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碩士論文

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Master’s Thesis

早期抗病毒藥物治療降低兒童流感相關住院風險:多中心病例對照研究

Early Antiviral Therapy Reduces Risk of Influenza-Related Hospitalization in Children: A Multi-Center Case-Control Study

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中文摘要

研究背景與研究目的

季節性流感持續對全球兒童健康造成重大公共衛生威脅，特別是在五歲以下幼童中，更是導致住院與死亡的重要原因之一。在美國，2010 年至 2023 年間，此年齡層每年約有 6,000 至 25,000 名流感相關住院個案。雖然世界衛生組織（WHO）與美國感染症醫學會（IDSA）均建議早期使用神經胺酸酶抑制劑或其他抗病毒藥物，因其已證實可縮短症狀持續時間，但在預防流感相關住院的效果，尤其針對幼兒族群，仍缺乏有力的證據。本研究旨在評估兒科門診及急診病童接受早期抗病毒治療對於降低流感相關住院風險的有效性。

研究方法

本研究採用配對病例對照研究設計，納入 2020 年 1 月 1 日至 2023 年 10 月 31 日間，於台灣北部馬偕紀念醫院體系就醫並經實驗室確診為流感之 18 歲以下兒童與青少年。病例組定義為流感相關住院或死亡，並依就診年份、月份及年齡分層進行配對。早期抗病毒治療定義為自上呼吸道或發燒等症狀開始後兩日內使用抗病毒藥物。主要研究結果為接受早期抗病毒治療與未接受早期抗病毒治療者之流感相關住院風險，並以校正勝算比（adjusted odds ratio, aOR）表示。校正變項包括年齡、性別、潛在疾病、早期抗生素使用、早期類固醇使用及其他合併感染。我們也進一步進行分層分析，以探討 5 歲以下及 5 歲以上兒童的治療效果，也針對不同種類的抗病毒藥物進行分層分析，比較之間的治療效果。

研究結果

本研究共納入 1,492 名兒童（病例組 354 人，對照組 1,138 人），平均年齡為 7.1 歲（範圍 2.5 – 11.7 歲）。流感相關住院的顯著危險因子包括：年齡較小（aOR 每增

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加一歲為 0.93；95% CI, 0.87 – 0.99）、潛在疾病（aOR, 2.76；95% CI, 1.91 – 3.99）、早期使用抗生素使用（aOR, 7.32；95% CI, 5.14 – 10.42）以及合併感染（aOR, 3.88；95% CI, 1.99 – 7.59）。早期抗病毒治療與顯著降低流感相關住院風險相關，在所有兒童中顯著降低 81% 流感相關住院風險（aOR, 0.19；95% CI, 0.14 – 0.27），在五歲以下兒童中降低 80% 住院風險（aOR, 0.20；95% CI, 0.12 – 0.32）而在五歲以上的兒童與青少年中中降低 83% 住院風險（aOR, 0.17；95% CI, 0.10 – 0.28）。

結論

本研究結果顯示，對於經實驗室確診的流感兒童，早期使用抗病毒藥物治療可以顯著降低 80% 流感相關住院的風險。此保護效果在五歲以下幼童中同樣存在。本研究為首篇針對幼兒族群評估早期抗病毒藥物治療對兒童流感相關住院風險影響的研究。研究結果支持現行 WHO 與 IDSA 的治療指引與建議，並強調提升抗病毒藥物之及時可近性與快速診斷能力，對於減輕兒童流感疾病負擔具有重要意義。

關鍵字： 早期、抗病毒藥物、抗病毒治療、兒童、流感、流感相關住院、住院風險

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英文摘要

Background and Study Aim

Seasonal influenza remains a significant public health concern for children globally, particularly those under five years of age, among whom it is a leading cause of hospitalization and mortality. In the United States, influenza resulted in an estimated 6,000 to 25,000 hospitalizations per year in this age group between 2010 and 2023. While both the World Health Organization (WHO) and the Infectious Diseases Society of America (IDSA) recommend early initiation of neuraminidase inhibitors or other antiviral agents based on their efficacy in reducing symptom duration, the evidence remains inconclusive regarding their effectiveness in preventing influenza-related hospitalization—especially in young children. To evaluate the effectiveness of early antiviral therapy in preventing influenza-associated hospitalization in pediatric outpatients.

Method

This matched case-control study included all children (<18 years) with laboratory-confirmed influenza who sought care at MacKay Memorial Hospital System in northern Taiwan from January 1, 2020, to October 31, 2023. Cases were defined as influenza-related hospitalization or death and matched to controls by year, month of visit, and age strata. Early antiviral therapy was defined as initiation within 2 days of symptom onset during the influenza episode. The primary outcome was the adjusted odds ratios (aOR) for influenza-associated hospitalization in subjects who received early antiviral therapy,

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compared with those who did not receive early antiviral therapy. Adjusted variables included age, sex, underlying conditions, early antibiotic use, early steroid use, and co-infection. The subgroup analyses assessed effects in children younger than 5 years and those 5 years or older.

Results

Among 1,492 participants (354 cases and 1,138 controls), the mean age was 7.1 years (range, 2.5–11.7 years). Risk factors for influenza-related hospitalization included younger age (aOR per one-year increment, 0.93; 95% CI, 0.87–0.99), underlying conditions (aOR, 2.76; 95% CI, 1.91–3.99), early antibiotic use (aOR, 7.32; 95% CI, 5.14–10.42), and co-infection (aOR, 3.88; 95% CI, 1.99–7.59). Early antiviral therapy was associated with a reduction in influenza-related hospitalization by 81% in all children (aOR, 0.19; 95% CI, 0.14–0.27), by 80% in children younger than 5 years (aOR, 0.20; 95% CI, 0.12–0.32), and by 83% in children aged 5 years or older (aOR, 0.17; 95% CI, 0.10–0.28).

Discussion and Conclusion

Our findings show that early antiviral therapy was significantly associated with reduced risk of influenza-associated hospitalization in children with confirmed influenza infection. This protective effect persisted in children under five years of age, even after adjusting for potential confounders including age, sex, underlying medical conditions, early antibiotic or corticosteroid use, and co-infections. To our knowledge, this is the first study to

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specifically evaluate the impact of early antiviral treatment on hospitalization risk in this highly vulnerable age group. These findings reinforce the current WHO and IDSA guidelines and underscore the importance of timely antiviral access and rapid diagnostic capacity in mitigating the pediatric burden of influenza.

Keywords: early, antiviral agents, antiviral therapy, children, influenza, influenza-associated hospitalization, hospitalization

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Early Antiviral Therapy Reduces Risk of Influenza-Related Hospitalization in Children: A Multi-Center Case-Control Study

第一章 Introduction

Seasonal influenza remains a leading cause of hospitalization and mortality among children worldwide, particularly among those under five years of age, who are at the highest risk for severe illness.[1-8] Between 2010 and 2020, an estimated 870,000 children under five were hospitalized annually due to influenza globally.[9] In the United States, influenza-related hospitalizations in this age group ranged from 6,000 to 25,000 per year between 2010 and 2023.[10] The World Health Organization (WHO) and the Infectious Diseases Society of America (IDSA) recommend early administration of neuraminidase inhibitors (NIs) or other antivirals after illness onset for both severe and non-severe cases of confirmed or suspected influenza in community settings, based on its efficacy in shortening symptom duration.[11, 12] However, data on the effectiveness of early antiviral therapy in preventing influenza-associated severe illnesses in young children are lacking.[13-19] In a 2024 nationwide survey of clinicians in the United States, fewer than half of respondents reported that they would prescribe oseltamivir for children with influenza in the outpatient setting, highlighting substantial uncertainty regarding its effectiveness in pediatric outpatients.[20, 21]

Two systematic reviews of randomized controlled trials (RCTs), using intention-to-treat infected (ITTi) analyses, demonstrated that prompt initiation of oseltamivir in children with laboratory-confirmed influenza significantly reduced the duration of illness by 17.6 to 36 hours.[22, 23] Oseltamivir also significantly reduced the incidence of acute otitis media in children aged one to five years by 34%.[23] However, evidence remains inconclusive regarding whether

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early administration of NIs prevents influenza-related hospitalization, primarily due to limited statistical power in previous studies examining this outcome, especially among children younger than 5 years.[24, 25]

This multicenter, matched case-control study aimed to evaluate whether early antiviral therapy reduces influenza-associated hospitalization or death risk in children during the 2020–2023 influenza seasons, with particular emphasis on children under five years of age.

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第二章 Materials and Methods

2.1 Settings

This multicenter, matched case-control study was conducted within a hospital system in northern Taiwan. All participating hospitals are major providers of primary pediatric care in the region.

2.2 Ethical Statement

The study procedure was approved by the Ethics Committee of MacKay Memorial Hospital (IRB No. 19MMHIS098e). The Ethical Committee waived informed consent.

2.3 Data Source

Data were extracted from electronic medical records at the study hospitals. Data on antivirals, antibiotics, and corticosteroids prescribed outside the study hospitals were retrieved from the Taiwan National Health Insurance Cloud Medication Record System**.** Publicly funded influenza vaccination status was obtained from Taiwan's National Immunization Information System (NIIS).

2.4 Eligibility Criteria

We included all patients under 18 years of age with laboratory-confirmed influenza diagnosed between January 1, 2020, and October 31, 2023. Influenza diagnosis was confirmed via rapid influenza diagnostic tests (RIDTs), polymerase chain reaction (PCR), or

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viral culture. Patients without laboratory confirmation were excluded. Influenza-related hospitalizations and deaths were identified using diagnosis codes from the International Classification of Diseases, Ninth Revision (ICD-9; codes 487, 488) and Tenth Revision (ICD-10; codes J09, J10, J11). Patients with diagnoses made more than 14 days after hospital admission or hospitalizations unrelated to influenza were excluded.

2.5 Case Definition and Control Matching

Cases were defined as children who were hospitalized within 14 days of influenza diagnosis, admitted to the intensive care unit (ICU), or died within 14 days of symptom onset. Controls were children with laboratory-confirmed influenza seen in the outpatient setting or emergency department who were not hospitalized. All eligible cases were matched to all eligible controls by year and month of the initial visit and age strata (≤6 months, 7 months–2 years, 3–5 years, and 6–18 years), rather than using a fixed number of controls per case.

2.6 Clinical Presentation and Underlying Diseases

The clinical presentation of influenza was categorized as one of the following diagnoses: acute bronchitis, acute bronchiolitis, bronchopneumonia, sinusitis, acute otitis media, pneumonia, febrile convulsion, croup, acute gastritis, dehydration, encephalitis, meningitis, myositis, or Kawasaki disease. Underlying conditions were classified into the following categories: neurological disorders (e.g., cerebral palsy, encephalopathy); history of preterm birth; asthma; kidney disorders (e.g., vesicoureteral reflux, nephrotic syndrome); obesity; endocrine disorders (e.g., diabetes or thyroid disease); hematologic or immunologic disorders; heart conditions (e.g., Kawasaki disease, congenital heart disease); and other genetic

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disorders.

2.7 Early antiviral therapy

Early antiviral therapy was defined as treatment initiated within 48 hours of symptom onset, based on 2024 WHO and IDSA guidelines.[11, 12] Patients receiving antivirals after 48 hours or not at all were classified as not receiving early antiviral therapy.

2.8 Outcome

The primary outcome was influenza-associated hospitalization or death. Hospitalizations due to fever or respiratory illnesses within 14 days of symptom onset were considered influenza related, and deaths within 14 days of illness onset were considered influenza associated. The secondary outcome was severe influenza-related illness, defined as clinical deterioration requiring intensive care unit (ICU) admission and/or mechanical ventilation, resulting in death, or the development of complications such as Kawasaki disease or acute necrotizing encephalopathy with long-term neurologic sequela.[11, 12]

2.9 Statistical Analysis

Conditional logistic regression was used for analyzing matched case-control data to estimate the adjusted odds ratios (aORs) of influenza-related hospitalization. Effectiveness of early antiviral therapy was estimated as (1 – aOR) *100%. All covariates, including age, sex, comorbidities, early antibiotic use (within 2 days of symptom onset), early corticosteroid use (within 2 days of symptom onset), co-infections (culture-confirmed bacterial or viral co-infections), and publicly funded influenza vaccination, were included in the analysis.

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Each variable was initially assessed using a univariable model. Publicly funded influenza vaccination status was not included in the final model because self-paid influenza vaccinations were not recorded in the national database and thus did not reflect true population coverage of influenza vaccination. Multicollinearity was evaluated using the variance inflation factor (VIF), with values >5 considered indicative of multicollinearity.[26]

Subgroup analyses were stratified by age group (≤5 years vs >5 years) and by antiviral agent (oseltamivir vs zanamivir). We conducted sensitivity analyses by sequentially excluding (1) patients who received no antiviral therapy, presumed to have very mild illness; (2) those treated with intravenous peramivir, presumed to already have severe illness at the initial visit; and (3) those who received baloxavir marboxil, to specifically assess the effectiveness of NIs.

To assess the robustness of the results to potential unmeasured confounding, we calculated E-values for the observed odds ratios using the method proposed by VanderWeele and Ding.[27] The E-value represents the minimum strength of association that an unmeasured confounder would need to have with both the exposure variable and the outcome variable, conditional on the measured covariates, to fully explain away the observed association.

All statistical analyses were performed using R software (version 4.3.3; R Foundation for Statistical Computing) and SAS software (version 9.4; SAS Institute Inc). A two-sided *p*-value < .05 was considered statistically significant. Data analyses were conducted between September 2024 and August 2025.

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第三章 Results

3.1 Participants

Figure 1 illustrates the enrollment process. Of 1,539 children with laboratory-confirmed influenza, 1,531 met the eligibility criteria. After age strata- and influenza season-matching, 1,492 children (354 hospitalized cases and 1,138 non-hospitalized controls) were included in the final analysis. The mean (SD, standard deviation) age of participants was 7.1 (4.6) years, and 654 (43.8%) were female (Table 1). Most patients (86.7%) were infected with influenza A. Figure 2 shows the monthly number of hospitalized and non-hospitalized children with laboratory-confirmed influenza included in this study. A marked decline in cases was observed during the 2021–2022 influenza season, coinciding with Taiwan's Zero-COVID policy during the first two years of the pandemic.

3.2 Clinical Presentation and Comorbidities

Fever was the most common initial symptom (97.9%), followed by cough and rhinorrhea. Most children presented with acute bronchitis or bronchiolitis (69.1%). Among the 354 hospitalized children, the most common discharge diagnoses were bronchopneumonia, sinusitis, or acute otitis media (37.9%); acute gastritis or dehydration (18.4%); acute bronchitis or bronchiolitis (16.7%); pneumonia (9.0%); and myositis or rhabdomyolysis (5.9%). Comorbidities were present in 17.6% of all patients, most commonly asthma (7.7%), preterm birth (2.9%), and neurologic disorders (2.0%) (Table 1).

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3.3 Antiviral Therapy and Outcomes

Among the 1,492 children, 1,206 (80.8%) received early antiviral therapy within two days of symptom onset, with oseltamivir being the most commonly prescribed agent (56.2%) (Table 1). Severe influenza-related illness occurred in 18 patients (1.2%). Two children developed long-term neurologic sequelae resulting from acute necrotizing encephalopathy. No deaths occurred. Children who received early antiviral therapy had significantly lower rates of hospitalization (16.1% [194 of 1,206] versus 55.9% [160 of 286]; $P < .001$) and severe influenza-related illness (0.7% [9 of 1,206] vs 3.1% [9 of 286]; $P < 001$) compared with those who did not receive early antiviral therapy (Supplementary Table 1).

3.4 Risk Factors for Influenza-associated Hospitalization

Younger age (aOR, 0.93; 95% CI, 0.87–0.99), presence of comorbidities (aOR, 2.76; 95% CI, 1.91–3.99), early antibiotic use (aOR, 7.32; 95% CI, 5.14–10.42), and co-infection (aOR, 3.88; 95% CI, 1.99–7.59) were independently associated with increased risk of influenza-related hospitalization (Table 2 and Supplementary Table 2). In contrast, early antiviral therapy was associated with an 81% lower risk of hospitalization (aOR, 0.19; 95% CI, 0.14–0.27). Multicollinearity was assessed using the variance inflation factor (VIF), with a maximum value of 1.2.

3.5 Risk Factors for Hospitalization: Stratified Analysis by Age and Antiviral Agents

Age-stratified analysis revealed that early antiviral therapy was associated with a reduction in risk of hospitalization by 80% among children aged ≤5 years (aOR, 0.20; 95% CI, 0.12–0.32)

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and by 83% among children older than 5 years (aOR, 0.17; 95% CI, 0.10–0.28) (Table 3). Risk factors for influenza-related hospitalization were similar across both age groups. We conducted stratified analyses comparing the effectiveness of early oseltamivir and zanamivir therapy in preventing hospitalization, which showed consistent results across both agents shown in Supplementary Table 3.

3.6 Sensitivity Analyses

Sensitivity analyses, summarized in Supplementary Tables 4–6, demonstrated that the estimated effectiveness of early antiviral therapy in preventing influenza-related hospitalization remained robust across sensitivity analysis, ranging from 80% to 82%. The E-value for the main analysis was as high as 10.0, with values ranging from 9.47 to 12.82 across subgroup analyses (Supplementary Table 7)—indicating that an extremely strong unmeasured confounder would be required to fully explain the observed associations.

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第四章 Discussion and Conclusion

4.1 Discussion

In this multicenter case-control study of 1,492 children with laboratory-confirmed influenza, designed to evaluate the primary outcome of influenza-associated hospitalization, matching by time of initial visit and age strata was used to account for time-varying influenza strains and population immunity. Early antiviral therapy initiated within 48 hours of symptom onset was associated with an 81% reduction in hospitalization risk. This protective effect remained robust among children aged ≤5 years, with an observed 80% reduction. The estimated effectiveness of early antiviral therapy was consistent across sensitivity analyses, with an E-value as high as 10.0—indicating that the observed association is highly unlikely to be explained by unmeasured confounding.

To our knowledge, this is the first study specifically evaluating the effectiveness of early antiviral therapy in preventing influenza-associated hospitalization among children under five years—a population particularly vulnerable to severe influenza-related complications. Current IDSA guidelines endorse early antiviral treatment for children younger than two years, those presenting with severe or progressive disease, or children with chronic underlying conditions to shorten illness duration; for other pediatric patients, early antiviral therapy initiated within 2 days of symptom onset may also be considered, however, data supporting this recommendation are limited.[11, 17, 23, 25, 28-36] In 2024, the WHO expanded its influenza treatment guidelines to include use of antivirals in non-severe outpatient influenza cases to shorten illness duration and decrease intra-familiar transmission.[12] Our findings provide new evidence supporting the implementation of early antiviral therapy among

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pediatric outpatients—not only for shortening illness duration or preventing otitis media but also for reducing the risk of hospitalization.

The timing of antiviral therapy may be decisive in determining its effectiveness. Individual patient data meta-analyses of RCTs in predominantly adult participants have reported conflicting findings regarding the effectiveness of antivirals in preventing influenza-related hospitalization. These discrepancies may stem from nuanced differences in the timing of treatment initiation (i.e., early vs unspecified). The observed effectiveness of early antiviral therapy in children in our study aligns with findings by Dobson et al., who reported a significant reduction in the risk of influenza-related hospitalization among adults when oseltamivir was initiated within 36 hours of symptom onset (relative risk [RR], 0.37; 95% CI, 0.17–0.8).[29] In contrast, Hanula et al. found that oseltamivir use, when timing of initiation was not specified, did not significantly reduce hospitalization risk among outpatients aged ≥12 years with confirmed influenza (RR, 0.73; 95% CI, 0.41–1.29).[37] Similarly, Jefferson et al. and Gao et al. reported that NIs and other antiviral use, without reference to timing, did not reduce the risk of hospitalization among predominantly adult populations.[28, 38 39] It is noteworthy that none of the prior RCTs enrolled young children aged ≤5 years to evaluate the efficacy of early antiviral therapy in preventing hospitalization in this highly vulnerable age group.[22, 23, 28-30, 32, 37, 38, 40-47]

Previous real-world studies on the effectiveness of antiviral therapy in preventing influenza-related hospitalization had been limited by a high rate of missing data due to the retrospective study design. For example, a cohort study conducted in 2009-2010 reported that community-based use of NIs significantly reduced the risk of hospitalization among

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participants younger than 16 years with confirmed or suspected influenza (odds ratio [OR], 0.25; 95% CI, 0.18–0.34),[23] but data on the timing of antiviral initiation were missing for up to 86% of participants.[25] In contrast, the present study—conducted using electronic medical records in the 2020s—captured complete information on the timing of antiviral therapy for all included cases and controls, with minimal missing data.

We observed that antibiotic use within the first two days of illness appeared to be associated with an increased risk of hospitalization.[18] Antibiotic use in the context of influenza-associated hospitalization may serve as a marker of more severe disease at presentation, although we cannot exclude the possibility that inappropriate early antibiotic use may adversely affect influenza outcomes. Previous studies have shown that early antiviral therapy may reduce the need for antibiotics prescribed for influenza-related complications and may lower the risk of secondary bacterial infections, such as otitis media and pneumonia.[23, 29, 42, 48-50] Further research is warranted to clarify whether antibiotic use reflects disease severity or directly contributes to poorer outcomes.

Our results also underscore the challenge posed by co-infection with other respiratory or bacterial pathogens. Despite seasonal variations in circulating viruses among different pediatric age groups, the prevalence of influenza co-infection observed in our study remains consistent with previous reports, even in the context of the COVID-19 pandemic.[51-53] Approximately 5% of children with influenza in our study were co-infected with additional viral, bacterial pathogens. Such co-infections were associated with an elevated risk of hospitalization, likely due to increased clinical severity and accelerated disease progression. The mechanisms contributing to enhanced severity in influenza co-infections are

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multifactorial and not yet fully understood.[54-56]

4.2 Limitations

This study has several important limitations. First, our study is observational and may be subject to confounding by indication. Physicians are more likely to prescribe antiviral therapy to children presenting with more severe illnesses, who were also at higher risk of hospitalization compared with those who did not receive early antiviral therapy. However, such bias would likely attenuate the observed protective effect, leading to an underestimation of the true effectiveness of early antiviral treatment. Therefore, the actual benefit of early antiviral therapy in pediatric outpatients with influenza may be greater than our findings suggest. The high E-values for the main analysis, up to 10.0, indicate that the observed effectiveness is extremely unlikely to be explained by an unmeasured confounder. Second, influenza vaccination is expected to reduce the risk of severe disease and hospitalization; however, data on self-paid influenza vaccinations were not available in the NIIS and therefore could not be included in our analysis. In addition, children younger than 6 months are not eligible for influenza vaccination in Taiwan. These limitations prevented a comprehensive assessment of the impact of vaccination on hospitalization risk in the current study. Nevertheless, because all included cases and controls had laboratory-confirmed influenza with viral shedding—rather than mild breakthrough infections detected by serologic testing—it is unlikely that vaccination status would substantially influence clinical outcomes in our study population. Third, this was hospital-based rather than a population-based study, which may limit the generalizability of our findings. Nevertheless, Taiwan's National Health Insurance system allows unrestricted access to hospitals without referral from community clinics, and the study hospitals serve as major providers of primary pediatric care in northern

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Taiwan, making our study population reasonably representative of the broader pediatric population. Fourth, our study was retrospective rather than prospective. However, the comprehensive electronic medical record systems in our hospitals enabled complete capture of relevant clinical data with minimal missing information, thereby reducing the potential for information bias inherent in retrospective data collection. Finally, although antiviral effectiveness may vary across agents,[46] our subgroup analysis showed that early oseltamivir and zanamivir use reduced hospitalization risk by 80% and 85%, respectively, with no significant difference between the two drugs. These results are consistent with a nationwide quasi-experimental study demonstrating comparable effectiveness of inhaled zanamivir and oral oseltamivir in preventing influenza-related hospitalization or death.[57] Therefore, the timely initiation of antiviral therapy may be more critical than agent selection, particularly given variations in pediatric prescribing practices across countries.

4.3 Conclusion

In conclusion, the results of this multicenter, age and season-matched case-control study provide new evidence strongly supporting the effectiveness of early antiviral therapy in reducing the risk of hospitalization among children, particularly those aged ≤5 years—the most vulnerable pediatric population. Our findings demonstrate that the benefits of antiviral therapy prescribed within 48 hours of symptom onset extend beyond symptom shortening.[11, 12] Expanding timely access to antiviral treatment, coupled with rapid diagnosis, has the potential to substantially reduce the global burden of influenza in children.

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Figure 1. The enrollment process

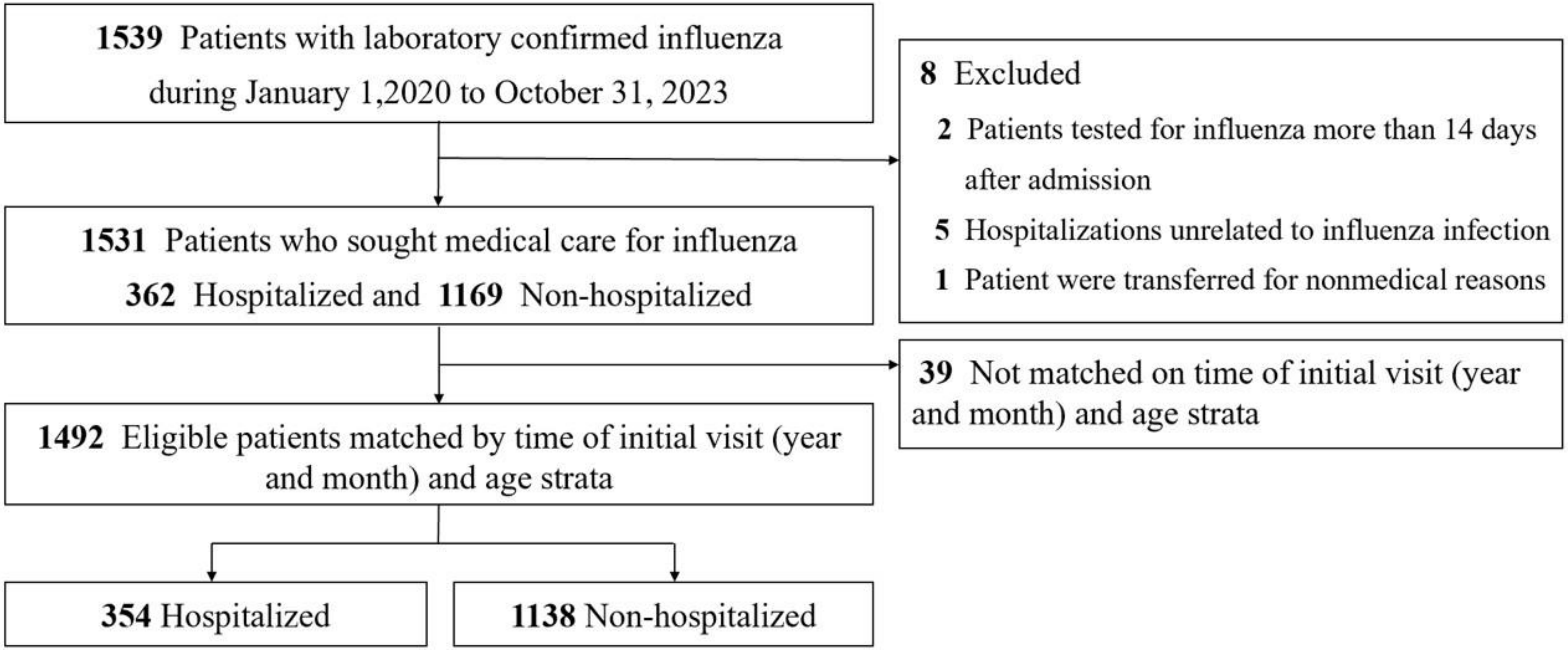

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Figure 2. Monthly number of hospitalized and non-hospitalized children with laboratory-confirmed influenza included in this study, January 2020 to October 2023

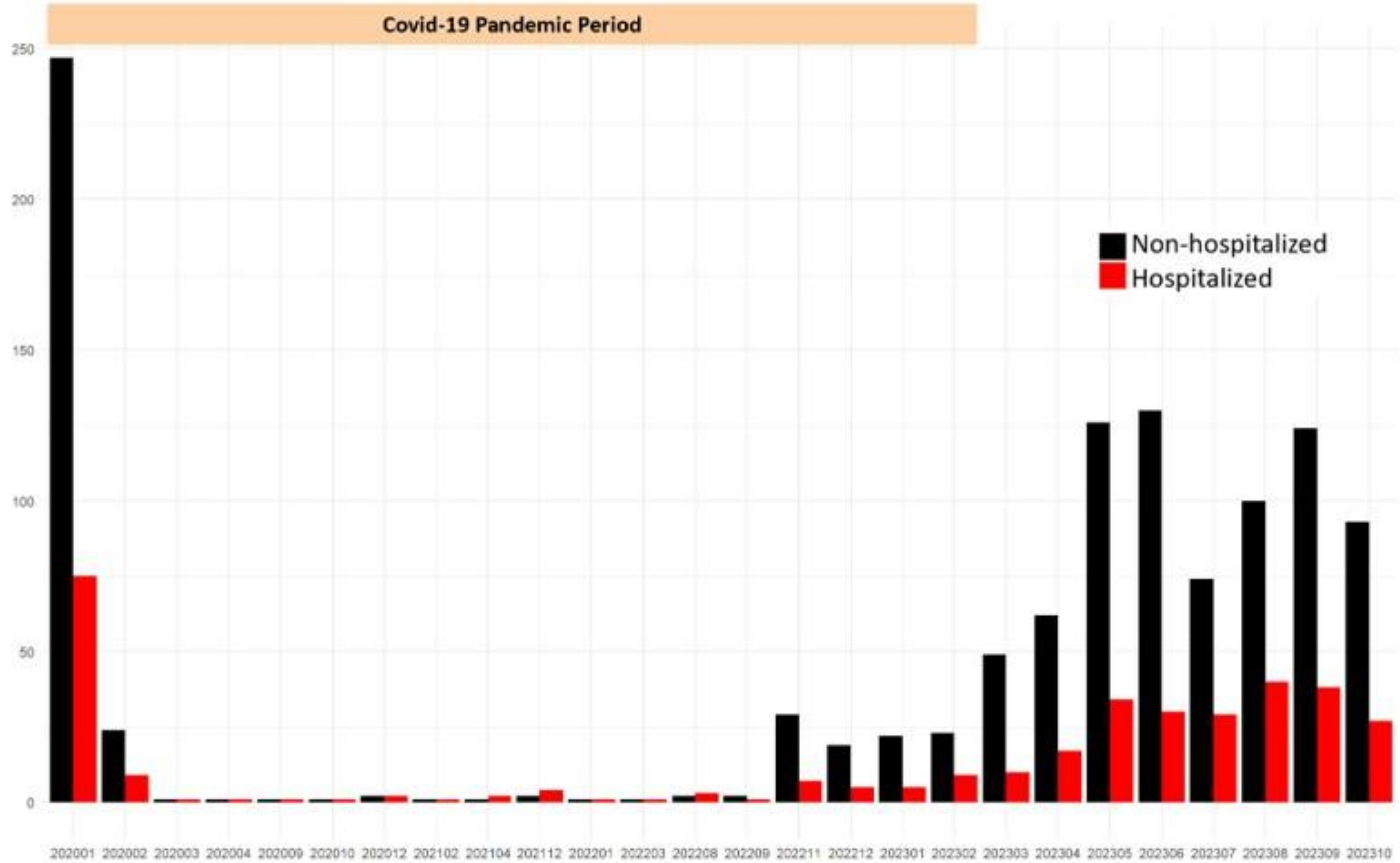

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Table 1. Demographic Data and Clinical Characteristics of Study Participants with Laboratory-Confirmed Influenza

	All n = 1492	Hospitalized n = 354	Non-hospitalized n = 1138	*p*-value [a]
Age				
Mean (SD), years	7.1 (4.6)	5.8 (4.1)	7.5 (4.7)	< .05
≤ 6 months	39 (2.6)	21 (5.9)	18 (1.6)	
7 months - 2 years	203 (13.6)	57 (16.1)	146 (12.8)	
3 years - 5 years	414 (27.7)	113 (31.9)	301 (26.4)	
6 years - 18 years	836 (56.0)	163 (46.0)	673 (59.1)	
Sex				
Female	654 (43.8)	169 (47.7)	485 (42.6)	.09
Male	838 (56.2)	185 (52.3)	653 (57.4)	
Underlying diseases				
No underlying disease	1230 (82.4)	250 (70.6)	980 (86.1)	< .05
Underlying disease	262 (17.6)	104 (29.4)	158 (13.9)	

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Neurological disease	30 (2.0)	20 (5.6)	10 (0.9)	
Preterm	43 (2.9)	12 (3.4)	31 (2.7)	
Asthma	115 (7.7)	44 (12.4)	71 (6.2)	
Renal disease	16 (1.0)	4 (1.1)	12 (1.0)	
Obesity/overweight	3 (0.2)	0 (0.0)	3 (0.3)	
Endocrine disease	5 (0.3)	5 (1.4)	0 (0.0)	
Hematological neoplasms	17 (1.1)	5 (1.4)	12 (1.1)	
Heart disease	15 (1.0)	5 (1.4)	10 (1.0)	
Others	18 (1.2)	9 (2.5)	9 (0.8)	
Influenza vaccination in the past year				
Publicly financed vaccination	552 (37.0)	204 (57.6)	348 (30.6)	< .05
Self-paid vaccination or no vaccination	940 (63.0)	150 (42.4)	790 (69.4)	
Types of influenza virus				
A	1294 (86.7)	311 (87.8)	983 (86.4)	
B	188 (12.7)	40 (11.3)	148 (13)	.10
A+B	8 (0.5)	1 (0.3)	7 (0.6)	
Unspecified	2 (0.1)	2 (0.6)	0 (0.0)	
Symptoms at presentation				

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Fever	1460 (97.9)	347 (98)	1113 (97.8)	< .05
Cough and rhinorrhea	1306 (87.5)	291 (82.2)	1015 (89.2)	< .05
Malaise/myalgia	510 (34.2)	277 (78.2)	233 (20.5)	< .05
Headache	249 (16.7)	32 (9.0)	217 (19.1)	< .05
Early AV (≤2 days of symptom onset)	1206 (80.8)	194 (54.8)	1012 (88.9)	< .05
No early AV (Late or No AV)	286 (19.2)	160 (45.2)	126 (11.1)	
Antiviral therapy				
No antiviral treatment	17 (1.1)	4 (1.1)	13 (1.1)	1.0
Oral oseltamivir	839 (56.2)	161 (45.5)	678 (59.6)	< .05
Inhaled zanamivir	397 (26.6)	15 (4.2)	382 (33.6)	< .05
Intravenous peramivir	146 (9.8)	102 (28.8)	44 (3.9)	< .05
Oral baloxavir marboxil	3 (0.2)	1 (0.2)	2 (0.2)	.56
NIs combination therapy	90 (6.0)	71 (20.1)	19 (1.7)	< .05
Other treatment				
Antibiotics (≤2 days of symptom onset)	288 (19.3)	178 (50.3)	110 (9.7)	< .05
Corticosteroids (≤2 days of symptom onset)	58 (3.9)	32 (9.0)	26 (2.3)	< .05
Final diagnosis				
Acute bronchitis/acute bronchiolitis	1030 (69.1)	59 (16.7)	971 (85.3)	< .05

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Bronchopneumonia/sinusitis/AOM	197 (13.2)	134 (37.9)	64 (5.6)	< .05
Pneumonia	38 (2.5)	32 (9.0)	5 (0.4)	< .05
Febrile convulsion	27 (1.8)	16 (4.5)	11 (1.0)	< .05
Croup	24 (1.6)	9 (2.5)	15 (1.3)	.14
Acute gastritis/dehydration	130 (8.7)	65 (18.4)	65 (5.7)	< .05
Encephalitis/meningitis/encephalopathy	18 (1.2)	17 (4.8)	1 (0.1)	< .05
Myositis/Rhabdomyolysis	25 (1.7)	21 (5.9)	4 (0.3)	< .05
Kawasaki disease	1 (0.01)	1 (0.3)	0 (0.0)	.24
Co-infection	69[b] (4.6)	51 (14.4)	18 (1.6)	< .05
Virus infection	30 (2.0)	21 (5.9)	9 (0.8)	< .05
Bacterial infection	42 (2.8)	32 (9.0)	10 (0.9)	< .05
Severe influenza-related illness [c]	18 (1.2)	18 (5.0)	0 (0.0)	< .05
Long-term neurological sequelae [d]	2 (0.1)	2 (0.6)	0 (0.0)	.06

Data are no. (%) of patients, unless otherwise indicated

Abbreviations: SD, standard deviation; AV, antiviral treatment; AOM, acute otitis media

[a] P-values were calculated using the chi-square test, Fisher's exact test, Student's t test, or ANOVA.

[b] Some patients had more than one co-infections: 18 cases of Mycoplasma pneumoniae, 15 of adenovirus, 6 of SARS-CoV-2, 6 of respiratory syncytial virus (RSV), 5 of Streptococcus pyogenes, 4 of Staphylococcus aureus, 3 of Streptococcus pneumoniae, 3 of rotavirus, 3 of Salmonella infection, 2 of Campylobacter jejuni, 2 of Escherichia

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coli, 2 of Enterococcus faecalis, 1 of Haemophilus influenzae (non-type B), 1 of Citrobacter koseri, 1 of parainfluenza virus, 1 of herpes simplex virus.

[c] Clinical deterioration requiring ICU admission and/or mechanical ventilation, resulting in death, or the development of complications such as Kawasaki disease or acute necrotizing encephalopathy

[d] Long-term neurologic sequelae resulting from acute necrotizing encephalopathy

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Table 2. Risk Factors for Influenza-related Hospitalization Among Children with Laboratory-Confirmed Influenza

	Univariable Model		Multivariable Model	
	Crude OR (95 % CI)	***p*-value**	**Adjusted OR (95 % CI)**	***p*-value**
Demographic data				
Age (years)	0.91 (0.86-0.96)	0.001	0.93 (0.87-0.99)	0.023
Male sex	0.81 (0.63-1.04)	0.10	0.81 (0.60-1.10)	0.17
Management				
Early antiviral therapy	0.15 (0.11-0.20)	<0.05	0.19 (0.14-0.27)	<0.05
Antibiotics (≤2 days)	10.87 (7.92-14.92)	<0.05	7.32 (5.14-10.42)	<0.05
Steroids (≤2 days)	4.71 (2.62-8.45)	<0.05	1.68 (0.83-3.41)	0.13
Presentation				
Having underlying disease	2.81 (2.08-3.79)	<0.05	2.76 (1.91-3.99)	<0.05
Having coinfection	9.86 (5.53-17.56)	<0.05	3.88 (1.99-7.59)	<0.05
Virus infection	7.69 (3.31-17.89)	<0.05	-	-
Bacterial infection	10.32 (4.92-21.67)	<0.05	-	-

Abbreviations: OR, odds ratio.

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Table 3. Risk Factors for Influenza-related Hospitalization: Subgroup Analysis of Age with Laboratory-Confirmed Influenza

	Multivariable Model Age ≤ 5 years (n= 656)		Multivariable Model Age 6-18 years (n= 836)	
	Adjusted OR (95 % CI)	*p*-value	Adjusted OR (95 % CI)	*p*-value
Demographic data				
Age (years)	0.85 (0.63-1.32)	0.26	0.93 (0.87-1.00)	0.040
Male sex	0.80 (0.53-1.23)	0.31	0.85 (0.55-1.33)	0.49
Management				
Early antiviral therapy	0.20 (0.12-0.32)	<0.05	0.17 (0.10-0.28)	<0.05
Antibiotics (≤2 days)	4.63 (2.80-7.64)	<0.05	11.46 (6.94-18.91)	<0.05
Steroids (≤2 days)	1.50 (0.59-3.81)	0.39	2.05 (0.69-6.15)	0.20
Presentation				
Having underlying disease	3.26 (1.86-5.70)	<0.05	2.43 (1.47-4.01)	0.001
Having coinfection	3.91 (1.64-9.33)	0.002	3.48 (1.21-10.00)	0.021

Abbreviations: OR, odds ratio.

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Supplementary Table 1. Demographic Data and Clinical Characteristics of Children Receiving Early vs Late or No Antiviral Therapy

	Early Antiviral Therapy, n = 1206	Late or No Antiviral Therapy, n = 286
Age, mean (SD), years	7.3 (4.7)	6.4 (4.2)
Sex		
Female	519 (43.0)	135 (47.2)
Male	687 (57.0)	151 (52.8)
Underlying conditions		
No underlying disease	1008 (83.6)	222 (77.6)
Underlying disease	198 (16.4)	64 (22.4)
Antiviral therapy		
No antiviral treatment	0 (0.0)	17 (5.9)
Oral oseltamivir	701 (58.1)	138 (48.2)
Inhaled zanamivir	349 (28.9)	48 (16.8)
Intravenous peramivir	89 (7.4)	57 (19.9)
Oral baloxavir marboxil	3 (0.2)	0 (0.0)
NIs combination therapy	64 (5.3)	26 (9.1)
Other treatment		
Antibiotics (≤2 days of symptom onset)	168 (13.9)	120 (41.9)
Corticosteroids (≤2 days of symptom onset)	36 (3.0)	22 (7.7)
Final diagnosis		
Acute bronchitis/acute bronchiolitis	920 (74.4)	110 (38.5)

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Bronchopneumonia/sinusitis/AOM	102 (8.5)	96 (33.6)
Pneumonia	15 (1.2)	22 (7.7)
Febrile convulsion	25 (2.1)	2 (0.7)
Croup	17 (1.4)	7 (2.4)
Acute gastritis/dehydration	102 (8.5)	28 (9.8)
Encephalitis/meningitis/encephalopathy	13 (1.1)	5 (1.8)
Myositis/Rhabdomyolysis	10 (0.8)	15 (5.2)
Kawasaki disease	0 (0.0)	1 (0.3)
Co-infection	39 (3.2)	30 (10.5)
Admission	194 (16.1)	160 (55.9)
Severe influenza-related illness [a]	9 (0.7)	9 (3.1)
Long-term neurological sequelae [b]	0 (0.0)	2 (0.7)

Data are no. (%) of patients, unless otherwise indicated

Abbreviations: SD, standard deviation; AOM, acute otitis media

[a] Clinical deterioration requiring ICU admission and/or mechanical ventilation, resulting in death, or the development of complications such as Kawasaki disease or acute necrotizing encephalopathy

[b] Long-term neurologic sequelae resulting from acute necrotizing encephalopathy

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Supplementary Table 2. Variance Inflation Factors (VIFs) for Multicollinearity among Variables Associated with Influenza-related Hospitalization

Variables	VIFs
Age (years)	1.01
Male sex	1.00
Early antiviral therapy	1.10
Antibiotics (≤2 days)	1.12
Steroids (≤2 days)	1.07
Having underlying disease	1.05
Having co-infection	1.09

Note: Multicollinearity was assessed using the variance inflation factor (VIF), with values greater than 5 indicating multicollinearity.

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Supplementary Table 3. Risk Factors for Influenza-related Hospitalization: Subgroup Analysis of Oseltamivir vs Zanamivir (n = 1326)

	Multivariable Model Oseltamivir (n= 901)		**Multivariable Model Zanamivir (n= 425)**	
	Adjusted OR (95 % CI)	***p*-value**	**Adjusted OR (95 % CI)**	***p*-value**
Demographic data				
Age (years)	0.91 (0.82-1.00)	0.06	1.02 (0.89-1.16)	0.82
Male sex	0.66 (0.45-0.98)	0.04	1.40 (0.60-3.29)	0.44
Management				
Early antiviral therapy	0.20 (0.12-0.31)	<0.05	0.15 (0.06-0.37)	<0.05
Antibiotics (≤2 days)	7.32 (4.59-11.66)	<0.05	12.22 (4.91-30.40)	<0.05
Steroids (≤2 days)	1.55 (0.61-3.93)	0.36	4.29 (0.64-28.84)	0.13
Presentation				
Having underlying disease	2.31 (1.42-3.77)	<0.05	3.10 (1.26-7.67)	0.014
Having co-infection	3.42 (1.38-8.49)	0.008	0.86 (0.10-7.49)	0.89

Abbreviations: OR, odds ratio.

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Supplementary Table 4. Risk Factors for Influenza-related Hospitalization among Children with Laboratory-Confirmed Influenza, Excluding Patients Who Did Not Receive Antiviral Therapy (n = 1475)

	Univariable Model		**Multivariable Model**	
	Crude OR (95 % CI)	***p*-value**	**Adjusted OR (95 % CI)**	***p*-value**
Demographic data				
Age (years)	0.91 (0.86-0.96)	0.001	0.93 (0.87-0.99)	0.022
Male sex	0.82 (0.64-1.06)	0.13	0.82 (0.61-1.12)	0.21
Management				
Early antiviral therapy	0.14 (0.10-0.19)	<0.05	0.18 (0.13-0.25)	<0.05
Antibiotics (≤2 days)	11.09 (8.06-15.27)	<0.05	7.42 (5.19-10.61)	<0.05
Steroids (≤2 days)	4.97 (2.74-8.99)	<0.05	1.82 (0.88-3.74)	0.11
Presentation				
Having underlying disease	2.76 (2.05-3.74)	<0.05	2.71 (1.86-3.92)	<0.05
Having co-infection	9.22 (5.15-16.53)	<0.05	3.69 (1.87-7.28)	<0.05

Abbreviations: OR, odds ratio.

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Supplementary Table 5. Risk Factors for Influenza-related Hospitalization among Children with Laboratory-Confirmed Influenza, excluding Patients Who Did Not Receive Antiviral Therapy and Patients Who Received Intravenous Peramivir Therapy (n = 1239)

	Univariable Model		**Multivariable Model**	
	Crude OR (95 % CI)	***p*-value**	**Adjusted OR (95 % CI)**	***p*-value**
Demographic data				
Age (years)	0.87 (0.80-0.94)	0.001	0.87 (0.79-0.96)	0.004
Male sex	0.69 (0.49-0.97)	0.03	0.57 (0.38-0.85)	0.006
Management				
Early antiviral therapy	0.15 (0.10-0.22)	<0.05	0.20 (0.13-0.31)	<0.05
Antibiotics (≤2 days)	10.01 (6.65-15.08)	<0.05	6.74 (4.26-10.66)	<0.05
Steroids (≤2 days)	6.48 (3.08-13.61)	<0.05	2.65 (1.02-6.87)	0.05
Presentation				
Having underlying disease	2.22 (1.48-3.33)	<0.05	2.09 (1.28-3.42)	0.003
Having co-infection	7.90 (3.71-16.84)	<0.05	3.46 (1.47-8.14)	0.004

Abbreviations: OR, odds ratio.

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Supplementary Table 6. Risk Factors for Influenza-related Hospitalization among Children with Laboratory-Confirmed Influenza, Restricted to Oseltamivir or Zanamivir Use (n = 1236)

	Univariable Model		**Multivariable Model**	
	Crude OR (95 % CI)	***p*-value**	**Adjusted OR (95 % CI)**	***p*-value**
Demographic data				
Age (years)	0.87 (0.80-0.95)	0.002	0.87 (0.79-0.96)	0.007
Male sex	0.68 (0.48-0.96)	0.03	0.56 (0.37-0.83)	0.004
Management				
Early antiviral therapy	0.15 (0.10-0.22)	<0.05	0.20 (0.13-0.31)	<0.05
Antibiotics (≤2 days)	9.97 (6.62-15.02)	<0.05	6.71 (4.24-10.63)	<0.05
Steroids (≤2 days)	6.48 (3.08-13.61)	<0.05	2.64 (1.02-6.84)	0.05
Presentation				
Having underlying disease	2.24 (1.49-3.36)	<0.05	2.15 (1.31-3.53)	0.002
Having co-infection	8.10 (3.76-17.47)	<0.05	3.67 (1.53-8.80)	0.004

Abbreviations: OR, odds ratio.

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Supplementary Table 7. E-Values for Association between Early Antiviral Therapy and Reduced Risk of Influenza-related Hospitalization

Analysis	E-value (Upper Confidence Limit of 95% CI)
Main analysis (all children)	10.00 (6.86)
Children ≤ 5 years	9.47 (5.71)
Children > 5 years	11.24 (6.60)
Oseltamivir subgroup	9.47 (5.91)
Zanamivir subgroup	12.82 (4.84)
Sensitivity analysis (excluding No antiviral)	10.60 (7.46)
Sensitivity analysis (excluding No antiviral and Peramivir)	9.47 (5.91)
Sensitivity analysis (restricted to Oseltamivir/Zanamivir)	9.47 (5.91)

Note: E-values were calculated to estimate the minimum strength of association that an unmeasured confounder would need to have with both early antiviral therapy and influenza-related hospitalization to explain away the observed effect, conditional on the measured covariates. Higher E-values indicate greater robustness to unmeasured confounding.

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