

# Effectiveness of early oseltamivir treatment in children with pandemic 2009 A/H1N1 influenza in the Vilnius University Children Hospital

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**Background.** Oseltamivir is recommended for treatment of pandemic influenza in children. The therapy should be started as soon as possible, however, data on the effectiveness of such a treatment is rather limited. This study was accomplished in order to evaluate the effectiveness of oseltamivir depending on the time of the beginning of treatment.

**Materials and methods.** Medical records of 72 children hospitalised to the Vilnius University Children's Hospital (VUCH) because of laboratory confirmed pandemic influenza during November–December 2009 were analysed retrospectively. Duration of fever and frequency of complications in children treated with oseltamivir starting on days 1–2 and those who were started to treat  $\geq$  day 3 from the beginning of flu symptoms were compared to those who did not receive oseltamivir.

**Results.** 40 patients were treated with oseltamivir: 20 children were commenced on treatment within 48 hours of their illness and the other 20 were started on oseltamivir on day 3 or later. 32 children were not treated with oseltamivir. Fever lasted  $2.1 \pm 0.8$  days if the treatment with oseltamivir was started within 48 hours of illness and  $4.1 \pm 1.9$  days if the treatment was started later ( $p < 0.0001$ ). There were no complications in patients who were treated with oseltamivir within 1–2 days from the onset of flu symptoms; however, complications were recorded in 6 (30.0%) children who were commenced on treatment on day 3–7 of their illness ( $p < 0.01$ ).

**Conclusions.** Our data suggest that treatment of pandemic influenza A/H1N1 with oseltamivir in children is mostly effective when started within 48 hours from the onset of a flu-like illness.

**Key words:** influenza, pandemic, oseltamivir, children, paediatrics

## INTRODUCTION

In June 2009 the World Health Organization (WHO) declared the first influenza pandemic of

the 21st century. It was due to the fact that pandemic influenza A/H1N1 virus has spread rapidly resulting in lots of laboratory confirmed cases and over 18 000 deaths in over 200 countries (1). Influenza related children deaths were reported in many countries (2, 3). In Lithuania during the period of influenza pandemic the peak of morbidity was

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registered on week 48 (46–52) while annually the peak morbidity of seasonal influenza is reached on January–March (Fig. 1) (4, 5).

Development of sufficient amount of vaccines for pandemic influenza takes time and it is not possible to deliver these vaccines for all regions of the world at the beginning of the pandemic (6), therefore antiviral drugs played a significant role as the first line of defence during the H1N1 influenza pandemic. Two antiviral drug classes are available to treat influenza: M2 inhibitors (e. g. amantadine, rimantadine) and neuraminidase inhibitors (e. g. oseltamivir, zanamivir) (7). High level of resistance of circulating A/H3N2 influenza viruses to M2 inhibitors has been reported (8). A/H1N1 novel influenza virus is also resistant to M2 inhibitors, however, neuraminidase inhibitors, including oseltamivir, are active against pandemic A/H1N1 influenza virus (9).

During the 2009–2010 pandemic WHO recommended influenza treatment with neuraminidase inhibitors (oseltamivir or zanamivir). Oseltamivir was recommended as the first line drug and approved for use to all patient groups including children and neonates. Weight-based dosage of oseltamivir twice daily for five days was advised for influenza treatment in children (9).

Treatment with oseltamivir is the most effective when it is started within 48 hours from the beginning of the disease (10). European Centre for Diseases Prevention and Control (ECDC) has announced that people with more severe influenza ill-

ness, even if they are outside the 48-hour window, should be the priority group for oseltamivir treatment (9).

The aim of the study was to evaluate the effectiveness of oseltamivir depending on the time of starting antiviral therapy. Duration of fever and frequency of complications in children treated with oseltamivir starting day 1 or 2 of their illness and those who received antiviral treatment later ( $\geq 3$  days) was compared with analogous data in children who did not receive oseltamivir.

Dynamics of children hospitalisation to the Vilnius University Children's Hospital (VUCH, recently – Children's Hospital, Affiliate of Vilnius University Hospital Santariskiu Clinics) because of flu-like disease in the 2009–2010 flu season was retrospectively analysed using the data of VUCH.

Medical records of 72 children with pandemic influenza hospitalised to VUCH during November–December were analysed. Data on demographics, their clinical history, symptoms and findings from physical examination, results of laboratory tests and the clinical course during the hospital stay was collected.

Influenza A/H1N1 virus infection in all these patients was confirmed by the reverse transcription-polymerase chain reaction (RT-PCR) at the Laboratory of the Centre for Communicable Diseases and AIDS of Lithuania which is the National Laboratory of Lithuania in Influenza Surveillance System.

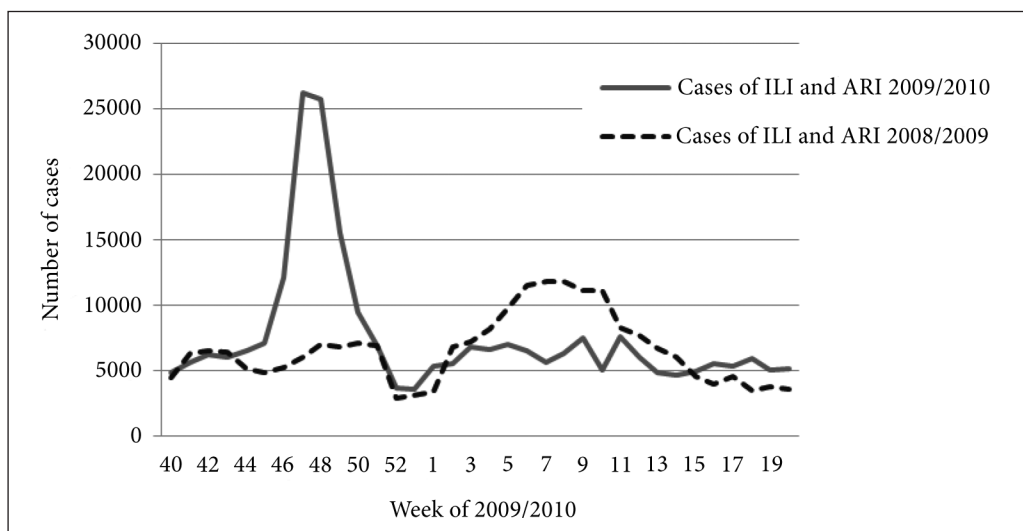


Fig. 1. Number of cases of influenza like illness (ILI) and acute upper respiratory illness (ARI) during 2008/2009 and 2009/2010 influenza seasons in Lithuania

The effectiveness of oseltamivir was evaluated comparing duration of fever and frequency of complications between those who were treated with oseltamivir according to antiviral treatment initiation and those who were not treated.

## RESULTS

In Lithuania during last influenza seasons before the pandemic of 2009/2010, the peak of influenza was from January to March (Fig. 1). The first case of pandemic influenza A/H1N1 at our hospital was registered in June 2009 and it was related to the travel to Latin America where this virus was already present. Several single cases, mostly related to travel, were also hospitalised later. The steep rise of the hospitalisation rate began on October 2009 with a peak on November (Fig. 2).

At the first stage of this rise all patients with suspected flu were sampled and RT-PCR was performed. In November 113 patients were sampled and 63% of them were positive for pandemic A/H1N1. In December the number of samples was reduced as A/H1N1 was proven to be the main circulating virus. The number of hospitalizations was still high in December, however, only 41 patients were sampled and only 17% of samples were A/H1N1 positive.

Subset of 72 children with RT-PCR proven A/H1N1 influenza was included into analysis of effectiveness of antiviral treatment. All children were

hospitalised within 1 to 7 days (mean  $2.3 \pm 1.5$ ) from occurrence of the first symptoms.

All children were divided in two groups: the first group was not treated with antiviral drugs ( $n = 32$ ) and the second group ( $n = 40$ ) was treated with oseltamivir according to WHO recommendations. For 20 out of 40 children from the second group the first dose of oseltamivir was given within 48 hours from beginning of the first flu symptoms and for the rest 20 patients oseltamivir treatment was started  $\geq 3$  day from the beginning of the disease. Apart from oseltamivir, standard treatment according to the protocol of our clinic was given to all patients included in the study.

Selected characteristics of all patients are shown in Table 1. The youngest child was 6 months and the oldest one was 17 years of age (mean age  $6.8 \pm 5.6$  years). There were 24 children aged 1–4. Underlying medical conditions were recorded in 6 children (4 children with bronchial asthma and 2 with congenital pathology), 2 of whom were not treated with oseltamivir. None of our patients received pandemic A/H1N1 2009 vaccination.

On admission 66 (91.7%) patients had influenza-like symptoms (e. g. cough, sore throat, malaise, headache, rhinitis), 4 (5.5%) had gastrointestinal symptoms (e. g. diarrhoea and vomiting) and for two (2.8%) children influenza pneumonia was diagnosed. All children had fever. The highest measured temperature was as follows:  $\geq 39.1$  °C – 40 children, 38.1–39 °C – 31 children and  $< 38$  °C – 1 child.

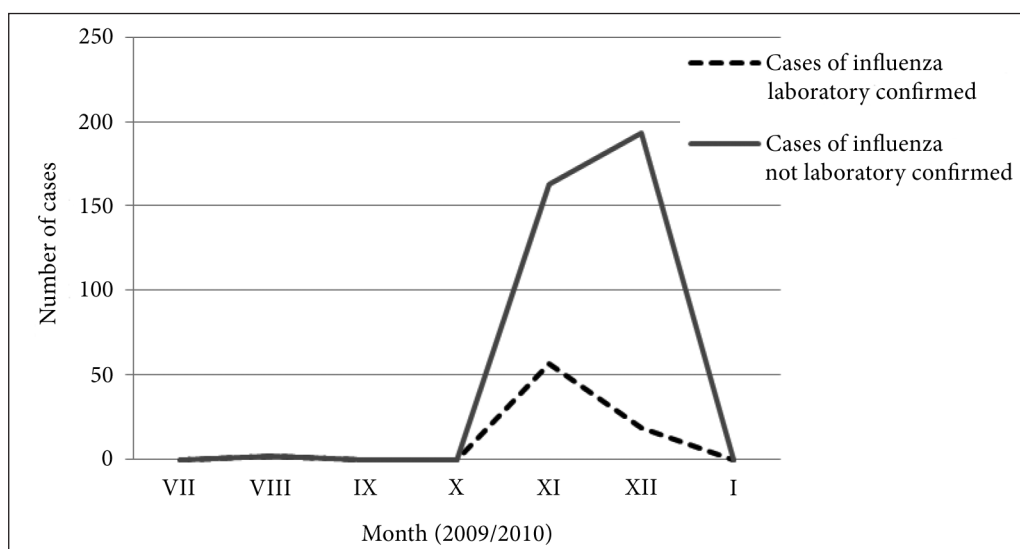


Fig. 2. Number of cases of influenza laboratory confirmed and not confirmed in VUCH during the 2009/2010 influenza season

**Table 1.** Demographical and basic clinical data of children included into the analysis

Characteristic	Total, %	Oseltamivir- non treated	Oseltamivir- treated	The beginning of oseltamivir therapy	
				1–2 d. o. s.	3–7 d. o. s.
Number of patients, %	72 (100)	32 (100)	40 (100)	20 (100)	20 (100)
Age, years (mean $\pm$ SD)	6.8 $\pm$ 5.6	10.1 $\pm$ 5.3	4.1 $\pm$ 4.2	3.5 $\pm$ 3.6	4.7 $\pm$ 4.8
Range of age	6 mos–17 yr	7 mos–17 yr	6 mos–14 yr	6 mos–12 yr	6 mos–14 yr
Number of infants, %	9 (12.5)	1 (3.1)	8 (20.0)	3 (15.0)	5 (25.0)
Boys, %	49 (68.1)	25 (78.1)	24 (60.0)	12 (60.0)	12 (60.0)
Underlying medical conditions, %	6 (8.3)	2 (6.3)	4 (10.0)	1 (5.0)	3 (15.0)
Mean duration of time from the first symptoms of influenza until hospitalization, days	2.3 $\pm$ 1.5	2.5 $\pm$ 1.5	2.1 $\pm$ 1.5	1.4 $\pm$ 0.5	2.8 $\pm$ 1.8
Mean duration of fever from the first symptoms until hospitalization, days	1.8 $\pm$ 1.5	2.0 $\pm$ 1.6	1.7 $\pm$ 1.3	1.1 $\pm$ 0.2	2.4 $\pm$ 1.6
Treated in PICU, %	4 (5.6)	3 (9.4)	1 (2.5)	1 (5.0)	0 (0)
Mean duration of hospitalisation, days	4.4 $\pm$ 1.9	3.9 $\pm$ 1.4	4.8 $\pm$ 2.2	4.3 $\pm$ 2.0	5.4 $\pm$ 2.3

d. o. s. – days from the beginning of symptoms, SD – standard deviation, mos – months, yr – years, PICU – Paediatric Intensive Care Unit.

The mean duration of fever (before and during the hospitalization) in the children who received oseltamivir was  $3.1 \pm 1.7$  days, and in the children who were not treated with oseltamivir it was  $3.7 \pm 1.6$  days. Duration of fever was shorter in the oseltamivir treated group as compared to the not treated group, but this difference was not statistically significant ( $p > 0.05$ ). Early beginning of antiviral treatment had an important influence on the effectiveness of this treatment. Duration of fever in the children to whom oseltamivir treatment was started within 48 hours from the first symptoms was  $2.1 \pm 0.8$  days and it was statistically significantly ( $p < 0.0001$ ) shorter as compared to duration of fever ( $4.1 \pm 1.9$ ) in the patients to whom this treatment was started later.

In 9 or 12.5% out of 72 study patients complications (secondary bacterial pneumonia, otitis media, epistaxis, pyelonephritis) occurred and there was no difference in frequency of complications between oseltamivir treated and non-treated children, however, in the oseltamivir treated group all 6 complications occurred in the children to whom treatment was started on days 3–7 from the first symptoms and no complications were observed in the patients who were given oseltamivir within

1–2 days from the first symptoms ( $p < 0.01$ ). The effectiveness of oseltamivir for the children with influenza A/H1N1 is shown in Table 2.

## DISCUSSION

“Spanish flu” pandemic of 1918–1919 is reported as the deadliest public-health crises in human history killing estimated 50–100 million people worldwide (11). During that pandemic three morbidity waves were indicated: the first occurred in the Northern Hemisphere during spring–summer 1918 and was associated with high morbidity but low mortality, the two following waves (in summer–fall 1918 and winter 1918–1919) were both deadly (12). The latest 2009–2010 pandemic influenza also began in spring–summer and apart from a few countries (mainly the United Kingdom and Spain) most of the early experience with the pandemic was from outside Europe: North America and then the Southern Hemisphere (13). In Europe a relatively small spring/summer wave was registered and a much higher autumn/winter wave occurred, peaking around week 48/2009 (13). The weekly incidence of 2009–2010 pandemic influenza was different from seasonal influenza, which in Europe is

**Table 2.** Characteristics of oseltamivir-treated and oseltamivir-non treated children with laboratory confirmed influenza A/H1N1

Characteristic	Total n = 72	Oseltamivir- non treated <sup>(1)</sup> n = 32	Oseltamivir- treated <sup>(2)</sup> n = 40	The beginning of oseltamivir therapy		p-value (between studied groups shown in columns and num- bered in brackets)
				1–2 d. o. s. <sup>(3)</sup>	3–7 d. o. s. <sup>(4)</sup>	
				n = 20	n = 20	
Duration of fever, days (mean ± SD)	3.4 ± 1.7	3.7 ± 1.6	3.1 ± 1.7	2.1 ± 0.8	4.1 ± 1.9	p <sup>1-2</sup> > 0.05 p <sup>1-3</sup> < 0.0001 p <sup>1-4</sup> > 0.05 p <sup>3-4</sup> < 0.0001
Complica- tions, %	9 (12.5)	3 (9.4)	6 (15.0)	0 (0)	6 (30.0)	p <sup>1-2</sup> > 0.05 p <sup>1-3</sup> > 0.05 p <sup>1-4</sup> > 0.05 p <sup>3-4</sup> < 0.01

d. o. s. – days from the beginning of symptoms, n – number of patients, SD – standard deviation.

epidemic between October and March every season and in most recent years it has peaked early, usually around New Year (7).

WHO states that earlier treatment with antiviral medications is associated with better outcomes but they may also be used at any stage of active disease when ongoing viral replication is anticipated or documented (9). Very similar recommendations were prepared by Centers for Disease Control and Prevention (14).

Our study has revealed that oseltamivir brings the best results when it is started as soon as possible at the beginning of the illness. Comparing children who were commenced on antiviral treatment within 48 hours with those who got antivirals later than 48 hours, we found statistical validity of oseltamivir efficiency reducing the duration of fever and the frequency of complications. Although the administration of oseltamivir later than 48 hours was not beneficial, consequently only the administration of oseltamivir is not of big value, it is important to administer it early.

Early diagnosis of influenza can enable prompt initiation of antiviral therapy when it is most effective (15). The advantage of early oseltamivir administration was presented in the studies on pandemic influenza treatment accomplished in other countries. There was a study of 127 children performed in Spain which revealed that children who were given antivirals after 72 hours of beginning of their illness had a more severe disease (16). When analysing the deaths associated with the pandemic influenza A/H1N1 2009 among children in Japan, it was shown that before the

life-threatening event, 46% of patients received oseltamivir and 12% zanamivir, however, antivirals were given after confirmation of influenza by a rapid test performed within 2 days after the onset of fever (2). Results of this study might illustrate lower effectiveness of antivirals when beginning of treatment was delayed.

Studies comparing seasonal and pandemic influenza reveal that the course of pandemic influenza is more complicated because of higher prevalence of complications and deaths (17–19). The retrospective study comparing seasonal and pandemic influenza in children was conducted in Buenos Aires. The later study shows that among children who were diagnosed with pandemic influenza 25 (9.9%) children had bacterial pneumonia (confirmed or presumptive) with empyema developing in 4 of them and 13 (5%) children died (17). The study of 43 children performed in Australia during the pandemic influenza reveals that 5 patients (11.6%) were readmitted with complications including secondary pneumonia, ongoing and exacerbation of asthma, no deaths among these children were registered (20). In our study, the most frequent complication was otitis media. Because of small comparative groups we cannot state if there were more complications among children with underlying medical conditions. There were no death cases among the study participants.

Studies on influenza virus shedding accomplished in China, Singapore and Taiwan reported that earlier administration of antivirals decreases the duration of virus shedding (21–24). The study from Hong Kong demonstrated that oseltamivir is

more effective when initiated  $\leq 2$  days post-symptom onset as it reduces the duration of symptoms and viral load (21). The study from China suggests that oseltamivir reduces the risk of radiographically confirmed pneumonia, and early treatment within two days of the symptoms onset can reduce the duration of fever and viral RNA shedding (23). Although in the studies from China adults were included, almost half of the patients were children as they were very vulnerable to pandemic influenza.

## CONCLUSIONS

Our study confirmed that the treatment of the pandemic 2009 influenza A/H1N1 with oseltamivir in children was the most effective when started within 48 hours from the onset of influenza. During the influenza season antiviral treatment should be given as soon as flu-like symptoms are recognised in young children, even if laboratory confirmation is not available at this moment.

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Vytautas Usonis, Irena Narkevičiūtė, Vilija Guntaitė

## VAIKŲ, SERGANČIŲ PANDEMINIU A/H1N1 GRIPU IR 2009 M. GYDYTŲ VILNIAUS UNIVERSITETO VAIKŲ LIGONINĖJE, ANKSTYVO GYDYMO OSELTAMIVIRU VEIKSMINGUMAS

### *Santrauka*

**Įvadas.** Vaikų pandemiją gripą rekomenduojama gydyti oseltamiviru. Toks gydymas turėtų būti pradėtas kuo greičiau, tačiau labai trūksta objektyvių duomenų apie vaikų, sergančių patvirtintu pandeminiu gripu, gydymo veiksmingumą. Šio tyrimo tikslas – įvertinti oseltamiviro veiksmingumą priklausomai nuo jo paskyrimo laiko.

**Medžiaga ir metodika.** Retrospektyviai išanalizuotos 72 vaikų, 2009 m. lapkričio–gruodžio mėnesiais gydytų Vilniaus universiteto Vaikų ligoninėje (VUVL, šiuo metu – Vaikų ligoninė, Viešosios įstaigos Vilniaus universiteto ligoninės Santariškių klinikų filialas) dėl laboratoriniais tyrimais patvirtinto pandeminio gripo, ligos istorijos. Palyginta vaikų, kuriuos pradėta gydyti 1–2 ligos dieną ir  $\geq 3$  dieną, bei oseltamiviru negydytų vaikų karščiavimo trukmė ir komplikacijų dažnis.

**Rezultatai.** Oseltamiviru buvo gydyta 40 ligonių: 20 pradėta gydyti per pirmas 48 ligos valandas, kiti 20 – trečią ligos dieną ir vėliau. Oseltamiviru negydyti 32 vaikai. Pradėjus gydymą oseltamiviru per pirmas 48 valandas, karščiavimas truko  $2,1 \pm 0,8$  dienas, pradėjus gydymą vėliau –  $4,1 \pm 1,9$  dienas ( $p < 0,0001$ ). Vaikai, kuriuos pradėta gydyti per pirmas dvi paras, komplikacijų nepatyrė, tačiau jos pasireiškė 6 vaikams (30,0 %), kurių gydymas buvo pradėtas 3–7 ligos dieną ( $p < 0,01$ ).

**Išvados.** Mūsų tyrimo duomenimis, vaikų pandeminio gripo A/H1N1 gydymas oseltamiviru yra veiksmingiausias, kai pradėdamas per pirmas 48 ligos valandas.

**Raktažodžiai:** gripas, pandeminis, oseltamiviras, vaikai, pediatrija