REVIEW ARTICLE

Clinical Efficacy and Therapeutic Effectiveness of Oseltamivir in Pediatric Influenza Treatment: A Systematic Review

Charan Lingutla[1], Sriharsha Lankala[2], Neeraj Pavan Reddy Telugu[1], Monish Konda[3], Krishna Priya Kanteti[1]

[1]Department of General Medicine, Gandhi Medical College and Hospital, Hyderabad, Telangana, India, [2]Department of General Medicine, Maheshwara Medical College and Hospital, Hyderabad, Telangana, India, [3]Department of General Medicine, Shri B. M. Patil Medical College, Hospital and Research Centre, Bijapur, Karnataka, India

Abstract

Influenza viruses cause significant morbidity and mortality worldwide each year. Diagnosing influenza based on clinical symptoms is challenging and requires laboratory confirmation for a precise diagnosis. Oseltamivir is fundamental in managing influenza; however, its effectiveness in children remains under scrutiny due to resistance. This systematic review assessed the clinical effectiveness of oseltamivir in treating children with influenza. The review included five studies that assessed the effectiveness of oseltamivir in treating influenza in children and adults across different settings. Studies have shown that oseltamivir decreases illness duration when administered early, and its combination with clarithromycin and naproxen reduces fever duration and hospital stay. Peramivir showed slightly faster fever reduction than oseltamivir, though clinical outcomes remained similar. Shorter courses of oseltamivir prophylaxis may be equally effective, potentially reducing costs. Adding oseltamivir to standard care is cost-effective, particularly in older adults with health conditions. This review confirms the limited effectiveness of oseltamivir in reducing flu symptoms in children when administered promptly, with potential benefits from combination therapy in severe pediatric cases.

Key words: Antiviral, children, influenza, oseltamivir, symptoms

INTRODUCTION

Influenza viruses cause contagious respiratory diseases, seasonal outbreaks, and pandemics. The clinical manifestations of influenza have evolved due to viral evolution and genomic reassortment.[1] These viruses are major causes of severe respiratory infections worldwide, affecting public health and travel medicine.[2]

In the Middle East, the prevalence of influenza ranges from 0.5% in Qatar to 70% in Syria, with an average of 10.2%.[3] In China, the seasonal influenza incidence was 31% among children aged 5–17 and 21% among adults aged 18–59 years.[4] Influenza cases vary between seasons, ranging from 0.24 to 21.69 cases per 1000 patients.[5] The prevalence of headaches in patients with influenza was 66.1% overall and up to 80.1% in certain seasons, being more common in women and individuals aged 15–65 years. Influenza B subtypes are associated with more headaches than influenza A subtypes.[5]

Influenza, often called the flu, is a highly infectious respiratory disease caused by influenza viruses of the *Orthomyxoviridae* family.[6] The illness presents with fever and cough are the most reliable indicator of infection in communities.[7] In children, fever is prominent, with 95% experiencing it and 50% having fever ≥39.0°C, along with cough (77%) and rhinitis (78%). Headache and muscle pain, which are common in adults, are not typical in children.[8] In

Address for correspondence:
Dr. Krishna Priya Kanteti, Department of General Medicine, Gandhi Medical College and Hospital, Secunderabad, Telangana, India.
E-mail: kpriya.kantheti@gmail.com

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adults, cough, chills, and nasal congestion have the highest predictive value for diagnosing influenza.[7]

Diagnosing influenza based solely on clinical symptoms is challenging. Research has shown that diagnoses using clinical indicators often overestimate laboratory-confirmed cases and misclassify others.[9] Laboratory confirmation is necessary for the precise diagnosis and management of influenza, particularly in hospitals, where typical symptoms show low sensitivity.[7]

Polymerase chain reaction testing shows greater sensitivity than culture methods, with a median influenza load of 5.9 $\log_{10}$ copies/mL at diagnosis.[10] Although oseltamivir is commonly used for treatment, concerns exist regarding drug-resistant strains. By December 2008, many circulating influenza A/H1N1 viruses were resistant to oseltamivir,[11] highlighting the need for combination therapy and updated treatment guidelines.

Recent biosensor technologies have facilitated swift and precise on-site disease diagnosis.[12] For critical patients, molecular tests are preferred over antigen detection assays because of their greater sensitivity.[13] Studies have shown that neuraminidase inhibitors, especially oseltamivir, improve survival rates.[13] New antiviral strategies with innovative mechanisms and lower drug resistance are needed to manage influenza.[14]

Oseltamivir (Tamiflu) is an antiviral medication used to treat and prevent influenza A and B infections.[15] It works against seasonal, pandemic, and avian influenza strains, such as H5N1.[15] This drug blocks viral neuraminidase enzymes, which are essential for viral replication.[16] When administered early, before the onset of respiratory failure, oseltamivir reduces symptom severity and duration in infected individuals and helps prevent infection in exposed individuals.[16] However, resistance can develop during treatment, potentially worsening the clinical outcomes.[17] Its metabolite, oseltamivir carboxylate, persists in aquatic environments, potentially fostering viral resistance in natural hosts such as dabbling ducks.[18] Combining oseltamivir with antivirals, such as favipiravir, shows synergistic effects against both sensitive and resistant strains.[19]

Oseltamivir remains fundamental in managing influenza, as endorsed by the World Health Organization for pandemic, seasonal, and avian flu.[15] The treatment should begin promptly in severe cases, particularly with laboratory confirmation of the diagnosis.[20] Research has focused on developing derivatives and combinations to enhance their effectiveness against resistant strains.[21] The drug's cost-effectiveness and pandemic mitigation role remain under review.[15]

Considering the worldwide health challenges posed by influenza and viral resistance, enhancing antiviral treatment strategies is crucial, especially for at-risk pediatric groups. Oseltamivir plays a key role in managing influenza; however, its effectiveness in children remains under scrutiny due to resistance and changing guidelines. This systematic review compiles recent evidence on the therapeutic use of oseltamivir in pediatric influenza, examining clinical outcomes, recovery time, and safety. By analyzing pertinent studies from the past decade, this review aims to elucidate the role of oseltamivir in pediatric influenza management and guide clinical decisions. This review aimed to assess the clinical effectiveness and therapeutic outcomes of oseltamivir in treating and aiding the recovery of children with influenza.

METHODS

This systematic review adhered to the preferred reporting items for systematic reviews and meta-analyses guidelines to ensure transparency and methodological rigor.[22]

The inclusion criteria were as follows: original research articles presenting primary data, studies in peer-reviewed journals between 2014 and 2024, articles in English, studies with pediatric populations (aged 0–18 years), and research on oseltamivir for treating influenza. The exclusion criteria were reviews, meta-analyses, case reports, editorials, studies without full texts, articles unrelated to pediatric influenza or oseltamivir treatment, and studies outside the specified timeframe.

A literature search was performed using three databases: PubMed, Scopus, and Web of Science. The search strategy used the terms: ("Oseltamivir" AND "Influenza"), utilizing Boolean operators to retrieve relevant studies. Filters were applied to limit the findings to human subjects, English language, and publications from the past decade.

The search results were entered into a reference management tool to eliminate duplicates. Two reviewers independently screened the titles and abstracts according to the inclusion and exclusion criteria. The full texts of potentially eligible articles were reviewed for final inclusion. Any discrepancies were resolved through discussion or by consulting a third reviewer, if necessary.

From the chosen articles, the following information was systematically gathered using a predetermined data extraction form: Study characteristics (authors, publication year, country), study design and setting, sample size and age group, intervention details (oseltamivir dosage and duration), comparator (if any), outcomes measured (e.g., symptom duration, fever resolution, hospitalization length, side effects), and key findings.

RESULTS

The initial search across PubMed, Scopus, and Web of Science identified 76 articles. After applying the inclusion

and exclusion criteria, 19 studies were removed due to the lack of full-text availability. Of the 57 remaining studies, 49 were excluded as they did not fulfill the inclusion criteria. Of the eight studies that underwent full-text eligibility checks, three were excluded due to insufficient data. Five studies were included in the systematic review.[23-27] Figure 1 illustrates the selection process, and Table 1 outlines the characteristics of the included studies.

The five included studies assessed oseltamivir's effectiveness in treating and preventing influenza and influenza-like illness (ILI) in children and adults in outpatient and inpatient settings. The studies included randomized controlled trials, a non-inferiority trial, and an economic evaluation, showing the clinical and economic benefits of oseltamivir.

Evidence shows that oseltamivir slightly decreases illness duration when it is administered early. The ALIC4E trial found an average half-day reduction in recovery time for primary care patients with ILI who received oseltamivir, with greater benefits in high-risk groups, including the elderly and those with severe symptoms.[23] A Taiwanese study of

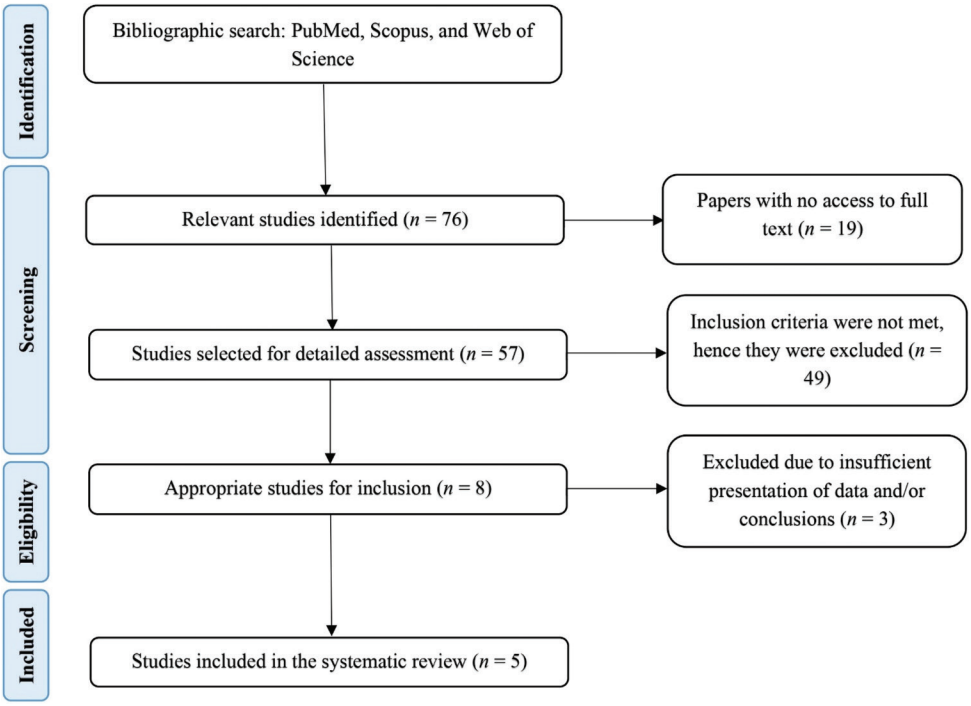

Figure 1: Flow diagram of literature search and study of selection for systematic review (preferred reporting items for systematic reviews and meta-analyses flow chart)

Table 1: Characteristics of selected studies on the evaluating oseltamivir for influenza and influenza-like illness

Study details	Study design	Population/setting	Intervention versus comparator	Key findings
Butler *et al.* (2020)[23]	Open-label, pragmatic RCT	Patients with ILI in primary care	Oseltamivir+general care vs general care	Fasterrecovery (~0.5 days); greater benefit in high-risk groups
Lee *et al.* (2021)[24]	Multicenter comparative study	Hospitalized pediatric patients with influenza	Oseltamivir+clarithromycin+ naproxen versus oseltamivir alone	Shorter fever duration, hospital stay, and fewer ICU admissions
Xu*et al.* (2023)[25]	Observational comparative efficacy study	Hospitalized children with influenza (0–5 years)	Oseltamivir versus peramivir	Slightly faster fever resolution with peramivir; no difference in outcomes
Li *et al.* (2023)[26]	Economic evaluation along side RCT	Patients with ILI in primary care	Oseltamivir++general care vs general care (economicanalysis)	Cost-effective in mostscenarios; especially in older/comorbidpatients
Wrotek and Jackowska (2024)[27]	Open-label, randomized non inferiority trial	Hospitalized children exposed to influenza	3-day versus 7-day oseltamivir post-exposure prophylaxis	Non-inferiority of 3-day prophylaxis; similar infection rates

RCT: Randomized-controlled trial, ILI: Influenza-like illness, ICU: Intensive care unit

hospitalized children showed that combining oseltamivir with clarithromycin and naproxen reduced fever duration and hospital stay compared to oseltamivir alone, suggesting that anti-inflammatory and antibacterial therapies may improve outcomes in complicated cases.[24]

Studies comparing antiviral treatments in children have provided key insights. In hospitalized patients aged 0–5 years, peramivir showed slightly faster fever reduction than oseltamivir, although clinical outcomes such as hospital stay duration and complications remained similar.[25] Oseltamivir has the advantages of oral administration and outpatient care, where intravenous access is limited.

The duration of post-exposure prophylaxis (PEP) is vital for managing healthcare outbreaks. A non-inferiority study comparing 3-day and 7-day oseltamivir prophylaxis in hospitalized children found no notable difference in infection rates, suggesting that shorter courses might be equally effective, potentially reducing costs and improving adherence.[27]

An economic analysis from the ALIC4E trial showed that adding oseltamivir to standard care is cost-effective, particularly in older adults and those with health conditions. The incremental cost-effectiveness ratio was within acceptable limits across most of the 15 European countries studied, supporting the inclusion of oseltamivir in primary care during flu outbreaks.[26]

DISCUSSION

Oseltamivir offers established benefits for adults, with a meta-analysis showing that it reduces median symptom relief time by 17.8 h compared to placebo (95% confidence interval: 27.1–9.3).[28] Butler *et al*. studied 428 children under 12 years with mild symptoms and no comorbidities, finding that oseltamivir shortened recovery by 0.7 days from 5.1 days.[23]

In a clinical trial by He *et al*., among 73 children with influenza, the median illness duration was 61.2 h for those treated with oseltamivir, significantly shorter than the 116.0 h in the control group ($P < 0.05$).[29] In this trial, the median duration was 69.9 h in the oseltamivir group versus 75.4 h in the control group, although the difference was not statistically significant ($P > 0.05$). The median fever duration was 34.8 h with oseltamivir, significantly <53.3 h in controls. The study found that 10% of oseltamivir-treated patients experienced side effects, mainly gastrointestinal issues such as stomach pain, diarrhea, and vomiting, yet concluded that the treatment was safe.[29]

Administering antiviral influenza drugs within 48 h–14 days after LAIV4 may reduce vaccine effectiveness. Clopidogrel inhibits oseltamivir hydrolysis, thereby diminishing its effectiveness.[30] Hung *et al*. found that combining clarithromycin, naproxen, and oseltamivir reduced high dependency unit admissions ($P = 0.009$) and shortened acute care stays ($P < 0.001$), benefiting adult and pediatric patients.[31] Lee *et al*. found in children, combination therapy led to greater viral titer reduction from day 1 to 3 compared to oseltamivir alone (39% vs. 19%, $P = 0.001$).[24] Rhinorrhea resolved faster in the combination group (Day 1 vs. Day 3, $P = 0.041$). However, there were no differences in alleviating symptoms such as cough, sputum, sore throat, chills, wheezing/stridor, headache, dizziness, shortness of breath, chest pain, vomiting, diarrhea, muscle pain, and abdominal pain.

Lee *et al*. found that fever duration was shorter in the group treated with Oseltamivir, Naproxen, and Clarithromycin combination (13.2 h vs. 32.1 h, $P = 0.002$), with lower temperatures on days 3 and 4.[24] Quick fever reduction is vital for children, enhancing their well-being by alleviating discomfort, irritability, and fatigue while reducing high fever complications. These findings suggest that this combination could be considered as a standard influenza treatment protocol. However, further randomized controlled trials are needed to confirm its safety and effectiveness. Potential contraindications, side effects, drug interactions, and antimicrobial resistance should be evaluated. Healthcare systems should tailor protocol implementation to their specific contexts and populations. Xu *et al*. found that children with influenza A had more fevers and seizures than those with influenza B (IAV: 28.1% vs. IBV: 15.5%, $P > 0.05$) and responded better to oseltamivir.[25] Neurological diseases were more common in strain A than in strain B (27.7% vs. 12.2%, $P < 0.001$). Myocardial, kidney, and liver injuries, myositis, and sepsis were observed during hospitalization.

Wrotek and Jackowska examined the effectiveness of oseltamivir as PEP for influenza in hospitalized children, comparing 3-day and 7-day treatments.[27] The findings show that both durations are effective, with the 3-day regimen achieving 100% efficacy in intention-to-treat analysis, while the 7-day regimen reached 93.6%. In the per-protocol analysis, the efficacy rates were 100% and 93.1%, respectively, with no significant difference between the two regimens. The discovery that 3-day PEP matches 7-day PEP effectiveness is notable, suggesting that a shorter treatment may prevent influenza in exposed children. This reduces the treatment burden and adverse events while offering potential cost savings. The lower frequency of adverse events with 3-day PEP indicates better tolerability and adherence in the pediatric population.

In addition to enhancing the understanding of oseltamivir effectiveness in pediatric PEP, this study examined treatment optimization, safety, and resource efficiency in hospitalized children with influenza. Xu et al. showed that children with influenza A and bacterial infections responded better to oseltamivir than to peramivir (21% vs. 3.7%).[25] Comparing influenza A and B strains, there was no significant difference in recovery rates (12.9% vs. 11.1%) or hospitalization

duration, both of which averaged 4 days ($P > 0.05$). Children with influenza A had more fevers and seizures than those with influenza B (IAV: 28.1% vs. IBV: 15.5%, $P > 0.05$) and showed a better response to oseltamivir. Neurological diseases were more common in patients infected with the A strain than in those infected with the B strain (27.7% vs. 12.2%, $P < 0.001$). During hospitalization, myocardial, renal, and liver injuries, myositis, and sepsis occurred, although they were not related to drug use.

Li *et al*. revealed that incorporating oseltamivir into standard treatment for ILI across 15 European nations is economically viable when the willingness to pay exceeds €22,459 per quality-adjusted life year gained.[26] From a societal viewpoint, oseltamivir was cost-saving for adults/adolescents and cost-effective for children, with a willingness to pay of €8,344 per quality-adjusted life year gained. However, uncertainties were noted in subgroups with comorbidities, particularly among children, requiring further validation. The study showed that variations in the incremental cost-effectiveness ratio among countries (EVPI ranging from €1 to €35 per patient) reflect differences in healthcare systems and ILI treatment costs.[26] These findings can inform policy decisions regarding the inclusion of oseltamivir in ILI treatment protocols, potentially improving healthcare efficiency in Europe.

Moreover, conducting research to confirm oseltamivir's cost-effectiveness in various countries is essential, despite its established efficacy in treatment. Healthcare expenses and infection trends vary significantly across regions. In less developed nations, assessing costs versus benefits is vital, considering the differences in antiviral resistance among populations. Cultural obstacles and variations in healthcare systems affect treatment access and effectiveness. Localized studies help customize health policies and optimize resources, ensuring that treatments are tailored to diverse populations. Confirming cost-effectiveness in specific settings provides crucial data for public health decision-making.

This review affirms oseltamivir's limited effectiveness in reducing the duration and severity of flu symptoms in children when administered promptly. The potential benefits of combining therapies with anti-inflammatory and antibiotic agents suggest advantages in severe pediatric cases. Differences in outcomes, tolerability, and cost-effectiveness among populations emphasize the need for further trials. Future studies should consider regional resistance patterns, antiviral availability, and healthcare capabilities to enhance the therapeutic application of oseltamivir.

CONCLUSION

This systematic review indicates that oseltamivir provides limited clinical benefits in treating pediatric influenza when administered within 48 h of symptom onset. Evidence shows that it can shorten fever duration, reduce hospital stay, and decrease viral shedding. Combining oseltamivir with clarithromycin and naproxen improves outcomes in hospitalized children, while its oral form is suitable for outpatient care. Despite support from global health organizations, the role of oseltamivir needs to be refined because of resistance and regional healthcare differences. Local assessments of cost-effectiveness, safety, and treatment protocols are essential for proper access. Policymakers and providers should integrate clinical evidence, resistance monitoring, and economic factors when considering oseltamivir use for seasonal and pandemic preparedness.

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