017 influenza season (363 (86.2%) cases) and influenza B virus during 2017/2018 influenza season (292 (84.8%)). The distribution of influenza virus types during two influenza seasons was shown in Fig. 1.

Additionally, 116 randomly selected nasopharyngeal swabs positive for influenza B virus by rapid test were further analysed using RT-PCR. Influenza B virus lineages were identified. Victoria lineage dominated in 2016/2017 influenza season (14 (100%)) and there were no cases of Yamagata lineage. In 2017/2018 influenza season 94 (92.1%) cases of Yamagata and 8 (7.9%) of Victoria lineages were identified.

There were only few cases of influenza B during 2016/2017 season and just few cases of influenza A during 2017/2018 season, therefore data on influenza A cases from 2016/2017 season and influenza B cases from 2017/2018 season were compared. A total of 655 influenza cases were analysed. Among them 355 (54.2%) were boys and 300 (45.8%) girls.

The total average age of our influenza patients was 6.25±2.1 years of age: in influenza A group – 5.5±4.5 years, and in influenza B – 7.2±4.3 years. For more detailed analysis, all the patients were divided into four age groups: below 2 years – 153 (23.4%), 2–5 years – 151 (23.1%), 6–12 years – 239 (36.5%), more than 12 years – 112 (17.1%). In 2016/2017 influenza season influenza was detected statistically significantly more frequent in children below 2 years of age – in 110 (30.3%) of all 2016/2017 influenza season children, in 2017/2018 season – in 6–12 years and over 12 years of age, accordingly 128 (43.8%), 62 (21.2%) (p=0.001). The distribution of influenza by age groups and sex is shown in Fig. 2.

The incidence of influenza B is increasing in children under 12 years of age and the incidence of influenza A is decreasing with increasing age of children (p=0.00). The distribution of influenza virus types in different age groups is shown in Fig. 3. Based on binary logistic regression analysis we

can predict that children over 54 month of age are at higher risk to get influenza B (OD=2.693).

We did not find any statistically significant relationship between influenza B lineages, and influenza incidence by age and sex.

Three participants were vaccinated with trivalent flu vaccine (0.5%). One of them was in age group up to 2 years and two children were in age group from 6 to12 years. One of them had influenza A, another two – B. No one of the influenza vaccinated children was hospitalized or had complications.

Most of the youngest patients (<2 years of age) and school-age (5–12 years of age) referred to medical attention on the first three days of the disease during both influenza seasons. Differences between the illness day during the approach to CH and influenza type is shown in Fig. 4. For 12 patients who have been diagnosed with influenza during 2016/2017 influenza season, day of illness during visit day to the CH is not known.

The main symptoms were fever 647 (98.8%), cough 387 (59.1%) and rhinitis 302 (46.1%). The frequency of the symptoms for the different types of influenza is presented in Fig. 5.

In total 148 (22.6%) children had influenza-related complications. Non-bacterial complications (serous otitis media, acid-base imbalance, benign acute childhood myositis) had 143 (21.8%) children. Secondary bacterial infection (acute bacterial otitis media, bacterial pneumonia) had 15 (2.3%) and mixed complications – 10 (1.5%) children. Complications were found more common in children with influenza A – 82 (55.4%) and in the age group above 12 years (28/112 (25%) had complications). Complications developed more frequently for children with chronic diseases – 29 (39.7%) (p=0.00). Children with chronic diseases are more likely to develop non-bacterial complications – 28 (38.4%) (p=0.001).

Out of 655 study participants 159 (24.3%) children were hospitalized. Influenza A was confirmed in 90/159 (56.6%) and influenza B – in 59/159 (37.1%) of all hospitalised patients. Boys were hospitalised more often – 87 (54.7%): 52 (57.8%) in 2016/2017 season and 35 (50.7%) in 2017/2018 season. Children under 2 years of age were hospitalized because of influenza more often (51/153 (33.3%)) comparatively with children from other age groups (p=0.011). Children who came to CH after the third day of disease

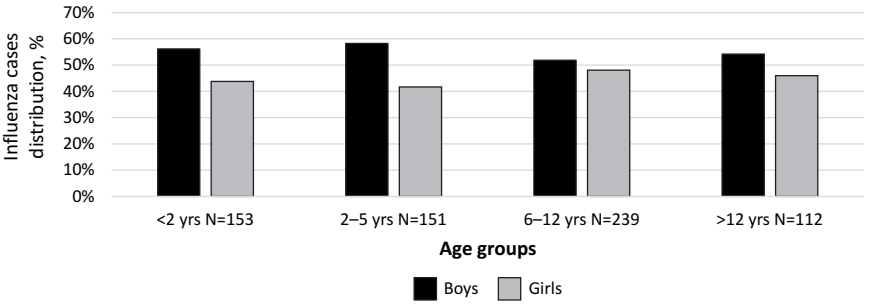



Fig. 2. **The distribution of influenza cases in different age and sex groups (2016/2017 and 2017/2018 influenza seasons)**

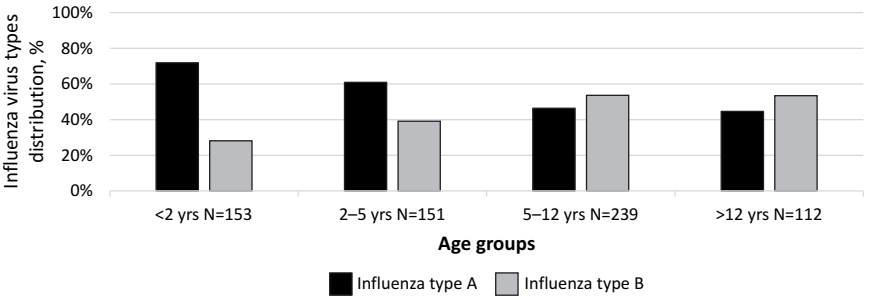



Fig. 3. **The distribution of influenza types in different age groups (2016/2017 and 2017/2018 influenza seasons)**

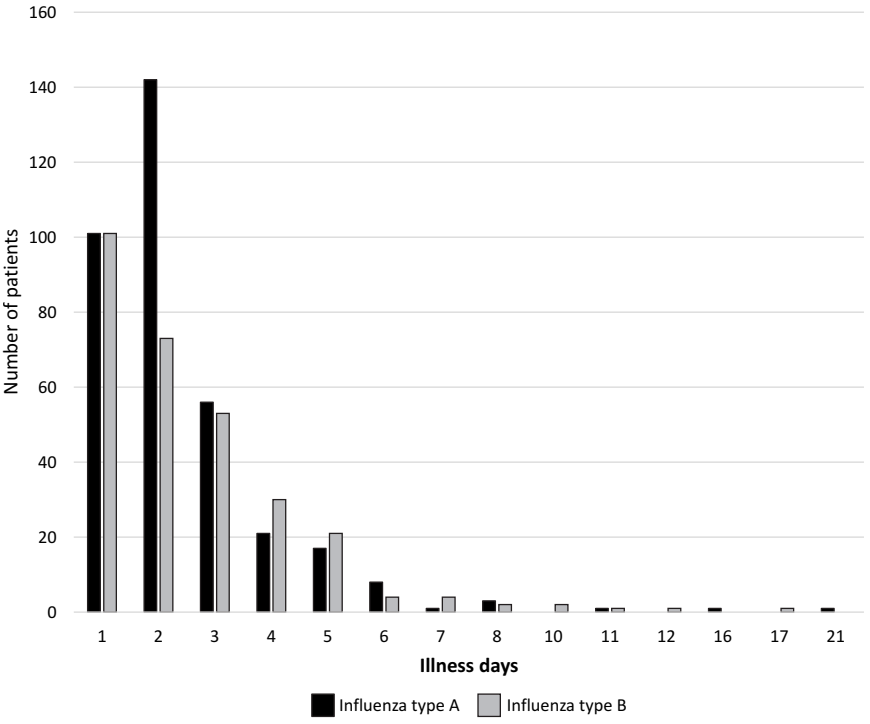



Fig. 4. **The differences between the illness day of referral to CH and influenza type (2016/2017 and 2017/2018 influenza seasons)**

(46/138 (33.9%)) or had leukocytosis (WBC>$15\times10^9$) in complete blood count (25/60 (40.3%)) also comparatively were hospitalized more often (for both p=0.007).

## DISCUSSION

The peculiarities of children flu are described. Data was collected during two influenza seasons: 2016/2017 and 2017/2018 years at Children's hospital in Vilnius. Two different types of influenza virus were circulating. Type A was dominating during the 2016/2017 influenza season and type of influenza B – during the 2017/2018 season. Global Influenza Surveillance and Response System (GISRS) reported domination of influenza A during 2016/2017 years, and influenza B dur-

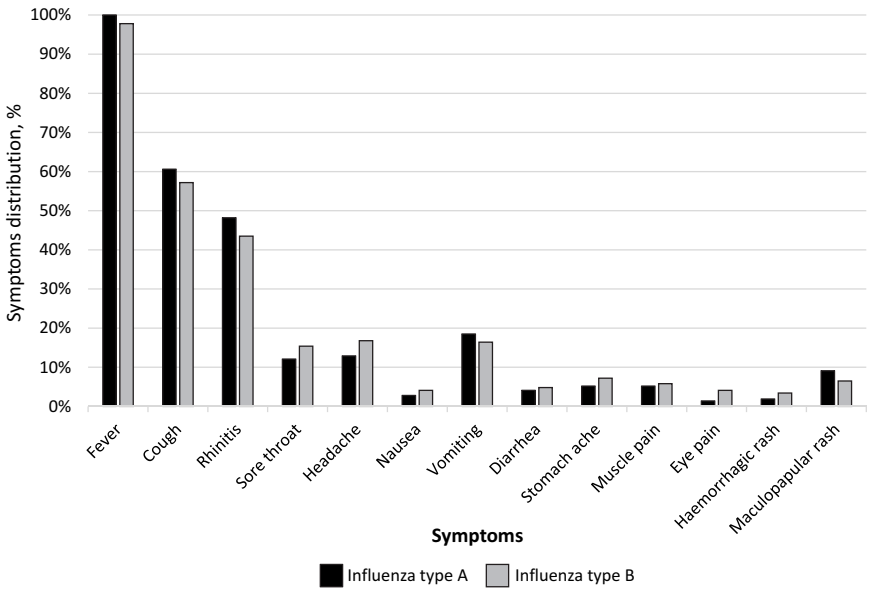



Fig. 5. **The distribution of the symptoms for the different types of influenza virus (2016/2017 and 2017/2018 influenza seasons)**

ing 2017/2018 influenza season in Lithuania. Influenza A virus dominated during both seasons worldwide, however in the European Union countries higher than usual proportion of influenza B compared to influenza A has been detected in sentinel sources in 2017/2018. The B/Yamagata lineage virus has greatly outnumbered the B/Victoria lineage [7]. The comparable proportions of circulating types and subtypes of influenza virus were shown also in our study.

Influenza B is responsible for about 20% of all influenza cases, with fluctuation of either Victoria or Yamagata lineage and it was commonly accepted that influenza B causes milder clinical symptoms and less complications in comparison with influenza A. Epidemiology and clinical manifestations of influenza A virus induced diseases is widely described in the scientific sources, whilst influenza B virus is considered to be less important pathogen [6]. Results of the large scale clinical studies and reviews published recently changes such an understanding of influenza epidemiology and illustrates growing importance of influenza B virus as aetiological factor of severe diseases [8–10].

Recent reviews report the changing burden of influenza in different age groups and virus type [11]. We do believe that our study will contribute to better understanding of the importance of different influenza virus types in epidemiological process and clinical manifestation in children.

Differences between circulation of influenza A and B type viruses and diseases caused by these viruses could be seen in French general practitioners-based influenza surveillance network study from 2003–2004 to 2012–2013. Screening of 49919 patients with flu like symptoms was positive in 32.6%. In our study, 763 samples out of 2660 taken (28.7%) were influenza positive. This illustrates the necessity of the rapid influenza tests to confirm the diagnosis and to prescribe antiviral treatment properly. In France during both season influenza B was responsible for 23.7% of all the cases, (viruses of the B-Yamagata and B-Victoria lineage caused 62.8% and 37.2% of influenza B cases, respectively) and no differences in the duration of influenza A and B epidemics were observed [12].

In France and Turkey during 2010–2011 and 2011–2012 seasons data from 774 influenza cases: 419 influenza B cases (209 in France and 210 in Turkey) and 355 influenza A cases (205 in France and 150 in Turkey) was reported. There were no differences between influenza A and B patients in terms of clinical presentation and number of consultations with a practitioner; however, the use of antivirals was higher among influenza B patients in both countries. In conclusion, findings of this study show that influenza B infection appears not to be milder disease than influenza A infection [13].

European Influenza Surveillance Network (EISN) data shows that interpretation of syndromic surveillance data without age group-specific virology data may be misleading. Surveillance at the European level would benefit from the reporting of age-specific influenza data as the review data from twenty-nine countries during 1999–2014 (N=358,796 influenza cases) highlight the importance of presenting burden of disease estimates by age group and virus type [11, 14]. According the results of the same study in France patients aged 5–14 years were more likely to be infected with type B viruses than children aged 0–4 years, those (OR 2.15, 95% CI 1.87–2.47) [9]. The same results are shown in our study – flu B was detected more frequently in older children in comparison with 0–2 year of age group.

No statistically significant differences between circulation of flu A and B across seasons was shown in "The Global Influenza B study" in which 935,673 influenza patients were included during 2000–2013 period. Overall, median proportion of influenza B was 22.6%. During seasons where influenza B was dominant or co-circulated (more than 20% of total detections), Victoria and Yamagata lineages predominated during 64% and 36% of seasons, respectively [15]. In our study influenza season of 2017/2018 was specific because Yamagata dominated and caused 80% of all influenza cases.

Clinical characteristics and outcomes of influenza in children below 17 years of age admitted due to laboratory-confirmed influenza B or A at 12 paediatric hospitals, participants of active surveillance Canadian Immunization Monitoring Program were compared. Influenza A patients compared with influenza B patients were more likely to have a vaccine-indicated condition. Symptoms more often associated with influenza B were headache, abdominal pain, and myalgia [16]. Similar differences in clinical signs we found in our study in Lithuania.

In US study combining data from four seasons (2004–2005 through 2007–2008), paediatric patients with influenza B were more likely to have a high-risk medical condition relative to those with influenza A (21% and 13%) and symptoms varied during different seasons. Cough and wheezing were significantly associated with influenza A during the 2004–2005 season (predominant subtype H3N2), but not during the other seasons. In the 2004–2005 season, 95% of patients with influenza A and 79% of patients with influenza B reported cough (p=0.05, exact Pearson chi-square); wheezing was reported by 51% of influenza A cases and 15% of patients with influenza B (p=0.02). Sore throat

and vomiting were associated with influenza A during the 2007–2008 season only (predominant subtype H3N2). Seventy-six percent of influenza A cases and 66% of influenza B cases reported sore throat (p=0.006); vomiting was reported by 19% of influenza A cases and 13% of patients with influenza B (p=0.05) [17]. In our study sore throat and headache as gastrointestinal signs (diarrhoea and stomach ache) were more common for influenza B.

In Canadian study among healthy children with influenza B, above 12 years of age was associated with the greatest odds of ICU admission [18]. In our study admission rates were similar both for A and B influenza cases.

Children with chronic diseases and influenza were treated in hospital more often than otherwise healthy children. Study in Turkey shows the same results as our study – children below 3 years of age with underlying chronic diseases are at the biggest risk to be treated in hospital [19].

All the children admitted to Children's Hospital were not vaccinated except three. All of them were vaccinated with trivalent vaccine; influenza B was diagnosed for 2 children. In studies from USA from 14 up to 54 out of 1000 vaccinated were diagnosed with flu. Up to now most vaccinated are not protected from influenza B, despite the fact that WHO from 2013–2014 influenza season recommend vaccinate with four-component vaccine. Vaccination program has caused meaningful reductions visits for influenza, even in years when the vaccine was not well matched to the dominant circulating influenza strain [18, 20]. None of vaccinated in our study required hospitalisation and this illustrates the importance of children vaccination against influenza. Even if the disease is not prevented completely, it is less severe and do not require the usage of the medical resources. Including Yamagata component in most of vaccines will be important in further reducing the morbidity and absenteeism particularly among school age children worldwide.

Limitation of our study is that it was retrospective study. Comparison of the clinical manifestations of influenza during different seasons might be considered as another limitation, however due to the seasonal fluctuations of the structures of influenza virus this is difficult to avoid.

## CONCLUSION

1. The incidence of influenza B is increasing in children under 12 years of age and the incidence of influenza A is decreasing with increasing age of children (p=0.00).
2. No significant statistical difference was fond in clinical signs, complications and hospitalisation rate among two influenza virus types.
3. Despite of the limitations mentioned above we do believe that the unexpected distribution of influenza B Victoria and Yamagata lineages during 2017–2018 season and comparison of clinical manifestations of the diseases caused by different influenza viruses will be interesting data to share. ◆

Gauta: 2020 06 02
Priimta spaudai: 2020 06 30

**Santrauka**

## VAIKŲ GRIPAS: DU SEZONAI, DU GRIPO TIPAI – SANTAROS KLINIKŲ VAIKŲ LIGONINĖS DUOMENYS

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***Įvadas.*** Nėra aprašyta gripo A ir gripo B skirtingų specifinių klinikinių požymių, tačiau manoma, kad gripas A sukelia sunkesnės eigos ligą nei gripas B.

***Tyrimo tikslas.*** Nustatyti galimus klinikinių požymių ir rutininių laboratorinių rezultatų skirtumus tarp gripo A ir B bei gripo tipo įtaką ligos eigai.

***Metodai.*** Retrospektyvusis tyrimas atliktas Vilniaus universiteto ligoninėje Santaros klinikose. Surinkti duomenys (demografiniai, klinikiniai, laboratoriniai) vaikų, kuriems per 2016–2017 ir 2017–2018 metų gripo sezoną laboratoriniu būdu buvo patvirtintas gripas.

***Rezultatai.*** Į tyrimą įtraukti 655 vaikų duomenys, iš jų 355 (54,2 %) berniukų. Išanalizuoti ir palyginti 2016–2017 metų šaltojo sezono gripo A ir 2017–2018 metų gripo B duomenys. Vidutinis amžius 6,25 ± 2,1 metų: gripo A – 5,5 ± 4,5, gripo B – 7,2 ± 4,3. Dominuojantys simptomai buvo karščiavimas (647 (98,8 %)), kosulys (387 (59.1%)) ir rinorėja (302 (46,1 %)). Gripo B grupėje dažniau pasitaikė viduriavimas, pilvo skausmas, mialgija, galvos skausmas. Komplikacijos dažnesnės gripo A grupės (82 (55,4 %)) ir vyresniems nei 12 metų vaikams (28/112 (25 %)). Hospitalizuoti 159 (24,3 %) vaikai, iš jų dėl gripo A 56,6 % vaikų.

***Išvados.*** Sergamumas gripu A mažėja didėjant vaiko amžiui, o sergamumas gripu B didėja iki 12 metų (p = 0,00). Klinikinių simptomų pasireiškimo, komplikacijų ir hospitalizacijos skirtumai tarp gripo A ir B grupių nebuvo statistiškai reikšmingi.

**Reikšminiai žodžiai:** gripas, vaikai, gripo tipai, klinikiniai požymiai.

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