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Posted Date: 15 August 2024

doi: 10.20944/preprints202408.1126.v1

Keywords: Oseltamivir; tolerability; influenza; children; clinical effectiveness; comorbidities

 doi:10.20944/preprints202408.1126.v1

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The Clinical Effectiveness and Tolerability of Oseltamivir in Unvaccinated against Influenza Pediatric Patients in Two Influenza seasons after the COVID-19 pandemic.The Impact of Comorbidities on Hospitalization for Influenza in Children

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Abstract: Antiviral therapy such as Oseltamivir has been recommended for hospitalized children with suspected and confirmed influenza for almost 20 years. The therapy is officially authorized for newborns two weeks of age or older, however, questions about its safety and effectiveness still surround it. Our goal was to assess the epidemiological features of two consecutive seasonal influenza cases in children following the COVID-19 pandemic and also to observe the clinical effectiveness and tolerability of oseltamivir in hospitalized children who were not vaccinated against influenza and who had different influenza subtypes, including A (H1N1), A (H3N2), and influenza B, and to identify specific comorbidities associated with influenza in children. We performed an observational study on 1300 children, enrolled between 1st October 2022 and 30th May 2023 and 1st October 2023-4th of May 2024, to the IX Pediatric Infectious Diseases Clinical Section of the National Institute of Infectious Diseases "Prof. Dr. Matei Balș". During the 2022-2023 influenza season, 791 pediatric patients tested positive for influenza and received Oseltamivir. Of these, 89% (704/791) had influenza A, with 86.4% subtypes A(H1N1) and 13.6% of cases had A(H3N2), and influenza B 11%(87/791) pediatric patients. Of the total group, 59% were male, and the median age was 2,4 years (1.02-9.28). For the 2023-2024 influenza season, 509 pediatric patients tested positive for influenza, 56.9% were male gender and were treated with Oseltamivir. 81.6 % had Influenza A, and 18.4% had influenza B. Treatment with neuraminidase inhibitors like Oseltamivir, 2mg/kg/dose twice daily for 5 days, was well tolerated by the children, and we recorded no deaths. The duration of fever hospitalization after the Oseltamivir administration was significantly longer for patients with A(H1N1) infection than A(H3N2), during both seasons. We identified more complications in the 2022-2023 season and a decreasing number of Influenza B for the 2023-2024 season. Among children with comorbidities, the most common were asthma, gastrointestinal disorders, and metabolic and endocrine diseases. In terms of effectiveness, oseltamivir significantly reduced the intensity of influenza symptoms, thus reducing the number of days of hospitalization (p=0.001) as well as post-infection complications (p=0.005) in both groups. Oseltamivir was less effective in Influenza A (H1N1) than A(H3N2), (p=0.0035). In this study, we evaluated the clinical effectiveness of oseltamivir therapy for all influenza types/subtypes in children, and the length of hospitalization. We identified comorbidities associated with prolonged duration of hospitalisation. Influenza vaccination should be the main tool in the prevention of influenza and its complications in children, especially with comorbidities.

 doi:10.20944/preprints202408.1126.v1

Keywords: Oseltamivir; tolerability; influenza; children; clinical effectiveness; comorbidities

1. Introduction

Every year, seasonal influenza epidemics and pandemics are brought on by influenza A (H1N1)pdm09, A(H3N2) and influenza B, which severely threaten the health of young people and have been connected to a considerable number of hospitalizations in children and adolescents and death in children under the age of five [1–3].

Seasonal influenza epidemics can result in 3–5 million severe cases globally annually, with 650,000 influenza-related fatalities linked to respiratory diseases [3,4]. The majority of them either show no symptoms at all or associate fever, cough, nasal congestion, myalgia, headache, and gastrointestinal symptoms [3–5].

Comorbidities affect the severity of respiratory infections, as the COVID-19 pandemic has shown [3,4,6]. As SARS-CoV-2 and influenza are both respiratory illnesses that produce pandemics, vaccination efforts against influenza are a crucial part of prevention [6]. It's also critical to research how comorbidities affect the severity of influenza [7].

The population's vulnerability to the influenza virus influences how each influenza season evolves in terms of severity, vaccination uptake, and duration [5–8]. Although influenza vaccinations have become more widely available and of higher quality, and the benefits of the disease in terms of lessening its effects on health and the economy are widely acknowledged, the majority of nations do not utilize enough vaccines to effectively control influenza [7–9]. Regarding the region, the cold season of 2022/2023 was dominated by viral infections in the paediatric population in Bucharest, Romania [2,4,7–11]. The evolution of acute respiratory infections, influenza and severe acute respiratory infections, as presented by the National Institute of Public Health from the Ministry of Health, Romania, reports at the end of February 2023, 81 deaths were due to influenza, and of these 2 are in the pediatric population aged between 0-1 years [7,9,10,12].

The total number of cases of acute respiratory infections in the first week of October 2022 (flu, pneumonia and acute upper respiratory tract infections), is increasing compared to the previous year. We saw an unexpected increase in influenza infections following two years (2020 to 2022) in which the virus had stopped spreading in our nation [13].

Oseltamivir usage is effective and secure in large observational studies [10–14]. Hospitalized adults showed substantial decreases in severe outcomes; however, these benefits were less and not statistically significant in children [13,14]. For many reasons, including safety concerns, oseltamivir is still disputable in some groups [14–16].

Influenza is a difficult-to-control seasonal respiratory virus due to its high degree of infectivity and the severe potential it can cause in certain population groups (infants, children and the elderly with comorbidities, immunosuppressed) [17–19]. Trivalent or quadrivalent inactivated vaccines are the only effective means of preventing seasonal influenza infection [20,21]. When it comes to preventing influenza infection, chemoprophylaxis medication shouldn't be utilized in place of the seasonal influenza vaccination [22–24]. The Romanian Ministry of Health advises influenza vaccine, especially for elderly individuals, small children, and those with weakened immune systems who are most at risk of influenza-related complications. The classic influenza-like sickness symptoms, including fever, sore throat, cough, headache, muscle and joint pain (especially in children), and severe malaise, are present in 20% to 40% of cases of influenza [25]. There are notable distinctions in flu symptoms in younger and older children, even though they may share many of the same symptoms. Infants and newborns can develop unexplained high temperatures [26]. Young children may develop convulsions, or febrile seizures when their body temperature rises above 39.5°C. In young children, the flu is a major contributor to lung infections, bronchiolitis and croup. In older children, stomach upsets, vomiting, diarrhea, and abdominal discomfort are more prevalent, and earaches are also more frequently reported [27]. Moreover, severe clinical symptoms and complications, including rhinosinusitis, pneumonia, myocarditis, encephalitis, gastroenteritis, otitis, and acute respiratory distress syndrome, are typically associated with seasonal influenza infections

 doi:10.20944/preprints202408.1126.v1

in children. These outcomes lead to notably elevated rates of hospitalization and mortality in children [25–29].

The variations of specific influenza types in the pediatric population show a direct relationship with the symptoms in children. Higher attention was seen for influenza A symptoms in comparison with B influenza, the fact that the B virus presents a limited higher level of severity and could be less virulent than Influenza Type A. While influenza A and B viruses can lead to hospitalization and various difficulties in children, type A Influenza is generally believed to cause more severe infections than type B viruses [30]. Children with influenza A are often younger than those with influenza B and since the illness's clinical presentation differs depending on age group, all results when comparing the severity of influenza A and B infections in children should be adjusted by age [28–31].

Oseltamivir, an oral administration neuraminidase inhibitor, has been the most often prescribed medication for the treatment of influenza, in children, since the year 2000, when was approved by the Food and Drug Administration (FDA) [2,9,11,26–28,30,31]. As a prodrug of oseltamivir carboxylate, its mechanism of action is to inhibit the release of the virus from the infected host cells and to reduce the spread of influenza virus in the respiratory tract. Neuraminidase inhibitors including zanamivir, laninamivir, and peramivir, have a fast beginning of action results in clinically substantial decreases in the length and intensity of symptoms, and it can be taken within a 1- to 2-day therapy window from the onset of symptoms. For pediatric influenza patients, oseltamivir medication effectively reduces the duration until symptoms subside [3,11,29–32], as well as the rate of hospitalization and complications, including pneumonia, acute otitis media, rhinosinusitis, myocarditis, encephalitis, gastroenteritis, and acute respiratory distress syndrome, [4]. Children treated with oseltamivir have also been shown to have antiviral-resistant strains [6–9,30–33].

Neuraminidase inhibitors, such as zanamivir, laninamivir, and peramivir, have a rapid onset of action that leads to significant reductions in the duration and severity of symptoms. Treatment with a neuraminidase inhibitor has been demonstrated to be successful in reducing the risk of fatalities and serious sequelae if initiated within two days of the beginning of symptoms, and in certain cases, even later [4]. These inhibitors can be given within a one to two-day therapeutic and effectively shorten the time it takes for symptoms to go away [31–34], and it also lowers the rate of hospitalization and complications [30–34], such as pneumonia, acute respiratory distress syndrome, myocarditis, encephalitis, gastroenteritis, and acute otitis media. Antiviral-resistant variants of the virus have also been found in children receiving oseltamivir treatment [34–36].

Nevertheless, the influenza burden persists as a large number of youngsters are still unvaccinated despite many vaccine recommendations from the World Health Organization for the risk groups population including children aged 6 months to 5 years, and people with specific comorbidities. In Romania, the Ministry of Health offers free of charge influenza vaccine for children aged 6 months to 59 months for vaccination in the eligible category in family doctor`s offices and pharmacies. During the 2022-2023 and 2023-2024 influenza seasons, the tetravalent influenza vaccine was available, with the antigenic composition recommended by the WHO, but the coverage across all populations was very low [31–33,37]. Influenza diagnostic tests are crucial because they enable the confirmation of the illness's existence and facilitate the implementation of targeted treatment [31,33,35–38].

Our study aimed to assess the clinical efficacy and tolerability of oseltamivir in children who have not received vaccinations and have various influenza virus types and subtypes in two consecutive influenza seasons in Romania and to offer more information about comorbidities associated with influenza in children.

2. Materials and Methods

We performed a single centre observational study of epidemiological, clinical and adverse events recorded of children aged ≤18 years who were infected with influenza A or B and required hospitalization between 1st October 2022 and 30th May 2023 and 1st October 2023 and 4th of May 2024. A clinical diagnosis of influenza was made based on the presence of a fever together with one or more of the following symptoms: sore throat, nasal congestion, pharyngeal erythema, upper

 doi:10.20944/preprints202408.1126.v1

respiratory tract symptoms (cough, rhinorrhea) headaches, myalgia, arthralgia, weakness, watery eyes, nausea, vomiting, and diarrhea. Pediatric patients with a clinical diagnosis of influenza were confirmed with polymerase chain reaction (PCR) for Influenza and included in the study. We utilised the AllplexTM Respiratory Panel 1 kit from Seegene in Seul, South Korea, and the GenXpert equipment from Cepheid, Sunnyvale, California, real-time RT-PCR to detect influenza A and influenza B in the pediatric group included in this investigation. The Ethics Committee of the National Institute of Infectious Disease "Prof. Dr. Matei Bals," located in Bucharest, Romania, approved all ethical problems, registration number C03608/05/04/2024.

We extracted data for demographic characteristics such as age, gender, and information from a past medical history including co-morbidities, medications, symptoms and signs of disease. We identified complications such as pneumonia, bronchitis, otitis, sinusitis, or other respiratory tract infections. When pediatric patients with comorbidities were hospitalized with influenza, we found that the outcomes varied. The following comorbidities were examined concerning the severity of influenza illness requiring hospitalization and length of hospital stay. The main comorbidities were overweight and obesity Class 1, dermatological diseases (atopic dermatitis, allergies), asthma and respiratory diseases such as chronic lung disease.

When assessing body fatness in children aged 2 to 20 years old, body mass index (BMI), is calculated using the formula weight/height^2; kg/m^2) [37]. Oseltamivir was administered orally for 5 days, 2 × 75 mg/day for patients weighing ≥37.5 kg, and 2 mg/kg/day for those weighing <37.5 kg.

The time of the onset of fever, time of administration of oseltamivir and time of resolution of fever were recorded. A temperature of 37.5 C was considered a fever. The patient`s body temperature was measured twice times per day (8 am, and 8 pm). When we found a lower temperature than 37.5C and maintained it for 24 h was defined as the time when the patient became afebrile. The cure was defined as the remission of all signs and symptoms used for clinical diagnosis.

The following statistical measures were computed: means, medians, and ranges for continuous variables, and counts and percentages for categorical variables. The Chi-squared test is used to compare frequency/percentage presentations of categorical variables, and the Student's t-test for continuous variables (n%). We performed a linear regression analysis to examine whether there was an association between the above variables and the duration of hospitalization in children with comorbidities. Multivariate logistic regression models included variables that were substantially correlated with the prescription of oseltamivir. Regardless of their correlation with problems or prescriptions for oseltamivir in the univariate analysis, diabetes mellitus, obesity, chronic respiratory illness, high-risk patients, and age were included in the multivariate analyses. A p-value less than 0.05 was defined to indicate statistical significance. The statistical evaluation was done in GraphPad, USA.

Written informed consent was obtained from the parents of minor children included in this study.

3. Results

A total of 1300 pediatric patients enrolled in this study, during the two following Influenza seasons, 2022-2023 and 2023-2024, met the inclusion criteria and tested positive for influenza and all were treated with Oseltamivir. The demographic characteristics of the pediatric patients are summarized in Table 1. Of the group hospitalized in season 2022-2023, 89% (704/791) had influenza A viral infection with 86.4% subtypes A(H1N1)pdm09, 13.6% of cases had A(H3N2), and influenza B had 11% (87/791) pediatric patients. 59% were male, and the median age was 2,4 years IQR (1.02-9.28). In patients hospitalized between 2023-2024 influenza season, 509 pediatric patients tested positive for influenza. 56.9% were male gender. Median age was 2,7 years, IQR (2.01-10.4). 81.6 % had Influenza A, with 83,4% subtype A(H1N1)pdm09, 16,6% of patients had subtype A(H3N2). 18.4% had influenza B.The patients arrived at the hospital median of two days (IQR, 1-4) following the beginning of symptoms. In the majority of age categories, the ratio of males was significantly greater than that for female cases. The demographic data of the index cases in the pediatric population are listed in Table 1. Regarding the distribution in the pediatric population of the number of cases of

 doi:10.20944/preprints202408.1126.v1

influenza, most cases of Influenza A(H1N1) were predominant (83.4%), and Influenza B, is more frequent in the 2023-2024 season in the 15-18 age group. There were differences in terms of gender criteria, the male part represented a percentage of 56.9% of total pediatric patients.

Table 1. Characteristics of patients with RT-PCR confirmed for Influenza; categorical data: n (%).

Characteristics	Overall n (%) 1300 (100)	Influenza A(H1N1) 2022-2023 season n (%) 608 (86.4)	Influenza A(H3N2) 2022-2023 n (%) 96(13.6)	Influenza B 2022-2023 n (%) 87(11)	Influenza A(H1N1) 2023-2024 n (%) 346 (83.4%)	Influenza A(H3N2) 2023-2024 n (%) 69(16.6%)	Influenza B 2023-2024 n (%) 94(18.4%)	p-value
Age: years old								
0-1	161(12.4)	60(9.8)	5(5.6)	2(2.7)	39(11.3)	6(8.9)	2(1.7)	
2-4	537(41.3)	227(37.3)	27(28.3)	13(14.6)	92(26.5)	16(23.6)	12(13.2)	
5-14	338 (26)	141(23.2)	34(35.2)	34(38.8)	120(34.7)	23(32.8)	42(44.2)	0.12
15-18	264(20,3)	180(29.7)	30(30.9)	38(43.9)	95(27.5)	24(34.7)	38(40.9)	
Gender (%)								
Female	560(43.1)	281(46.2)	44(45.3)	37(42.9)	150(43.5)	31(44.3)	40(42.1)	0.12
Male	740(56.9)	327(53.8)	52(54.7)	50(57.1)	196(56.5)	38(55.7)	54(57.9)	
Symptoms								
Fever	1222(94%)	600(98.68)*	85(88.54)	80(91.95)#	314(90.75)	63(91.3)	80(85.1)#	0.05#; 0.01*
Cough	1157(89%)	598(98.36)*	85(88.54)	47(54.02)	312(90.17)	60 (87)	55 (58.51)	0.13;0.01*
Weakness	832(64%)	342(56.25)	49(51.04)	74(85.05)	262(75.72)	27 (39.13)	78 (83)	0.10
Nasal congestion	598(46%)	218(35.86)	53 (55.2)	51(58.62)	181(52.31)	30 (43.48)	65 (69.15)	0.14
Sore throat	728(56%)	345(56.74)*	44(45.83)	43(49.43)	182(52.6)	31 (45)	64 (68)	0.2;0.005*
Headache	562(43.23%)	189(14.54)	40(41.67)	32(36.78)	203(58.67)	42(60.86)	56 (59.57)	0.3
Myalgia	561(43.15%)	132(21.71)*	35(36.46)	80(91.95)	231(66.76)	43 (62.32)	40 (42.55)	0.07
watery eyes	375(28.85%)	182(29.93)	23(24)	15(17.24)	102(29.5)	21 (30.43)	32 (34.04)	;0.0011*
nausea	272(20.92%)	107(17.6)	12(12.5)	21(24.14)	80(23.12)	27(70)	25 (27)	0.13
vomiting	677(52.08%)	308(50.66)	32(33.33)	42(48.28)#	210(60.7)	29 (42.03)	56 (59.57)#	0.12
diarrhea	575(44.23%)	274(45.07)	21(21.88)	74 (85)#	109 (31.5)	32 (46.38)	65(69.15)#	0.01# 0.05#
Complications n(%)								
Pneumonia	643(49.46)	328 (53.95)	56(58.33)	76(87.36)	87(25.14)	42 (60.86)	54(57.45)	
Sinusitis	440(33.84)	187(30.76)	46(47.92)	44(50.57)	121(34.97)	14(20.29)	28(29.79)	
Bronchitis	508(39.08)	279(45.89)	35(36.46)	39(44.83)	101(29.19)	22(31.88)	32(34.04)	

 doi:10.20944/preprints202408.1126.v1

Pharyngitis	407(31.31)	126(20.72)	67(69.79)	70(80.46)	110(31.79)	25(36.23)	9(9.57)	
Acute otitis media	417(32.08)	200(32.89)	30(31.25)	39(44.83)	98(28.32)	26(30.43)	24(25.53)	
Gastrointestinal disorders	649(49.92)	309(50.82)	55(57.29)	48(55.17)	180(52.02)	21(30.43)	36(38.29)	

Fever (94 %) and cough (89 %) were the most commonly reported symptoms, and myalgia was associated with Influenza B in the 2022-2023 season. The presence of fever, vomiting and diarrhoea were associated with statistical significance in the multivariate analysis ($p<0.001$) in patients with Influenza B, in both seasons, for clinical diagnosis. (#). Influenza A(H1N1) diagnosis is associated with fever, cough, sore throat and myalgia. (*)($p<0.05$).

We found complications in the total group (e.g., Gastrointestinal disorders in 49.92%, pneumonia in 49.46%, bronchitis, in 39.08%.). These were differently distributed between patients, and during the 2023-2024 Influenza season, the complications were lower than previous group. (See Table 1).

Table 2. Association of different comorbidities with influenza-related duration of hospitalization.

Hospitalisations (IQR) Comorbidities	Median Days of Median Days (IQR) No	Yes	p-Value
Obesity **0.001**	4(1–5)	7 (5-7)	
Endocrine or metabolic diseases 0.79	3 (1–4)	4(2–6)	
Asthma **0.02**	4(1–4)	9 (8–10)	
Respiratory disease 0.077	3 (2–4)	4 (2–6)	
Blood disorders 0.78	2 (1–6)	3 (2–5)	
Gastrointestinal disorders **0.089**	4 (1–6)	5(1–5.5)	
Eczema/ atopic dermatitis 0.46	2 (1–3)	3 (1–7)	
Renal disease 0.35	4 (1–6)	6 (2–7)	

Looking at the duration of hospitalisations among children with Influenza, we found three comorbidities with significant association. Obesity, asthma, and gastrointestinal disorders have the median days of hospitalisations longer than children without comorbidities. The median days of hospitalisations were statistically significant and longer among children with asthma (9 days vs. 4 days, $p = 0.02$); children with obesity were also significantly longer (7 days vs. 4 days, $p = 0.001$). The median hospitalization for children with Influenza and gastrointestinal comorbidity was longer (5 days vs 4 days, $p=0.089$).

We performed a linear regression to identify the association between influenza hospitalization and demographic characteristics (gender) of pediatric patients who had comorbidities. Children 5-14 years old and 15-18 years old were more likely to be admitted with influenza if they suffered from obesity (OR: 2.14; 95% CI: (0.21–20.42); $p=0.01$, and respectively (OR:12.85; 95% CI: (3,23-43.44);$p=0.03$. We also found statistical significance in children with asthma OR:12.34; 95% CI: (6,54-19.03); 0.0112,

 doi:10.20944/preprints202408.1126.v1

for the 5-14 age group. The most common comorbidity was gastrointestinal disorders for 2-4 years, OR:12.75; 95% CI (5.33-13.21);p=0.05. (see Table 3). Looking at gender, males with 2-4 years old and 5-14 old group had a significant association with influenza hospitalization.

Table 3. Association between comorbidities and hospitalizations for Influenza in children, by age group and gender. OR (95% CI), p-Value.

Variables	Age 0-1 years old	2-4 years old	5-14	15-18
Comorbidities				
Obesity	-	2.21(4.23-13.32);0.5	**2.14(0.21–20.42); 0.01**	**12.85(3,23-43.44);0.03**
Endocrine/metabolic disease	-	-	3.14(2.456-9.012);0.21	-
Asthma	-	-	**12.34(6,54-19.03);0.0112**	9.67(3.23-22.75);0.07
Respiratory disease	-	14.44(10..92-23.12);0.11	2.52 (0.15–13.24); 0.10	12.24(8,68-21.75);0.123
Gastrointestinal disorders	9.31(4.244-15.65);0.123	**12.75(5.33-13.21);0.05**	14.43(12.23-32,33);0.5	2.33(6.01-12.07);0.15
Renal disease	-	-	12(2.90-22-07);0.77	-
Atopic dermatitis	1.23(1.23-5.96);0.09	12.44(8.97-19.23);0.86	-	1.23(2.12-21.05);0.6
Gender Male Female	1.44(2.01-11.03);0.14 10.95(3.47–34.3);0.12	**15.45(2.59–89.87);0.03** 11.24(8.47-19.97);0.5	**8.63(2.34–3.01);0.01** 6.91(1.44-13.23);0.12	15.56(3.34-23.98);0.9 8.77(2.25-31.32);0.5

The treatment performed in the pediatric population with Oseltamivir alone, and the one associated with Antibiotic and Dexamethasone, had statistical significance when we compared this therapeutic combination between the types and subtypes from the two Influenza seasons (2022-2023 and 2023-2024 group). Patients who had changes in the laboratory analyses including C-reactive protein (CRP) show significant differences in values for A influenza (i.e., AH1N1 season 2022-2023 vs. AH1N1 in 2023-2024 (p=0.021). Hemoglobin (p=0.001), Aspartate Amino Transferase (AST)(p=0.05), and Alanine Amino Transferase (ALT) show a significant difference for B influenza when compared with A influenza (p=0.01).

The length of hospitalization is statistically significant in terms of the two consecutive seasons for both influenza A and B. We evaluated the median duration of hospitalization and recovery rates among those two groups treated with oseltamivir (See Table 4).

Table 4. Characteristics of patients by RT-PCR, treatment, laboratory parameters; categorical data: n (%).

Parameters	Influenza A(H1N1) 2022-2023 season n (%)608 (86.4)	Influenza A(H3N2) 2022-2023 n (%) 96(13.6)	Influenza B 2022-2023 n (%) 87(11)	Influenza A(H1N1) 2023-2024 n (%) 346 (83.4%)	Influenza A(H3N2) 2023-2024 n (%) 69(16.6%)	Influenza B 2023-2024 n (%) 94(18.4%)	p-value
Treatment n(%) **Duration of hospitalization days n(IQR)**	5(3-6) 402(66.12)	4(2-5) 59(61.46)	7(1-7) 39(44.83)	5(4-6) 214(61.85)	4(3-5) 17(24.64)	6(2-6) 18(19.15)	**0.01** **0.001**

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Oseltamivir	124(20.4)	22(22.91)	31(35.63)	49(14.16)	29(42.65)	14(14.89)	0.11
Oseltamivir and Dexamethasone							
Oseltamivir, Dexamethasone and Antibiotics	82(13.49)	15(15.63)	27(31.03)	83(24)	41(42.03)	32(34.04)	**0.001**
Laboratory n (%)							
AST, U/L>5xnormal values.	124(20.39)	76(60.32)	38(67.86)	24(6.94)	12(17.39)	36(53)	**0.05**
ALT, U/L >5xnormal values,	136(22.37)	89(92.71)	45(51.72)	42(12.14)	43(62.32)	21(22.34)	**0.01**
Haemoglobin	216(35.53)	70 (55.5)	36(64.3)	22(6.36)	29(42.03)	32(47.1)	**0.001**
Leukocyte	112(18.42)	67(69.79)	65(74.71)	24(6.94)	56(81.16)	18(19.15)	0.31
Lymphopenia	98(16.12)	34(27)	21(37.5)	14(4.05)	17(24.64)	12(17.6)	0.32
Neutrophilia	109(17.93)	23(23.96)	11(12.64)	32(9.25)	23(33.33)	13(13.83)	0.1
Low Thrombocyte	98(16.12)	37(29.4)	14(25)	33(9.54)	35(50.74)	21(30.9)	0.11
High Prothrombin time	123(20.23)	76(60.32)	44(78.6)	21(6.07)	29(42.03)	30(44.12)	0.23
LDH elevated	234(38.49)	51(40.5)	28(50)	40(11.56)	32(46.38)	22(32.35)	0.31
CRP elevated	112(18.42)	55(43.65)	32(57.14)	42(12.14)	44(63.77)	21(30.88)	**0.021**

In the 2022-2023 group,6.19% of 509 hospitalized children with obesity were hospitalized with a median of 14 days, vs 7 days for 16.9% 2023-2024 group of 509 pediatric patients. (p=0.001).

The median duration of hospitalization was also shorter in the oseltamivir group from the 2023-2024 influenza season with asthma than in the 2022-2023 similar group (p = 0.05).

After the onset of Oseltamivir, all pediatric patients evolved favourably, and no child died. After initiating treatment with oseltamivir, it was not necessary to interrupt its administration due to adverse reactions. Even if appeared during the treatment (diarrhoea 9%, nausea 11% of the total group) they were tolerated after the administration of the symptomatic medication**.**

4. Discussion

In our observational study, we enrolled a large number of pediatric patients, divided into Influenza A and Influenza B into two consecutive seasons after the COVID-19 pandemic. This study showed that a significant proportion of hospital admissions in pediatric patients are caused by influenza. The efficacy of oseltamivir was compared and showed a reduction in the duration of illness and hospitalisations. Regardless, the advantages of using oseltamivir need to exceed the disadvantages in terms of side effects and efficacity, as our study demonstrates. As the pandemic years and the COVID-19 illness have passed, it seems that the number of complications in pediatric influenza cases has decreased. However, the number of complications is higher than in the previously published studies, possibly as a result of having noted that all of the included patients in both groups studied in our clinic were not vaccinated against Influenza [31–34,37–40]. Our pediatric patients spent a median of four days in the hospital, in patients without comorbidities, and all of them got antiviral therapy while hospitalization. The study examined the correlation between the severity of influenza-related hospitalization and the duration of hospital stay among the following comorbidities: endocrine or metabolic disorders, asthma, respiratory, renal, gastrointestinal, and blood disorders, and eczema/atopic dermatitis. We also found that the longest hospitalization was in pediatric patients with Asthma and influenza. Similarly, other studies reported an increased number of lengths of stay in hospital due to comorbidities, including asthma [28,30,32]. There was no proof that oseltamivir made participants with asthmatic bronchoconstriction worse, as we compared the pediatric patients

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without comorbidities for the duration of hospitalization. Conversely, there was proof that children treated with oseltamivir returned to normal peak flow rates more quickly in the group hospitalized between the 2023-2024 Influenza season [16,19,26,28,39,41]. Importantly, children with obesity, in age groups 5-14 and 15-18 years old, had higher admission rates with influenza. Similar studies found that obesity is an independent risk factor for other viral diseases, including COVID-19, and also the severity of these diseases [41–43]. We recorded the median duration of hospitalization and recovery rates among those treated with oseltamivir alone and patients treated with oseltamivir associated with Dexamethasone alone, or in combination with Dexamethasone and Antibiotics between two consecutive Influenza seasons. In the group, with Influenza B, the recovery rates and duration of hospitalization were the longest, and with a plus for the 2022-2023 Influenza season.The recovery rate was greater in the 2023-2024 group than in 2022-2023 in the oseltamivir group with comorbidities, such as asthma, chronic pulmonary disease and obesity. ($p =<0.05$), which was similar to other studies [28,31,41–43]. The following comorbidities were the most common in the study group: respiratory-related diseases followed by nutritional and metabolic diseases (obesity). Our study provides the largest comparative analysis of oseltamivir using a large cohort of the study group of children, with laboratory-confirmed influenza. Data from our study based on hospitalization registers reported the incidence of Influenza in children below 18 years of age, and it should be mentioned that the data from this study can help make national decisions to reduce the risk of influenza complications, especially in children with comorbidities. One of the most important ways to reduce the risk is to prevent Influenza by vaccinations, with special attention in young children. Previous studies have revealed cases of dual influenza and bacterial coinfections in children [17,20,26]. In pediatric populations, coinfections between influenza and bacterial illnesses have been shown to happen 30–50% of the time [31,34]. A subsequent bacterial infection frequently coexists with or follows an influenza illness [21,22]. Antiviral and antibiotic treatments are advised in this situation to treat the coinfection of influenza and bacteria [32]. Because of this, the subgroup analyses of hospitalized children who received anti-influenza medication or who did not get conventional antibiotics were the main focus of our subsequent subgroup studies. There have been no new safety concerns found, and the safety profile shown in children under the age of 18 was very comparable to that previously seen in other studies [6,12,16]. Our findings support earlier research [5,15,17,20] in showing that younger children had a higher risk of respiratory virus infection than older children. Influenza virus was discovered in children between 2-4 years of age more frequently than in any other age group. As mentioned earlier, the majority of children infected with Influenza, A or B, had fever, myalgia, rhinitis, and cough [16–19], while the reports of concurrent gastrointestinal symptoms were appreciable in Influenza B in age category 5-14 and 15-18 years old [20]. Furthermore, in line with other studies, we did find appreciable variations in the clinical symptoms of the various viruses. Clinical similarities between children infected with Influenza A or B were found in similar studies [30]. Against Influenza viruses are effective preventative measures and treatment options available. Every year, a potent influenza vaccination becomes available. Nonetheless, only 7% of the Romanian population gets vaccinated, both in adult and pediatric populations [38]. Oseltamivir, an effective antiviral medication, can be provided to children with influenza virus infection if it is discovered during the first 48 hours of symptoms or if hospitalization is necessary [26]. Through follow-up studies, the clinical safety of oseltamivir has been thoroughly examined. Oseltamivir is suitable for treating influenza in pediatric populations; no significant safety concerns have emerged that limit its use. Similarly, when given for the purpose of chemoprophylaxis against influenza in adolescents, oseltamivir is well tolerated [31,33,41,42]. Oseltamivir is a valuable supplement to current influenza treatments for the control of influenza in communities, all the influenza viruses isolates had a normal inhibition of neuraminidase activity to oseltamivir. Also, the effectiveness of the treatment in the pediatric population, from one season to another is obvious. Otherwise, our study presents some limitations. Because the vaccination rate in our country is low, among pediatric patients, the comparative batch of vaccinated children could not be presented here. Other antiviral agents were not included in this comparative study, but the work will continue in the influenza viral seasons of the following years [36,41–43].

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5. Conclusions

Our findings suggest that influenza predominantly impacts children, and that virus strains in each season may be slightly different, and influenza hospitalization incidence among children aged <18 years in Romania can be related to age, comorbidities, seasons, duration of hospitalization and symptoms differences. The increasing trend in hospitalizations in recent years, which was observed in this study, indicates the urgent need to focus on influenza vaccination, especially in children with comorbidities. A long-term epidemiological study is needed to understand the changing features of influenza in Romania.

Author Contributions: Conceptualization, G.J., O.M.C.,M.L.L., C.P. and M.-M.M.; Methodology, G.J.; Software, G.J. and C.P.; Validation, G.J.,O.M.C., M.L.L., C.P. and M.-M.M.; Formal Analysis, C.P., G.J.; Investigation, G.J. and C.P.; Resources, G.J. and M.L.L.; Data Curation, G.J. and M.-M.M.; Writing—Original Draft Preparation, G.J.; Writing—Review & Editing, G.J., O.M.C.,M.L.L., C.P. and M.-M.M.; Visualization, G.J. and C.P.; Supervision, G.J.; Project Administration, G.J., M.L.L., C.P. and M.-M.M.; funding acquisition. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by Bioethics Committee of the National Institute for Infectious Diseases "Prof. Dr. Matei Balș".

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets generated and analyzed during the current study are available from the corresponding author upon request.

Acknowledgments: Publication of this paper was supported by the University of Medicine and Pharmacy Carol Davila, through the institutional program Publish not Perish.

Conflicts of Interest: The authors declare no conflict of interest.

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