

Association Between Oseltamivir Timing and Clinical Outcomes in Hospitalized Children with Influenza: A Retrospective Cohort Study

Hassan S Albohassan¹, Nadia Jradi², Aida Al Jabri¹, Hussain AlThani¹, Muhammed Ibrahim¹, Mohammed Ali Alomran²

¹Pediatric Department, Almoosa Specialist Hospital, Alahsa, Saudi Arabia; ²College of Medicine, King Faisal University, Hofuf, Saudi Arabia

Correspondence: Hassan S Albohassan, Email dr.binshaker@gmail.com

Background: Influenza is one of the most common viruses causing an acute course illness, mainly targeting the respiratory system. It is a communicable disease that spreads easily between individuals and is usually self-limiting in most cases. However, complications of influenza are numerous, including secondary bacterial infections, exacerbation of underlying respiratory conditions, and central nervous system-related complications. The risk of influenza-related hospitalization and complications is increased in children younger than 5 years and in those with underlying chronic diseases. Three classes of antiviral therapy are used in the treatment of influenza: neuraminidase inhibitors, adamantanes, and inhibitors of influenza cap-dependent endonuclease. Oseltamivir is considered the mainstay therapy for influenza treatment.

Objective: This study investigates the efficacy of early oseltamivir treatment compared to late treatment in improving recovery by reducing hospital length of stay and preventing influenza-related complications such as pneumonia, otitis media, and asthma exacerbations.

Methodology: This retrospective study analyzed data from 280 pediatric patients admitted to a tertiary care hospital between January 2020 and April 2023. Included patients were aged 1 month to 14 years, had laboratory-confirmed influenza A or B by polymerase chain reaction or point-of-care rapid testing, and received oseltamivir during hospitalization. Early oseltamivir treatment was defined as initiation within 48 hours of symptom onset, whereas initiation after 48 hours was considered late.

Results: The study included 151 (53.9%) males and 129 (46.1%) females. Children who received early oseltamivir treatment had a significantly shorter hospital length of stay of approximately one day (~16–19 hours) compared to those who started treatment after 48 hours [mean \pm SD: 3.28 \pm 1.46 vs 3.95 \pm 2.26 days; $P = 0.007$]. A weak positive correlation was observed between time to oseltamivir initiation and hospital length of stay ($r = 0.13$, $P = 0.02$). Early treatment was associated with a significantly lower incidence of pneumonia, otitis media, and acute asthma exacerbation compared to late treatment ($P < 0.05$ for all).

Conclusion: Early initiation of oseltamivir within 48 hours is effective in reducing hospital length of stay and preventing common influenza-related complications.

Keywords: influenza, oseltamivir, influenza-related complications, hospital length of stay

Introduction

Influenza is one of the most common viruses causing an acute course illness, targeting mainly the respiratory system. It is a communicable disease spread easily between individuals, usually with self-limiting course in most of cases.¹ Seasonal influenza accounts for approximately one billion cases annually, including 3 to 5 million cases of severe illness, and is responsible for 290,000 to 650,000 respiratory-related deaths each year.² Risk of influenza-related hospitalization is increased in children younger than 5 years and in those with underlying chronic diseases.³ In Saudi Arabia, influenza is a major contributor to pediatric hospitalizations for viral respiratory infections. Asseri et al reported that influenza accounted for 29.3% of upper respiratory tract infection admissions in the southwest region, with influenza B linked to the longest Pediatric Intensive Care Unit (PICU) stays compared to Influenza A, Respiratory Syncytial Virus (RSV) and Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).⁴



Antiviral therapy plays a key role in the management of influenza, The American Academy of Pediatrics (AAP) recommended the initiation of antiviral therapy regardless of illness duration in hospitalized suspected and confirmed children with influenza, with progressive or severe course or with underlying condition augmenting the risk of influenza complications.⁵ In alignment with these recommendations, the Saudi Ministry of Health Seasonal Influenza Therapeutic Protocol also endorses antiviral treatment for all patients hospitalized with influenza, regardless of the duration of illness prior to admission.⁶ Oseltamivir is considered the antiviral of choice for treating influenza A and B in children, due to its extensive use in pediatric populations, affordability, and ease of administration.⁵

Multiple international studies have shown that oseltamivir is most effective when initiated within 48 hours of symptom onset, leading to shorter hospital stays and fewer complications.^{7–10} However, data from Saudi Arabia remain limited, and local factors may influence treatment outcomes. This study aims to compare early versus late oseltamivir administration in hospitalized children with influenza, focusing on length of hospital stay and risk of complications. The findings may offer valuable insight to guide local clinical practice and support national therapeutic protocols.

Aim and Objectives

Aim

- To evaluate the input of early oseltamivir administration compared to late administration on clinical outcomes in hospitalized children with influenza.

Specific Objectives

- To compare length of hospital stay between children who received early versus late Oseltamivir.
- To assess risk of influenza related complications with pneumonia, otitis media, acute asthma exacerbation, febrile seizure, acute tonsillitis, croup and myositis, between these two groups.

Methodology

Study Design

This is a retrospective cohort study conducted using data extracted from the Health Information System of a tertiary hospital for pediatric patients admitted between January 2020 and April 2023 with a confirmed diagnosis of influenza by using polymerase chain reaction (PCR) or Point of Care Test (POCT). POCT is usually performed in the outpatient clinic and emergency room, whereas PCR testing is typically conducted in the ward, in accordance with insurance coverage policies. Baseline clinical severity was assessed using the Pediatric Early Warning Score (PEWS), which is automatically calculated within the electronic medical record. A PEWS of 3–4 is considered appropriate for ward admission, while a score of ≥ 5 prompts admission to the pediatric intensive care unit. The initial site of admission (ward versus PICU) was therefore used as a proxy measure of baseline severity for comparison between the early and late treatment groups (Table 1). All included patients received oseltamivir during hospitalization. Early oseltamivir initiation was defined as initiation within 48 hours of symptom onset, whereas initiation after 48 hours was considered late.

Study Population

Inclusion Criteria

- Confirmed positive influenza type A or B by (PCR) or (POCT)
- Hospitalized pediatric patients between 1 month and 14 years of age
- Started oseltamivir during hospitalization.

Exclusion Criteria

- Positive influenza patient who had not received oseltamivir during hospitalization.
- Patients started on oseltamivir before admission.
- Patients who are older than 14 years.
- Neonate

Table 1 Characteristics of the Study Population

Characteristic	All Participants	Early Oseltamivir	Late Oseltamivir	P Value
Number of Participants	280	106	174	
Gender				0.777
Male	151 (53.9%)	56 (52.8%)	95 (54.6%)	
Female	129 (46.1%)	50 (47.2%)	79 (45.4%)	
Median age in months (IQR)	36 (15–60)	32 (10.25–60.0)	36 (21.0–72.0)	0.121
Known case of asthma	26 (9.2%)	4 (3.8%)	22 (12.6%)	0.018 ^a
History of Prematurity	14 (5.0%)	6 (5.7%)	8 (4.6%)	0.709
Initial Site of Admission				0.999
Ward	265 (94.6%)	100 (94.3%)	165 (94.8%)	
PICU	15 (5.4%)	6 (5.7%)	9 (5.2%)	
Influenza Types (POCT and PCR)				0.725
Influenza A	202 (72.14%)	77 (72.64%)	125 (71.83%)	
Influenza B	77 (27.5%)	29 (27.35%)	48 (27.59%)	
Both Influenza A & B	1 (0.36%)	0 (0%)	1 (0.57%)	
Influenza A Subtypes (PCR)				0.512
H1N1	61 (21.8%)	22 (20.75%)	39 (22.41%)	
H3	108 (38.57%)	41 (38.68%)	67 (38.5%)	
Subtype unknown	69 (24.6%)	21 (19.81%)	48 (27.59%)	
Virus Co-infections (Any)	50 (17.9%)	20 (18.87%)	30 (17.24%)	0.728
Respiratory Syncytial Virus	10 (3.57%)	2 (1.89%)	8 (4.6%)	
Rhinovirus/Enterovirus	16 (5.71%)	10 (9.43%)	6 (3.45%)	
Parainfluenza Virus 2	1 (0.36%)	1 (0.94%)	0 (0%)	
Parainfluenza Virus 3	4 (1.42%)	2 (1.89%)	2 (1.15%)	
Adenovirus	2 (0.71%)	1 (0.94%)	1 (0.57%)	
Coronavirus NL63	2 (0.71%)	1 (0.94%)	1 (0.57%)	
Coronavirus 229E	1 (0.36%)	0 (0%)	1 (0.57%)	
Coronavirus OC43	5 (1.78%)	1 (0.94%)	4 (2.3%)	
Human Metapneumovirus	6 (2.14%)	2 (1.89%)	4 (2.3%)	
Sars-Cov-2	2 (0.71%)	1 (0.94%)	1 (0.57%)	

Note: ^aP < 0.05.

Abbreviations: IQR, Interquartile range; PICU, Pediatric intensive care unit; POCT, Point-of-care test; PCR, Polymerase chain reaction.

Study Area/Setting

The study was conducted in Almoosa Specialist Hospital, a tertiary hospital in Al-Ahssa region of Saudi Arabia. Samples were retrieved from Pediatrics Department with a large bed capacity up to 95 beds.

Sample Size Calculation and Sampling Technique

The study included all pediatric patients who met the inclusion criteria during the specified study period. A total of 280 patients with confirmed influenza who received oseltamivir during hospitalization were included, [Figure 1](#) shows flowchart of reported patients into the study population.

Data Management and Statistical Analysis

The collected data were reviewed, cleaned, and entered into a Microsoft Excel spreadsheet (latest version) before being exported to SPSS (latest version) for statistical analysis. Descriptive statistics were used to summarize continuous variables (median, interquartile range, and frequency distribution) and categorical variables (counts and percentages).

Since the data were not normally distributed, non-parametric tests were applied. The Mann–Whitney *U*-test was used to compare continuous variables between groups, while the Chi-square (χ^2) test was used to compare categorical variables. Correlation analysis was also performed to assess the relationship between the timing of oseltamivir initiation and hospital length of stay.

A p-value < 0.05 was considered statistically significant, and 95% confidence intervals were applied where appropriate.

Results

This study included 280 participants diagnosed with influenza, divided into two groups: 106 had received early oseltamivir treatment, and 174 received later treatment. [Table 1](#) shows baseline patients' characteristics of both groups. The gender distribution was similar across groups, with males comprising 53.9% of the total cohort.

The median age of participants was 36 months, slightly younger in the early treatment group (32 months) compared to the late group (36 months), though this was not statistically significant ($p = 0.16$). Asthma was more prevalent in the late treatment group. Other pre-existing respiratory conditions, including bronchopulmonary dysplasia and lung sequestration, as well as cardiac conditions such as cardiomyopathy, atrial septal defect, pulmonary regurgitation, and cardiac rhabdomyoma, were rare, clinically non-critical, and therefore excluded from the baseline comparative analyses. All other baseline characteristics were similar between groups with no statistically significant differences.

Correlation analysis, shown in [Figure 2](#), demonstrated a statistically significant but weak positive correlation between the time to oseltamivir initiation and hospital length of stay ($r = 0.130$, $P = 0.029$), suggesting that longer delays in

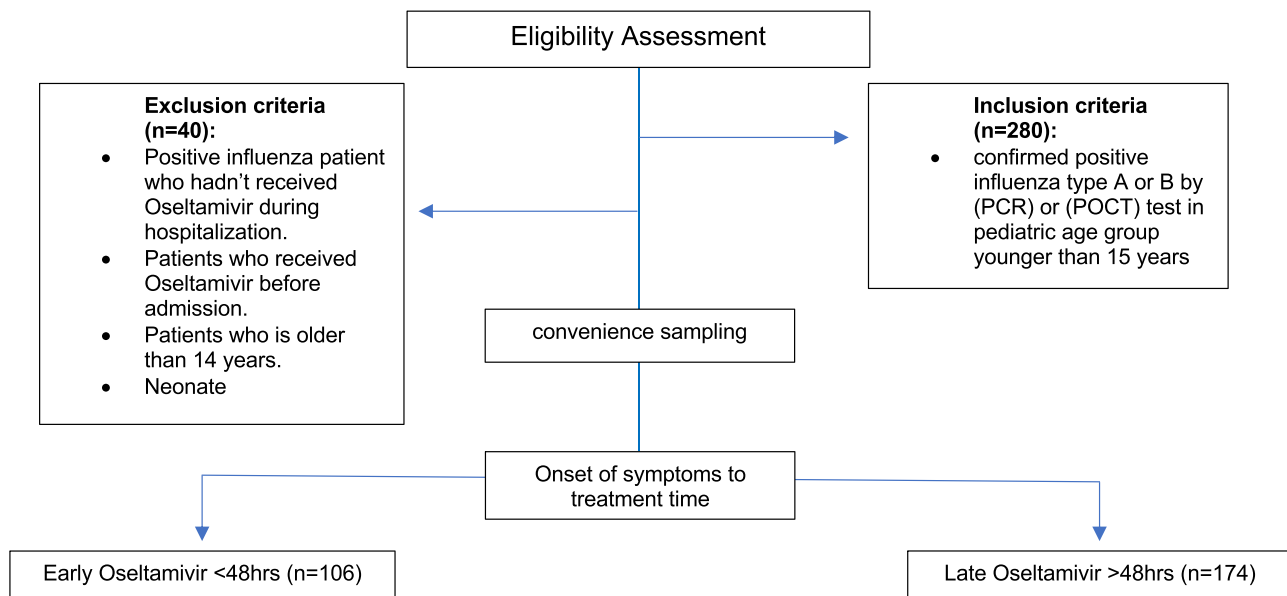


Figure 1 Flow diagram of patient selection and inclusion in the study. Description of screening, exclusions, and final cohort included in the analysis.

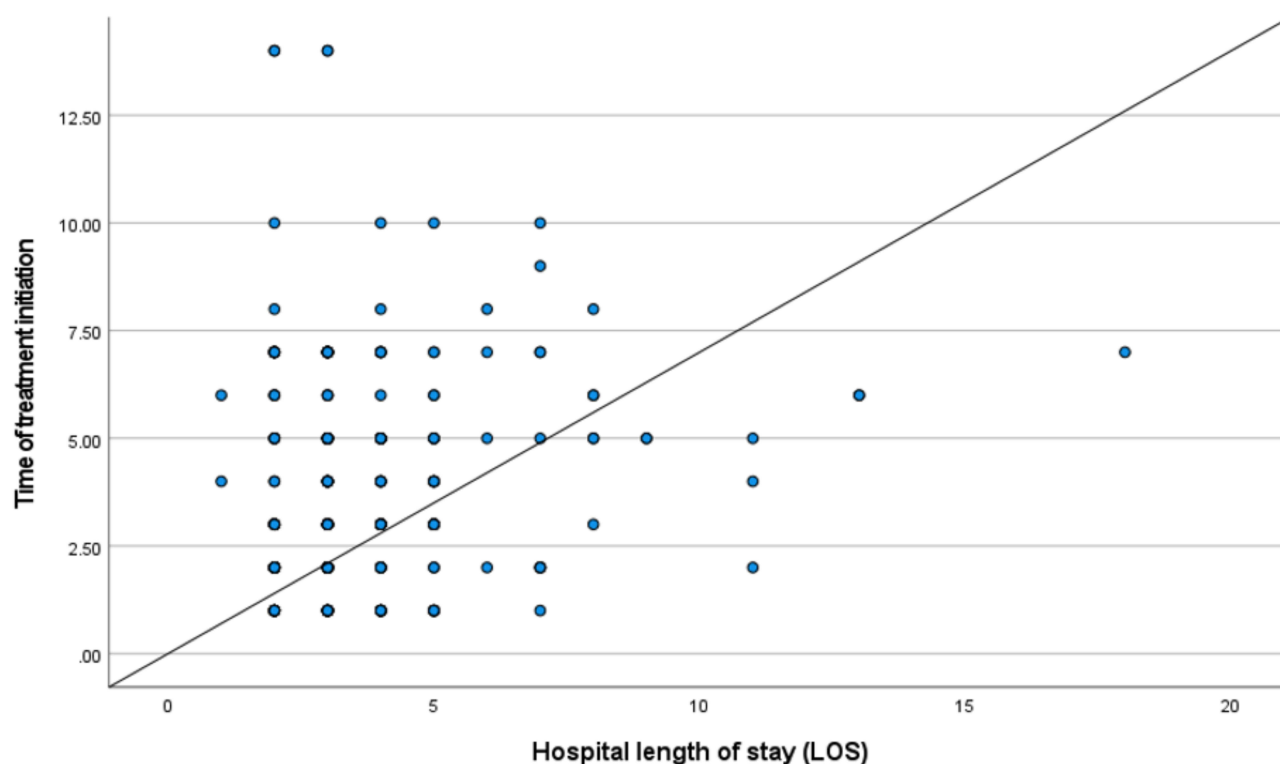


Figure 2 Correlation between time to oseltamivir initiation and hospital length of stay. Scatter plot demonstrating the relationship between time from symptom onset to initiation of oseltamivir and hospital length of stay, both measured in days.

starting treatment were associated with slightly longer hospitalizations. However, this weak association was interpreted as a supportive secondary finding. Further analysis of hospital length of stay results revealed a statistically significant shorter hospital stay of approximately 1 day (16–19 hours) in group receiving early treatment compared to late treatment group [(3.28 ± 1.46) vs (3.95 ± 2.26), $P = 0.007$].

The incidence of influenza-related complications between the two groups is shown in (Figure 3). Pneumonia occurred substantially more often in the delayed treatment group (27 cases) compared to early treatment (4 cases), marking a significant reduction with early initiation. Similarly, Otitis Media showed a significant benefit with early treatment: only 4 cases developed in the early group versus 26 in the late group. Acute asthma exacerbation was also more frequent in patients treated after 48 hours (10 vs 1), again demonstrating a significant protective effect from early antiviral therapy. No statistically significant difference was observed for the other complications, including acute tonsillitis, croup, and myositis.

Discussion

Our study found that patients who received oseltamivir within 48 hours of symptom onset had a significantly shorter hospital stay compared to those who received treatment later, with a mean reduction of approximately 16 hours (0.67 days). This reduction is not only statistically significant ($P = 0.007$) but also clinically meaningful, as even modest decreases in hospitalization duration can lead to substantial cost savings and reduced burden on healthcare resources. However, it is important to note that the confidence intervals overlap somewhat indicating variability, so the finding, while significant, should be interpreted with some caution. Additional studies with larger samples or prospective designs could help confirm these findings and provide more precise estimates. Baseline characteristics demonstrated a statistically significant difference between groups in the prevalence of asthma, which was more frequent in the late treatment group. Given the known association between asthma and influenza-related morbidity, this difference was considered a potential confounder. Therefore, asthma was analyzed separately as the primary respiratory comorbidity in the baseline

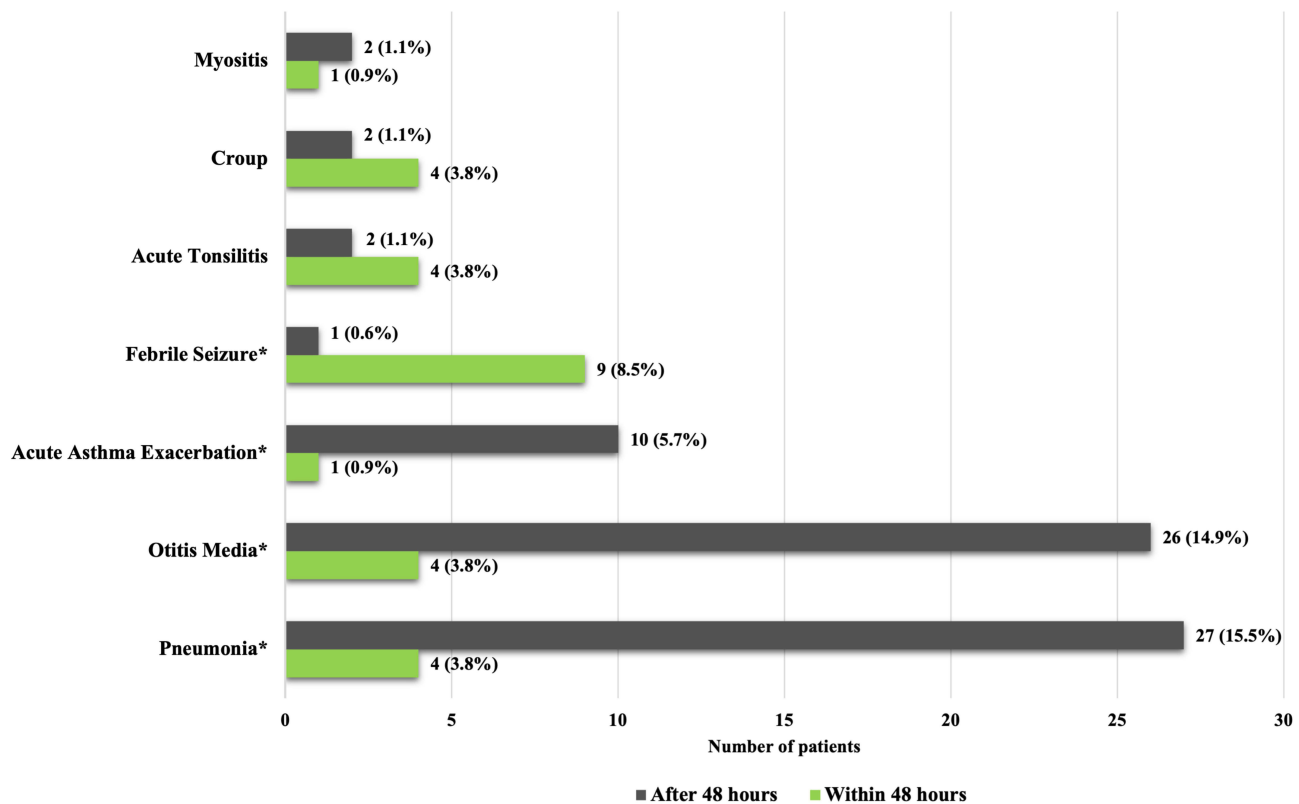


Figure 3 Development of influenza-related complications among hospitalized children treated with oseltamivir. Comparison of complications between children who received oseltamivir within 48 hours of symptom onset and those who received treatment after 48 hours. Data are presented as number (percentage). *Statistically significant difference between groups ($P < 0.05$).

characteristics to allow a clearer and more clinically meaningful comparison between groups. Other respiratory and cardiac conditions were infrequent and clinically non-critical and were not included in the baseline comparative analysis.

Correlation analysis (Figure 2) demonstrated a statistically significant association between the time to oseltamivir initiation and hospital length of stay, although the correlation was weak ($r = 0.130$, $P = 0.029$). While the primary cutoff for early treatment in this study was 48 hours, an exploratory analysis showed a weak but consistent positive correlation between oseltamivir initiation time and hospital length of stay when treatment was initiated up to 72 hours after symptom onset. This supports the knowledge that replication of influenza virus peaks 24–72 hrs after symptoms onset in the respiratory tract of infected patient,¹¹ which may explain the consistent positive correlation observed when oseltamivir is initiated within 72 hours of treatment window.

The IMPACT (IMmediate Possibility to ACcess oseltamivir Treatment) study on 2003, is the first study investigated between time to initiate oseltamivir and duration of symptoms using accelerated failure time (AFT) modelling. Resulted a complementary outcome, with a reduction about ~10hs in hospital duration for every 6 hrs the earlier the initiation of treatment.⁸ In the same previous study, the initiation oseltamivir within 12 hrs after onset of fever results in a reduction of total median duration of illness by 74.6 hrs (3.1 days; 41%) more than at 48 hrs of intervention. The previous study had used (AFT) model, which is specifically designed for modeling time-to-event outcomes and has the advantage of handling censored data.

A similar study in United States on pediatric age group, oseltamivir at ≥ 72 hours after symptoms onset had no significant effect on length of stay in hospitalized children either in ward or ICU. A median length of stay was 3 days for those not treated versus 2 days for those treated ≤ 48 hrs after symptom onset ($P = 0.005$).¹² This is in line with our finding, which is even after 48 hrs up to 72 hrs showed similar outcome in length of stay (Figure 2). Other studies have shown a consistent benefit of early oseltamivir treatment, using various time cutoffs such as within 48 hours, <6 hours, 6–24 hours, and >24 hours.^{13,14} These findings emphasize that the earlier the treatment is initiated, the better the clinical outcomes.

Various known influenza related complications and role of oseltamivir in preventing their development were assessed in this study (Figure 3). Respiratory-related complications, pneumonia and acute asthma exacerbation were less encountered with significant difference in those who started early comparing to late treatment [4 (3.8%) vs 27 (15.5%) and 1 (0.9%) vs 10 (5.7%), $P = 0.002$ and 0.045]. Additionally, otitis media showed significant difference between the two groups.

Febrile seizures were observed more frequently in the early treatment group (9 cases) compared to the late treatment group (1 case), with statistical significance. This likely reflects the natural timing of febrile seizure onset, which tends to occur early in the illness course in association with fever. Therefore, the occurrence of febrile seizures appears to be independent of oseltamivir administration and may be inevitable once fever begins, rather than influenced by the timing of antiviral therapy.

A multicenter randomized controlled trial study reported the overall incidents of complications development in high-risk population including tracheitis, bronchitis, pneumonia, nasosinusitis and pharyngitis were significantly lower in oseltamivir group in comparison to the controlled group [3 of 27 (11%) vs 13 of 29 (45%), $p = 0.0053$].¹⁵ This former mentioned study is consistent with this study, in effectiveness of oseltamivir in prevention of development of some influenza related complications.

This study has several limitations. First, its retrospective design may be subject to incomplete or missing data inherent to health informatics records. Second, the timing of oseltamivir initiation was defined based on caregiver-reported symptom onset, is commonly used in retrospective antiviral studies but may be subject to recall bias. Third, although all eligible patients during the study period were included, the overall sample size remains relatively small, and a formal power calculation was not performed to determine if the study was adequately powered to detect all clinically significant differences. Fourth, data on patients' influenza vaccination status were not available, which may have influenced disease severity and treatment outcomes. Finally, as this study was conducted at a single tertiary care center, the generalizability of the findings to other settings may be limited.

Conclusion

The study demonstrated that early initiation of oseltamivir within 48 hours is effective in reducing hospital length of stay and preventing common complications, including otitis media, pneumonia, and acute asthma exacerbation. Although the primary cutoff for treatment in this study was 48 hours, an exploratory analysis showed a weak but consistent correlation between later oseltamivir initiation and hospital length of stay when treatment was initiated up to 72 hours after symptom onset.

Abbreviations

Hrs, Hours; PICU, Pediatric Intensive Care Unit; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; RSV, Respiratory Syncytial Virus; AAP, American Academy of Pediatrics; PCR, Polymerase Chain Reaction; POCT, Point of Care Test; CI, Confidence Interval; SPSS, Statistical Package for the Social Sciences; IRB, Institutional Review Board; IQR, Interquartile Range; NCBE, National Committee of Bioethics; GCP, Good Clinical Practice.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are not publicly available due to institutional policies and patient confidentiality but are available from the corresponding author on reasonable request and with appropriate IRB approval.

Ethics Approval and Consent to Participate

The study protocol was reviewed and approved by the Institutional Review Board (IRB) at Almoosa Health Group – Almoosa Specialist Hospital (IRB Log No: ARC-23.4.06). The study was conducted in accordance with the ethical standards of the institutional research committee, the guidelines of the Saudi National Committee of Bioethics (NCBE), the Good Clinical Practice (GCP) guidelines, the principles of the Declaration of Helsinki, the policies and procedures of the Almoosa Research Center, and the regulations of the Government of Saudi Arabia. As the study involved retrospective analysis of de-identified data, informed consent was not required as per IRB regulations.

Consent for Publication

Not applicable. The study used anonymized, retrospective data that does not include any individual person's identifiable information.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure

The authors declare that they have no competing interests.

References

- Ghebrehewet S, MacPherson P, Ho A. Influenza. *BMJ*. 2016;355:i6258. doi:10.1136/bmj.i6258
- World Health Organization. Influenza (seasonal). Geneva: World Health Organization; 2024. Available from: <https://www.who.int/news-room/fact-sheets/detail/influenza>. Accessed March 7, 2025.
- Dawood FS, Jara J, Gonzalez R, et al. A randomized, double-blind, placebo-controlled trial evaluating the safety of early oseltamivir treatment among children 0–9 years of age hospitalized with influenza in El Salvador and Panama. *Antiviral Res*. 2016;133:85–94. doi:10.1016/j.antiviral.2016.07.007
- Asseri AA, Al-Qahtani SM, Alzaydani IA, et al. Clinical and epidemiological characteristics of respiratory syncytial virus, SARS-CoV-2, and influenza pediatric viral respiratory infections in southwest Saudi Arabia. *Ann Med*. 2025;57(1):2445791. doi:10.1080/07853890.2024.2445791
- Committee on Infectious Diseases; O’Leary ST, Campbell JD, Ardura MI. Recommendations for prevention and control of influenza in children, 2024–2025: technical report. *Pediatrics*. 2024;154(4):e2024068508. doi:10.1542/peds.2024-068508
- Ministry of Health, Saudi Arabia. Seasonal influenza therapeutic protocol. Riyadh: Ministry of Health. Available from: <https://www.moh.gov.sa/en/Ministry/MediaCenter/Publications/Pages/Protocols.aspx>. Accessed March 7, 2025.
- Walsh PS, Schnadower D, Zhang Y, Ramgopal S, Shah SS, Wilson PM. Association of early oseltamivir with improved outcomes in hospitalized children with influenza, 2007–2020. *JAMA pediatrics*. 2022;176(11):e223261. doi:10.1001/jamapediatrics.2022.3261
- Aoki FY, Macleod MD, Paggiaro P, et al. Early administration of oral oseltamivir increases the benefits of influenza treatment. *J Antimicrob Chemother*. 2003;51(1):123–129. doi:10.1093/jac/dkg007
- Lytras T, Mouratidou E, Andreopoulou A, Bonovas S, Tsioufas S. Effect of early oseltamivir treatment on mortality in critically ill patients with different types of influenza: a multiseason cohort study. *Clin Infect Dis*. 2019;69(11):1896–1902. doi:10.1093/cid/ciz101
- Rodriguez A, Diaz E, Martín-Loeches I, et al. Impact of early oseltamivir treatment on outcome in critically ill patients with 2009 pandemic influenza A. *J Antimicrob Chemother*. 2011;66(5):1140–1149. doi:10.1093/jac/dkq511
- Murphy BR, Baron S, Chalhub EG, Uhlenndorf CP, Chanock RM. Temperature-sensitive mutants of influenza virus. IV. Induction of interferon in the nasopharynx by wild-type and a temperature-sensitive recombinant virus. *J Infect Dis*. 1973;128:488–493.
- Campbell AP, Tokars JI, Reynolds S, et al. Influenza antiviral treatment and length of stay. *Pediatrics*. 2021;148(4). doi:10.1542/peds.2021-050417
- Hsu J, Santesso N, Mustafa R, et al. Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies. *Ann Internal Med*. 2012;156(7):512–524. doi:10.7326/0003-4819-156-7-201204030-00411
- Katzen J, Kohn R, Houk JL, Ison MG. Early oseltamivir after hospital admission is associated with shortened hospitalization: a 5-year analysis of oseltamivir timing and clinical outcomes. *Clin Infect Dis*. 2019;69(1):52–58. doi:10.1093/cid/ciy860
- Lin JT, Yu XZ, Cui DJ, et al. A multicentre, randomized, controlled trial of oseltamivir in the treatment of influenza in a high-risk Chinese population. *Curr Med Res Opin*. 2006;22(1):75–82. doi:10.1185/030079906X80297

Pediatric Health, Medicine and Therapeutics

Publish your work in this journal

Pediatric Health, Medicine and Therapeutics is an international, peer-reviewed, open access journal publishing original research, reports, editorials, reviews and commentaries. All aspects of health maintenance, preventative measures and disease treatment interventions are addressed within the journal. Practitioners from all disciplines are invited to submit their work as well as healthcare researchers and patient support groups. The manuscript management system is completely online and includes a very quick and fair peer-review system. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <http://www.dovepress.com/pediatric-health-medicine-and-therapeutics-journal>

Dovepress
Taylor & Francis Group