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MAJOR ARTICLE

Oseltamivir Reduces 30-Day Mortality in Older Adults With Influenza: A Pooled Analysis From the 2012–2019 Serious Outcomes Surveillance Network of the Canadian Immunization Research Network

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Background. Oseltamivir is recommended for the treatment of adults hospitalized with influenza, but adherence is often suboptimal. This may be due to doubts about the reliability of the evidence supporting its benefits, particularly when initiation is delayed. We aimed to assess the effectiveness of oseltamivir in reducing mortality in older adults hospitalized with influenza, with a focus on the timing of initiation.

Methods. The CIRN-SOS Network gathered data on severe respiratory illnesses across 5 Canadian provinces during the influenza seasons 2012–2019. Individuals aged ≥65 years with confirmed influenza and available antiviral prescription data were included. We compared the 30-day survival rates of hospitalized patients based on oseltamivir prescription status. Kaplan-Meier estimated survival probability and inverse probability of treatment (IPT)–weighted Cox proportional hazard models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality. The analyses considered the time to antiviral initiation (>48 vs ≤48 hours).

Results. Among the 8135 influenza patients studied, 2126 did not receive antiviral treatment, whereas 6009 were treated with oseltamivir. A total of 395 patients were hospitalized for >30 days. The overall mortality rate was 8.32 per 1000 person-days, with 53.9% of the deaths occurring within the first week. Oseltamivir recipients had a 18% lower risk of 30-day mortality (IPT-weighted HR, 0.82 [95% CI, .69–.98]). The benefit was significant for influenza A (IPT-weighted HR, 0.74 [95% CI, .61–.91]) but not for influenza B (IPT-weighted HR, 1.12 [95% CI, .81–1.56]). Oseltamivir remained effective even when initiated after 48 hours (IPT-weighted HR, 0.66 [95% CI, .49–.90]). Influenza vaccination did not mediate the effectiveness of oseltamivir in reducing mortality.

Conclusions. Oseltamivir significantly reduces mortality risk in older adults hospitalized with influenza, even when administered after 48 hours, independent of vaccination status.

Clinical Trials Registration. NCT01517191.

Keywords. antiviral; frailty; influenza; older adult; oseltamivir.

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The epidemiology of influenza in older adults is a complex issue with multiple facets [1]. As individuals age, their immune systems become dysregulated, making them more susceptible to infections, particularly respiratory illnesses [2]. Moreover, older adults may have existing medical conditions that can exacerbate the impact of influenza, increasing their risk of experiencing severe complications, such as hospitalization, cardiovascular complications, or even death [3–8]. Age-related differences have been identified in underlying comorbidities, presenting symptoms, and adverse clinical outcomes among hospitalized patients with influenza [1, 9]. Additionally, it is well-established that influenza vaccination can protect against adverse clinical outcomes [1, 10]. However, the effectiveness of the influenza vaccine depends on various factors, such as the type of vaccine, viral circulation, mismatches between the vaccine and circulating strains, and host factors, including age and frailty [11].

Antiviral treatment of influenza can effectively reduce the disease burden on the healthcare system and the odds of hospitalization [12, 13]. Additionally, timely administration of antiviral medication can significantly lower the likelihood of complications such as intensive care admission and even death [14]. Previous studies have shown that the most significant benefits of antiviral treatment are typically observed within the first 48 hours of symptom onset [10, 15, 16]. However, evidence also suggests that older adults, particularly those aged ≥80 years, can experience positive outcomes from treatment even beyond this 48-hour window. Specifically, antiviral treatment has proven effective for patients aged ≥40 years within 7 days of symptom onset, with continued protective benefits for those aged ≥80 years, even when initiated >7 days after symptom onset [13]. Despite these findings, there remains a reluctance to prescribe oseltamivir after 48 hours, which significantly affects clinical decision-making, particularly later in the course of the illness. Given the potential advantages of antiviral treatment for older adults with preexisting medical conditions that increase the risk of severe influenza complications [17], it is essential to reconsider these missed treatment opportunities.

We aimed to assess the effectiveness of oseltamivir in reducing 30-day mortality rates due to influenza among older adults admitted to hospitals. Furthermore, we performed additional analyses to examine whether the effectiveness of antiviral drugs differed depending on the timing of initiation (>48 vs ≤48 hours from the date of admission) and whether patients had received influenza vaccination in the current season. Additionally, we investigated a mediation hypothesis to explore whether vaccination status indirectly affected mortality by influencing the probability of receiving oseltamivir.

METHODS

Data Source

This study used a cohort design, and pooled data from the Serious Outcomes Surveillance (SOS) Network of the Canadian Immunization Research Network (CIRN) database. The SOS Network is an active influenza surveillance network that collects data from hospitals in various Canadian provinces [9, 18, 19]. The study examined data from 8 influenza seasons (2011–2012 to 2018–2019). During these seasons, participation varied between 13 and 40 hospitals across 4–7 provinces: British Columbia, Alberta, Manitoba, Ontario, Québec, New Brunswick, and Nova Scotia.

Study Design and Participants

The study included individuals aged ≥65 years with confirmed influenza infection and accessible information about their antiviral prescriptions. As part of the SOS Network Hospital surveillance protocol, all individuals with acute respiratory illnesses underwent nasopharyngeal swabs for influenza testing using reverse-transcription polymerase chain reaction [17]. Since almost all antiviral prescriptions were oseltamivir, we excluded the remaining prescriptions. For further clarity, refer to Supplementary Figure 1 for the detailed selection process of the participants.

The study protocol, which encompassed procedures for data collection, sample collection, and medical record screening, was approved by the research ethics board at each participating site and registered under the ClinicalTrials.gov identifier NCT01517191. For comprehensive information regarding the number of participating sites and additional locations beyond Halifax, readers are directed to consult the Ethics Approval and Participation Consent section, which provides a thorough overview of the study's ethical considerations and logistical arrangements.

Oseltamivir Prescriptions

Participants were initially divided into 2 groups based on whether they received oseltamivir. They were further classified into 3 groups: those who did not receive antivirals, those who were administered oseltamivir within 48 hours of hospital admission, and those who were prescribed oseltamivir after ≥48 hours.

Vaccination Status Assessment

Participants' influenza vaccination status was determined by reviewing their medical records, conducting interviews, and verifying their immunization information. We grouped participants as "current season vaccinated" if they had received vaccination at least 14 days before symptom onset and "not vaccinated in the current season" otherwise.

Data Collection

We collected data using a standardized SOS Network protocol, which included demographic data such as sex, age, location, and the influenza season when we collected the data. The general health data included smoking status, comorbidity burden,

need for regular support for activities of daily living, and perceived need for additional home support.

We used Quan and colleagues' updated Charlson Comorbidity Index (uCCI) to evaluate the comorbidity burden of participants [20]. We assessed comorbidity burden using a score and dichotomous variable. We set the cutoff point of the dichotomous variable to ≥4, indicating a 10-year mortality risk of ≥5%.

Function was measured as requiring assistance for activities of daily living. Depending on the patient's needs, these tasks may require assistance, which can be categorized as either regular or additional support. This support could have been provided by family and friends ("informal support") and/or by paid caregivers ("formal support").

Outcomes of Interest

The participants' progress was monitored from hospital admission until 30 days after discharge or death. The primary outcome of the study was to establish mortality within 30 days of hospital admission and to analyze whether the participants were prescribed oseltamivir. Additionally, the study aimed to assess the effectiveness of oseltamivir started within or after 48 hours of admission and to examine whether the effectiveness of oseltamivir against 30-day mortality varied based on the participants' influenza vaccination status.

Bias

We implemented several methodological strategies to address the potential sources of bias in our study. The use of a standardized SOS Network protocol ensured that participants were accurately classified into groups based on oseltamivir administration, thereby reducing the potential for misclassification bias. We employed the stabilized inverse probability of treatment weighting (IPTW) method to estimate the average treatment effect for the treated (ATT) [21]. The IPTW method facilitated a balanced distribution of baseline covariates between individuals who received oseltamivir and those who did not receive antiviral treatment by assigning weights that equalized the covariate distribution across treatment groups.

To minimize potential selection bias, all participants were included in the study regardless of hospitalization duration, encompassing those with stays >30 days. This decision was informed by the need to ensure representativeness and generalizability of the findings, as excluding participants based on hospitalization length could inadvertently skew the sample [22]. By maintaining a diverse participant pool, we aimed to capture the full spectrum of patient experiences and outcomes, thereby avoiding the systematic bias that could arise from differential inclusion.

Additionally, we used an inverse probability–weighted Cox proportional hazards model to assess the time-varying effects of oseltamivir prescriptions, thereby mitigating the risk of immortal time bias. This model allowed us to precisely capture and account for patient exposure periods throughout the follow-up period [23]. Furthermore, for variance estimation, we implemented a robust sandwich estimator to guarantee precise and dependable variance calculations.

Statistical Analysis

Descriptive statistics were used to compare features across exposure groups, focusing on those not administered antivirals versus those who received oseltamivir. Covariate imbalances were assessed using standardized mean differences and differences in proportion, with a strict threshold of 0.05 indicating a significant imbalance between the groups [24]. To address these imbalances, we employed the stabilized IPTW method by assigning weights that equalized the covariate distribution across treatment groups, thus estimating the ATT between those who received oseltamivir and those who did not. The Supplementary Material contains a detailed description of the methods applied to balance the covariates using IPTW.

Mortality. Mortality proportions from the time of hospitalization were analyzed for both cohorts. Subsequently, point estimates and measures of association strength were calculated. To evaluate the differences in mortality proportions within 30 days, we used the χ^2 test. Subsequently, we calculated mortality rates by incorporating person-time between hospitalization and oseltamivir prescription in the denominator for those who received oseltamivir. We then computed an "adjusted" mortality rate for patients who received oseltamivir, taking into account the exposed person-time and events among this group, starting from the time of oseltamivir prescription.

The Kaplan-Meier method was used to estimate survival probabilities at various time points, and the log-rank test was used to statistically compare survival times between the exposure groups. A Cox proportional hazards model was used to estimate the inverse probability of treatment (IPT)–weighted hazard ratio (HR), accounting for the time-varying effects of oseltamivir prescriptions. A robust sandwich estimator was used to ensure accurate variance estimation. An HR <1 indicated a lower risk among individuals administered oseltamivir.

Exploratory Analysis. We conducted a stratified analysis using the Cochran-Mantel-Haenszel (CMH) test to explore whether the effectiveness of oseltamivir varied according to influenza vaccination status. Furthermore, we used Preacher and Hayes' bootstrapping method [25] to investigate a hypothetical mediation chain of cause and effect, where receiving an influenza vaccine impacts the probability of being administered

oseltamivir, and thus affects the likelihood of death. For example, this could occur if patients who were at a higher risk of death due to being older or having more comorbidities were more likely to have been vaccinated and more or less likely to have received oseltamivir.

Statistical significance was assessed using a 2-sided $P < .05$. All analyses were performed using R (R version 4.4.0 "Puppy Cup" release) and RStudio IDE (RStudio 2024.04.0+735 "Chocolate Cosmos" release) software.

RESULTS

Study Participants

This study analyzed data from 8135 patients with laboratory-confirmed influenza. Of these, 2126 (26.1%) patients did not receive antiviral treatment, whereas 6009 (73.9%) received oseltamivir. The mean interval from hospitalization to antiviral treatment initiation was 0.931 days with a standard deviation of 1.60 days. Notably, of those who were treated with oseltamivir, 44.9% received it starting on the day of hospitalization. Furthermore, 35.8% of the patients commenced treatment 1 day posthospitalization and 11.3% initiated treatment 2 days posthospitalization (Supplementary Figure 2).

A significant number of patients (37.3%) were aged ≥85 years, followed by 35.7% aged 75–84 years and 27.0% aged 65–74 years. Slightly over half of the patients (53.5%) were female. Most patients lived in private houses (65.5%), required regular support for daily activities (57.1%), and received informal support (44.1%). More than one-third of the patients were former smokers (34.1%), and the majority had a median uCCI of 1 (first, third quartiles: 1, 2). The uCCI estimated that the 10-year mortality risk was ≥5% in 9.2% of the patients. Approximately 57.0% of the patients had not been vaccinated during the current season. Influenza A was identified in most of the patients (73.8%). Notably, a few differences were observed between the groups, including the influenza season, the need for regular informal and paid formal personal care support, and the number of positive cases of influenza B. Table 1 displays the outcomes of balancing both before and after the application of IPTW.

30-Day Mortality

Of the 8135 patients studied, 395 experienced prolonged hospitalization lasting >30 days. Please refer to Supplementary Figure 3 for detailed information on these extended hospital stays. The overall mortality ratio within 30 days of hospitalization was 8% (653/8135), with most deaths (53.9%) occurring during the first week of hospitalization (Supplementary Figure 4). On day 14, the Kaplan-Meier estimated probability of survival was 86.9% (95% confidence interval [CI], 85.7%–88.1%), but by day 21, it had declined to 80.6% (95% CI, 78.9%–82.4%). Finally, on day 30, the survival probability decreased to 74.2% (95% CI, 71.9%–76.7%).

There was a significant difference in the estimated 30-day survival probability between the patients who received oseltamivir and those who did not (log-rank $P < .001$). Among patients who were not administered antivirals, the crude 30-day mortality rate was 9.4% (199/2126), whereas for those who were administered oseltamivir, the rate was 7.6% (454/6009) ($P = .009$, χ^2 test; Table 2). The mortality crude incidence risk was 0.81 (95% CI, .69–.95) times lower in patients receiving oseltamivir than those not receiving antivirals.

The overall mortality rate across both groups was 8.32 per 1000 person-days. For patients who received oseltamivir, the mortality rate was marginally lower, at 7.62 per 1000 person-days, compared to 10.52 per 1000 person-days for those who did not receive such treatment. An "adjusted" mortality rate, accounting for time-varying exposure, was calculated for those initiated oseltamivir, resulting in a rate of 8.10 per 1000 person-days. The IPT-weighted HR accounting for time-varying exposure to oseltamivir was 0.82 (95% CI, .69–.98; $P = .034$). The HR was lower for influenza A (HR, 0.74 [95% CI, .61–.91]; $P = .005$) than for influenza B (HR, 1.12 [95% CI, .81–1.56]; $P = .476$).

The effectiveness of oseltamivir, categorized as administered ≤48 hours or >48 hours after hospital admission, was significantly reduced in the latter group (Table 3). However, one should consider that the imbalance of covariates between the groups could explain the loss of statistical significance. Supplementary Table 1 in the Supplementary Material compares the sociodemographic and clinical characteristics categorized by the timing of antiviral prescription. Analysis of the data using IPTW revealed that although the CI increased, the antiviral effect remained statistically significant (IPT-weighted HRs: 0.68 [95% CI, .56–.82] for oseltamivir ≤48 hours and 0.66 [95% CI, .49–.90] for oseltamivir >48 hours).

Exploratory Analysis

The initial analysis suggested a noticeable contrast in the probability of death between the 2 groups of individuals who received different exposures (oseltamivir vs no antivirals) and those who did not receive the influenza vaccine ($P = .009$, CMH test). The CMH odds ratio (OR) of 0.79 (95% CI, .66–.94) suggests that the mortality rate was lower in the group that received both oseltamivir and influenza vaccine than in those who received oseltamivir alone (Table 4).

To further investigate this connection, we analyzed a hypothetical chain of cause and effect where receiving an influenza vaccine affects the probability of being given oseltamivir and, thus, the likelihood of death. Our findings indicated that the effect of influenza vaccination on the relationship between oseltamivir prescription and the odds of death was not statistically significant (bootstrapped average causal mediation effects, $P = .794$). However, oseltamivir prescription had a direct effect (bootstrapped average direct effect, $P = .014$) and significant overall impact ($P = .014$).

Table 1. Sociodemographic and Clinical Characteristics of Study Participants

Level	Overall	No Antiviral	Oseltamivir	Standard Difference[a]	IPT-Weighted[a]
No.	8135	2126	6009	…	…
Age range, y					
65–74	2193 (27.0)	559 (26.3)	1634 (27.2)	0.0090	0.0113
75–84	2908 (35.7)	796 (37.4)	2112 (35.1)	−0.0229	−0.0107
≥85	3034 (37.3)	771 (36.3)	2263 (37.7)	0.0139	−0.0007
Sex					
Female	4352 (53.5)	1141 (53.7)	3211 (53.4)	0.0023	0.0028
Male	3783 (46.5)	985 (46.3)	2798 (46.6)		
Baseline living, %					
Assisted living/LTC facility	2106 (25.9)	565 (26.6)	1541 (25.6)	−0.0093	−0.0149
Community group home	66 (0.8)	28 (1.3)	38 (0.6)	−0.0068	−0.0051
Community private house	5330 (65.5)	1381 (65.0)	3949 (65.7)	0.0076	0.0246
Shelter/homeless	23 (0.3)	8 (0.4)	15 (0.2)	−0.0013	−0.0015
Unknown	610 (7.5)	144 (6.8)	466 (7.8)	0.0098	−0.0031
Influenza season					
2011–2012	344 (4.2)	150 (7.1)	194 (3.2)	−0.0383	0.0003
2012–2013	1409 (17.3)	521 (24.5)	888 (14.8)	**−0.0973**	0.0000
2013–2014	1144 (14.1)	321 (15.1)	823 (13.7)	−0.0140	0.0003
2014–2015	1348 (16.6)	390 (18.3)	958 (15.9)	−0.0240	0.0001
2015–2016	579 (7.1)	130 (6.1)	449 (7.5)	0.0136	0.0001
2016–2017	1140 (14.0)	226 (10.6)	914 (15.2)	0.0458	0.0000
2017–2018	1622 (19.9)	323 (15.2)	1299 (21.6)	**0.0642**	−0.0001
2018–2019	549 (6.7)	65 (3.1)	484 (8.1)	**0.0500**	−0.0008
Smoking status					
Current smoker	1808 (22.2)	484 (22.8)	1324 (22.0)	−0.0073	−0.0314
Former smoker	2770 (34.1)	735 (34.6)	2035 (33.9)	−0.0071	0.0031
Never smoked	2969 (36.5)	727 (34.2)	2242 (37.3)	0.0312	0.0468
Unknown	588 (7.2)	180 (8.5)	408 (6.8)	−0.0168	−0.0186
Comorbidity burden					
Charlson Comorbidity Index[b]	1 (1, 2)	1 (1, 2)	1 (1, 2)	0.0436	0.0327
Estimated 10-y mortality risk ≥5%	745 (9.2)	168 (7.9)	577 (9.6)	0.0170	0.0108
Influenza vaccination status					
Current season vaccination	3500 (43.0)	929 (43.7)	2571 (42.8)	−0.0091	0.0427
Not vaccinated in the current season	4635 (57.0)	1197 (56.3)	3438 (57.2)		
Baseline support for ADLs					
Requires regular support	4649 (57.1)	1092 (51.4)	3557 (59.2)	**0.0783**	−0.0002
Informal support	3590 (44.1)	833 (39.2)	2757 (45.9)	**0.0670**	0.0056
Paid formal nonnursing support	2245 (27.6)	532 (25.0)	1713 (28.5)	0.0348	−0.0022
Paid formal personal care support	2169 (26.7)	464 (21.8)	1705 (28.4)	**0.0655**	0.0349
Paid nursing support	1419 (17.4)	325 (15.3)	1094 (18.2)	0.0292	0.0058
The patient or family identifies a need for more support for the patient at the time of hospitalization	1782 (21.9)	416 (19.6)	1366 (22.7)	0.0317	0.0266
Influenza type					
Influenza A	6006 (73.8)	1472 (69.2)	4534 (75.5)	**0.0622**	−0.0007
Influenza A/B	3 (0.0)	0 (0.0)	3 (0.0)	0.0005	0.0005
Influenza B	2118 (26.0)	649 (30.5)	1469 (24.4)	**−0.0608**	0.0007
Unsubtyped	8 (0.1)	5 (0.2)	3 (0.0)	−0.0019	−0.0005

Values in bold indicate covariate imbalances that exceeded the threshold of 0.05, signifying a significant imbalance between the groups, as assessed using standardized mean differences and differences in proportion.

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ADLs, activities of daily living; IPT, inverse probability of treatment; LTC, long-term care.

[a]Standardized mean difference (for continuous variables) and differences in proportions (for categorical variables).

[b]Median (first, third quartiles).

Table 2. Effect of Oseltamivir on 30-Day Mortality

30-d Mortality	Exposure Group		Total, No.	*P* Value
	No Antivirals, No.	Oseltamivir, No.		
Deceased	199	454	653	.009
Survived	1927	5555	7482	
Point estimates				
Incidence risk ratio			0.81 (.69–.95)	
Attributable fraction in the oseltamivir group, % (95% CI)			−23.89 (−45.26 to −5.67)	
Attributable fraction in the study population, % (95% CI)			−16.61 (−30.25 to −4.40)	
Number needed to treat for benefit (95% CI)			55 (251–31)	
IPT-weighted hazard ratio (95% CI)			0.82 (.69–.98)	

Abbreviations: CI, confidence interval; IPT, inverse probability of treatment.

Table 3. Effect of Oseltamivir on 30-Day Mortality Based on Prescription Timing

30-d Mortality	Exposure Group			Total
	No Antivirals, No.	Oseltamivir ≤48 h, No.	Oseltamivir >48 h, No.	
Deceased	199	403	51	653
Survived	1927	5129	426	7482
Point estimates (95% CI)				
Incidence risk ratio				
Oseltamivir ≤48 h			0.78 (.66–.92)	
Oseltamivir >48 h			1.14 (.85–1.53)	
Attributable fraction in the oseltamivir group, %				
Oseltamivir ≤48 h			−28.49 (−51.13 to −9.24)	
Oseltamivir >48 h			12.45 (−17.13 to 34.57)	
Attributable fraction in the study population, %				
Oseltamivir ≤48 h			−19.07 (−32.74 to −6.81)	
Oseltamivir >48 h			2.54 (−3.43 to 8.16)	
IPT-weighted hazard ratio (95% CI)				
Oseltamivir ≤48 h			0.68 (.56–.82)	
Oseltamivir >48 h			0.66 (.49–.90)	

Abbreviations: CI, confidence interval; IPT, inverse probability of treatment.

DISCUSSION

We found a 30-day mortality rate of 8.32 per 1000 person-days among older adults hospitalized for influenza infection. Notably, most deaths occurred within the first week of hospitalization, highlighting the critical need for timely intervention in this demographic group. Our analysis revealed that 74% of hospitalized older adults with laboratory-confirmed influenza received oseltamivir (of whom 79% received it within 48 hours of admission). This swift initiation of antiviral treatment indicates an effective healthcare response; however, it also raises questions regarding 26% of patients who did not receive oseltamivir. Our findings showed that oseltamivir use was associated with an 18% lower risk of mortality compared to those not treated with antivirals, with this benefit being significant for influenza A but not for influenza B. Importantly, even when oseltamivir was initiated after the initial 48-hour window, it still resulted in a significantly lower risk of mortality compared to those who did not receive it.

Older adults are more vulnerable than other age groups to the harmful effects of influenza [1]. This is due to a combination of immunosenescence (gradual deterioration of the immune system) and accelerated accumulation of health deficits during the aging process. In this context, vaccination and antiviral therapy are crucial for preventing and treating influenza in older adults. Antiviral medications can help reduce symptoms, prevent hospitalization, and minimize adverse clinical outcomes in older adults with influenza [26]. Even so, there is a need for more data on the effectiveness of these antivirals among older adults, as most studies enrolled fewer older adults [27], and uncertainty remains regarding the utility of antivirals outside the initial 48-hour window.

Our study addresses the existing knowledge gaps by providing evidence demonstrating the effectiveness of oseltamivir in

Table 4. Exploratory Analysis of the Effectiveness of Oseltamivir in Reducing 30-Day Mortality Rates Based on Influenza Vaccination Status

Influenza Vaccination Status	30-d Mortality	No Antivirals	Oseltamivir	Total	*P* Value
Unvaccinated	Survived	1086	3169	4255	.126
	Deceased	111	269	380	
Vaccinated	Survived	841	2386	3227	.032
	Deceased	88	185	273	

Cochran-Mantel-Haenszel $\chi^2 = 6.7155$; degrees of freedom = 1; odds ratio, 0.79 (95% confidence interval, .66–.94); $P = .009$.

reducing mortality among older adults hospitalized with laboratory-confirmed influenza. This finding is consistent with earlier studies in younger age groups. An extensive systematic review investigated the link between neuraminidase inhibitor use and mortality in patients with pandemic influenza [28]. The study reviewed data from 78 studies that included 29 234 patients from different parts of the world admitted to hospitals with pandemic influenza A H1N1pdm09 virus infection, either clinically diagnosed or laboratory confirmed. The results showed that neuraminidase inhibitor treatment was associated with a reduced mortality risk compared to no treatment. Neuraminidase inhibitor treatment led to a 0.81-fold reduction in mortality risk (adjusted OR [aOR], 0.81 [95% CI, .70–.93]; $P = .0024$) compared with no treatment, regardless of timing. It is worth noting that the systematic review study did not capture the treatment effects for older adults, as the age was divided into 2 groups: adults (≥16 years) and children (<16 years).

The same study also showed that early treatment (within 2 days of symptom onset) led to a 0.50-fold reduction in mortality risk (aOR, 0.50 [95% CI, .37–.67]; $P < .0001$), but the mortality hazard rate increased as treatment initiation was delayed each day after symptom onset up to day 5, compared to treatment started within 2 days ($P < .0001$) [28]. In contrast, our findings indicate that while delayed administration of oseltamivir to older adults with influenza is still beneficial, earlier treatment within 48 hours of admission confers greater reductions in 30-day mortality. This finding is consistent with a recent study conducted in 11 European Union countries from 2010–2011 to 2019–2020, which revealed that initiating neuraminidase inhibitor treatment within 48 hours of symptom onset can lead to a 0.51-fold reduction in the risk of mortality (aOR, 0.51 [95% CI, .45–.59]), without significant changes compared to treatment initiation at 3–4 days (aOR, 0.59 [95% CI, .51–.67]) or 5–7 days (aOR, 0.64 [95% CI, .56–.74]). Moreover, antiviral treatment did not affect the outcomes in patients aged 0–19 and 20–39 years. However, the study found that treatment reduced the risk of death if it was started within 7 days of symptom onset for all other age groups. Antiviral treatment was effective for patients aged ≥40 years when administered within 7 days following the onset of symptoms. Of note, the protective benefits of the antiviral extended beyond this period exclusively for those aged ≥80 years, showing continued efficacy even when the treatment was initiated >7 days after symptom onset [14]. These findings highlight the importance of antiviral treatment in reducing the mortality risk in patients hospitalized with influenza, including older adults, regardless of when it is administered.

Notably, older adults are more likely to present with atypical symptoms, which in turn may be associated with delayed (or absent) testing for influenza, and thus with delayed oseltamivir initiation, which may be associated with hesitation [29]. Our findings suggest that such hesitation is unwarranted and that influenza should be treated as soon as it is identified, even if it occurs >48 hours after hospital admission. In our investigation, compared to those who received an oseltamivir prescription <48 hours after hospitalization, those who received a delayed prescription had a higher proportion of older adults living in private houses, a higher comorbidity burden score, and a lower need for regular formal personal care support.

Our results also showed that extended hospital stays were linked to worse outcomes, although this was not our primary focus. Supplementary Figure 4 shows that most participants either left the hospital or died within 14 days, with the majority being discharged. It is noteworthy that if an older adult was admitted with influenza and stayed in the hospital for 30 days, the chance of survival was approximately 50%. This evidence highlights the importance of recognizing that hospitalization for influenza can lead to short-term adverse effects and lasting declines in the functionality of older adults, affecting their 30-day survival.

It is also worth considering the differences among the studies regarding the timeframe they cover. Some studies have considered symptom onset using the definition of influenza-like illness (ILI). In contrast, others base it on when the influenza diagnosis is confirmed in the laboratory (known as a "laboratory-confirmed influenza infection") or when the patient is hospitalized due to 1 of the previous conditions. Our study used the date of hospitalization, which means that our 48-hour window is more conservative, given that symptoms likely arose in the hours to days leading up to admission. Of particular interest, our previous work showed that a significant number of older adults, particularly those who were frail, were overlooked by standard case definitions for ILI and severe acute respiratory illness [29]. ILI symptoms as a surveillance strategy are skewed toward identifying younger cases and fail to capture the entire influenza burden. Given the high proportion of cases that remain undetected, it is recommended that studies do not rely solely on such criteria for diagnosing and assessing the effectiveness of interventions against influenza. However, although these definitions of the timeframe have some overlap, they may also explain the differences found in effectiveness estimates due to prescription timing.

We conducted an exploratory analysis to investigate a potential prescription bias that could be influenced by the clinical characteristics associated with having received the influenza vaccine, which may also affect the probability of being given oseltamivir and, consequently, the likelihood of death. To the best of our knowledge, this is the first study to directly assess this possible bias and demonstrate that influenza vaccination status did not mediate the effectiveness of oseltamivir, confirming the benefit of using oseltamivir regardless of the individual's influenza vaccination status.

Our study has some limitations. First, residual confounding attributable to unmeasured factors that may differ between individuals treated with oseltamivir and those who were not could potentially influence mortality outcomes. The prescription of oseltamivir was not randomized, potentially introducing confounding factors according to indication. We addressed this by conducting an exploratory analysis stratified by influenza vaccination status, and attempted to minimize its impact through active surveillance with broad inclusion criteria and adjustments for clinical and demographic factors. Additionally, the absence of immunization registries in Canada posed challenges in gathering detailed information on the type and brand of influenza vaccine administered to patients. Our effectiveness estimates for oseltamivir represent an average across influenza seasons, which is necessary to gather a sufficient sample size for the analysis. However, it is worth noting the significant heterogeneity in circulating strains and possible vaccine mismatches, which potentially affected our results. Specifically, the lower effectiveness observed against influenza B might be attributed to mismatches in vaccine effectiveness during the 2017–2018 season, when a higher number of participants was included compared to other seasons. This period was marked by dominant B virus circulation, possibly leading to excess mortality among older adults, as documented in existing literature [30]. Oseltamivir resistance may have also influenced our findings, although such resistance was rarely detected (<0.5%) in Canada. Additionally, the apparent lack of benefit for influenza B could be due to a smaller sample size compared to influenza A or aligned with data showing reduced effectiveness against B strains [31]. Another limitation was the lack of consistent data on the time from symptom onset to hospitalization, which could help to determine whether the timing of prescription affects antiviral effectiveness. Our finding that delayed oseltamivir initiation (beyond 48 hours from admission) is likely a conservative estimate, as this timeline would usually be longer than the time from symptom onset. Last, it is essential to note that data and numbers from other studies discussed in our work were derived from different methodologies, meaning that our estimated HRs may not be directly comparable to incidence risk ratios or aORs from other studies. This highlights the necessity for cautious interpretation of our results within the broader context of the existing research.

Our study showed that oseltamivir significantly reduced 30-day mortality in older adults hospitalized with influenza, even 48 hours after admission. Despite its status as the standard of care, only 74% of patients receive treatment, highlighting a critical gap in practice. Our findings confirm the effectiveness of oseltamivir in a typically underrepresented group in clinical trials, challenging hesitancy toward late antiviral treatment and emphasizing prompt intervention. Healthcare providers should prioritize early oseltamivir administration to reduce the mortality risk and potentially redefine protocols for this high-risk group. Overall, our study advocates a more proactive antiviral approach to significantly reduce mortality in older adults, thereby advancing public health and influenza management.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. H. P.: Conceptualization, methodology, software, validation, formal analysis, and writing. M. K. A. and S. A. M.: Conceptualization, investigation, supervision, overall project administration, and writing. J. J. L., T. F. H., and M. E.: Investigation, resources, and writing. Z. S., M. K. N., L. Y., A. A., G. B., W. B., J. J., K. K., P. L.-W., M. L., A. McC., A. McG., A. P., J. P., D. R., M. S., S. S., D. S., G. S., S. T., and L. V.: Investigation, site-specific project administration, and writing. D. W.: Investigation, project administration, and writing. All authors provided critical insights into the interpretation of the analyses, contributed to the manuscript revisions, and approved the final manuscript.

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Ethics Approval and Participation Consent. This study was conducted in accordance with the ethical standards set forth by the local research ethics boards (REBs). Prior to supplemental testing and secondary use of data from the Canadian Immunization Research Network (CIRN) SOS Network, approval was obtained from the REBs at IWK (REB 1024817) and Nova Scotia Health (REB 1024818). The research protocol adhered to ethical guidelines across all participating institutions and received approval from the respective REBs, including Nova Scotia Health REB (Halifax site), Mount Sinai Hospital REB (Mount Sinai and Toronto Invasive Bacterial Diseases Network sites), Hamilton Health Sciences/McMaster Health Sciences REB (Hamilton site), University of British Columbia Clinical REB (Vancouver site), Ottawa Health Science Network REB (Ottawa site), Comité d'éthique de la recherche du Centre hospitalier universitaire de Québec (Québec City site), Comité d'éthique de la recherche sur l'humain du Centre Hospitalier Universitaire de Sherbrooke (Sherbrooke site), Horizon Health Network REB (Saint John site), Montreal General Hospital Research Ethics Committee (Montreal site), North York General REB (North York site), Toronto East General Hospital REB (Toronto East site), William Osler Health System REB (William Osler site), and Health Sciences North REB (Sudbury site). In accordance with local REB requirements, written consent was obtained from patients at the time of enrollment. In certain seasons, when there was no additional study involvement or collection of biological samples beyond influenza testing conducted as standard care, the REBs granted a waiver of consent for the collection of anonymized public health surveillance data because of the importance of the study in generating unbiased surveillance

information. This protocol, registered at ClinicalTrials.gov (NCT01517191), aligns with the necessary standards for conducting ethical research and reflects the requisite approval by the ethical committees.

Data collection, sharing, and management were conducted in compliance with ethical standards and privacy regulations, including the Memorandum of Understanding between the principal investigators, Dalhousie University, and the Public Health Agency of Canada. Data were securely entered into the Dacima web-based data capture system, in which personally identifiable information was coded and removed to ensure confidentiality.

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