The Impact of Immunization and Use of Oseltamivir on Influenza-Related Hospitalizations: A Population-Based Study

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Abstract

Background: As the COVID-19 pandemic continues into flu season, it is critical to minimize hospitalizations to maximize capacity and preserve critical care resources. We sought to identify risk factors for influenza-related hospitalization, specifically the role of immunization and oseltamivir prescriptions. **Methods:** Patients with influenza diagnoses were identified from the MarketScan database (2014-2018). Primary risk factors of interest were an influenza vaccination within 6 months prior to infection and oseltamivir prescriptions (filled on the day diagnosis, the following day, or 2-5 days). A multivariable logistic regression model was run to identify risk factors for influenza-related hospitalizations within 30 days of diagnosis. **Results:** Among 2 395 498 influenza infections, 0.27% were hospitalized. Of those prescribed oseltamivir the day of diagnosis, 0.13% were later hospitalized, compared to 0.67% among those who filled prescriptions the following day and 11.8% when filled within 2 to 5 days. Upon adjustment, oseltamivir prescriptions filled on the day of diagnosis were associated with significantly decreased odds of hospitalization (OR 0.51 CI 0.48-0.55). Prescriptions filled within 1 to 5 days of diagnosis were associated with significantly increased odds of hospitalization (1 day OR 2.01 CI 1.81-2.24; 2-5 days OR 34.1 CI 31.7-36.6). Flu vaccination was associated with a lower odds for hospitalization (OR 0.84 CI 0.74-0.95). **Conclusions:** We recommend oseltamivir be prescribed to patients when they first present with influenza-like symptoms to reduce the burden on the healthcare system. We also identified reduced odds of hospitalization associated with influenza vaccination, which is already well established, but particularly important this coming flu season.

Keywords

immunization, oseltamivir, influenza, Tamiflu, hospitalization

Introduction

Every year influenza viruses cause recurrent respiratory illness in humans with significant impact on healthcare systems and the economy.[1] They are associated with epidemics of varying severity annually with the course of disease ranging from mild rhinorrhea to pneumonia and severe lung injury resulting in tens of thousands excess deaths in the United States (US) alone.[2] Up to 10% of adults and 20% of children are infected annually, with 3.8% of all admissions for respiratory failure attributed to influenza virus infections.[3] Direct medical cost largely associated with hospitalization and economic losses due to lost working days in the US alone are estimated to account for at least 11 billion US dollars annually.[4]

Despite the substantial impact that annual influenza epidemics have on society, large-scale population-based analyses of the factors associated with hospitalizations are rare.[5-7] Additionally, the impact of interventions such as the use of immunizations and treatments on risk of hospitalization are

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not well quantified. Neuraminidase inhibitors (NAIs) such as oseltamivir are currently the only clinically effective class of anti-influenza therapy.[8] Indeed, existing oseltamivir safety and efficacy data suggest that initiation of therapy within 48 h of symptom onset confers the most benefits[8,9] and is considered the standard of care for all influenza patients.[10] However, patients often present to their health care provider over 48 h after symptom onset.

Given these information gaps and clinical challenges, our objective was to analyze data from a large national dataset of patients receiving commercial insurance through their employer to (1) describe characteristics associated with hospitalizations associated with influenza infection and (2) identify factors associated with altered odds of influenza-related hospitalization. We hypothesized that prior immunization and the timely use of oseltamivir, but not delayed administration, would be associated with reduced odds of hospitalization for influenza. This is of particular importance as we are in the midst of the COVID-19 pandemic where extra secondary care resources need to be allocated for the support and treatment of COVID-19 patients.

Methods

Study Design, Sample, and Cohort Definition

We conducted a retrospective cohort study of patients with influenza infections captured in the Truven Health MarksetScan database (Copyright © 2017 Truven Health Analytics Inc. All Rights Reserved) from 2014 to 2018.[11] Detailed cohort and covariate definitions are reported in the Supplemental Appendix. The MarketScan database is the largest convenience sample of the privately insured population in the United States. It contains inpatient, outpatient, and pharmaceutical claims data from over 150 employers in addition to several insurance plans that submit data directly. Approval for this study was obtained from our Institutional Review Board (IRB # 2017-0169).

We identified patients with an *International Classification of Diseases 9th or 10th Revision* (ICD-9, ICD-10) diagnosis code for influenza reported during an outpatient visit. The cohort was restricted to each patient's first reported instance of influenza arising during a traditional flu season: October 2014 to April 2015, October 2015 to April 2016, October 2016 to April 2017, or October 2017 to April 2018. We did so in order to retain patients who may have had more than 1 flu infection throughout the study period while simultaneously minimizing confounding from multiple influenza infections and avoiding misclassification of repeat office visits as novel influenza.

Study Variables

The primary outcome in this analysis was hospitalization with a recorded diagnosis of influenza within 30 days of the first reported diagnosis. The primary exposure of interest was a prescription for oseltamivir phosphate filled within 5 days of the initial influenza diagnosis. Prescription guidelines for oseltamivir recommend starting the medication within 48 h of symptom onset. Since oseltamivir is meant to be taken over a span of 5 days for treatment or we restricted our definition of oseltamivir exposure to prescriptions filled within 5 days of reported diagnosis. Oseltamivir prescriptions were categorized as those filled on the same day as the first office visit, within 1 day, within 2 to 5 days, or never filled. Of note, we do not have information on exact timing of symptom onset in our dataset; instead, we use the timing of the office visit as a proxy, recognizing that this may lead to some misclassification regarding the categorization of oseltamivir therapy initiation within the recommended time window. Conversely, prescriptions filled within 2 to 5 days after the office visit fall outside of the recommended time window. Patients who filled a prescription for osteltamivir within the 30 days prior to their first influenza diagnosis were excluded (n = 203 314) to limit confounding by prior flu diagnoses or prophylactic use. Similarly, patients who filled an oseltmivir prescription within 6 to 30 days following an initial office visit were excluded (n = 4255).

Additional potential risk factors of interest included patient characteristics such as age (0-4, 5-17, 18-49, 50-59, and 60+ years old), sex, location (urban vs rural), median household income (<$45 000, $45 000-$60 000, >$60 000; defined by linking Metropolitan Statistical Area with US Census Bureau American Community Survey income data[12]), individual Elixhauser comorbidities,[13,14] and sleep apnea. Flu-related characteristics were year of the flu season and flu vaccination history. Flu vaccination history was defined according to relevant procedure codes or pharmaceutical claims for a flu vaccine within the period of 6 months prior to influenza diagnosis.

Statistical Analysis

Descriptive analyses of all variables were conducted stratified by hospitalization status. Frequencies (%) were reported for all variables and univariate associations were evaluated via Chi-square tests.

A multivariable logistic regression model (including all aforementioned study variables) was run in order to identify risk factors for 30-day (influenza-related) hospitalization following influenza diagnosis. Odds ratios (OR) and 95% confidence intervals (CI) were reported. The model c-statistic is reported, indicative of its ability to distinguish patients by hospitalization status (discrimination). A c-statistic of 0.7 or greater generally indicates sufficient discrimination.

Results with a *P*-value less than .05 were considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Among 2 395 498 influenza infections (representing 2 276 525 unique patients), we observed 6441 (0.27%) influenza-related hospitalizations within 30 days of diagnosis.

In more than half of these infections (n = 1 280 927; 53.5%), oseltamivir was prescribed. Among those prescribed oseltamivir the same day as their initial office visit, 1630 were later hospitalized (0.13%). Among those who filled an oseltamivir prescription within 1 day, 400 were later hospitalized (0.67%). Patients taking oseltamivir outside of the recommended treatment window (filled within 2-5 days) experienced a significantly greater rate of hospitalization (11.8%; *P* < .001).

Hospitalization was significantly more common during the 2015 to 2016 flu season and among individuals 60 years and older (*P* < .001). Comorbid conditions associated with a considerably high incidence of influenza hospitalization (>2%) included congestive heart failure, pulmonary circulation disorders, peripheral vascular disease, paralysis, renal failure, lymphoma, metastatic cancer, coagulopathy, and fluid and electrolyte disorders (Table 1).

Upon adjusting for all other covariates, oseltamivir prescriptions filled on the day of diagnosis (compared to cases in which oseltamivir was either never prescribed or prescriptions never filled) were associated with significantly decreased odds of hospitalization (OR 0.51 CI 0.48, 0.55). While oseltamivir prescriptions filled within 1 to 5 days of diagnosis were associated with significantly increased odds of hospitalization (1 day OR 2.01 CI 1.81, 2.24; 2-5 days OR 34.1 CI 31.7, 36.6).

Additional significant risk factors included advanced age (60+ OR 1.29 CI 1.16, 1.44) and male sex (OR 1.11 CI 1.05, 1.17). A flu vaccination within the 6 months prior to infection was associated with a lower odds for hospitalization (OR 0.84 CI 0.74, 0.95). A number of comorbidities were associated with increased odds of hospitalization upon adjusting for other covariates, including congestive heart failure, pulmonary circulation disorders, paralysis, neurological disorders, chronic pulmonary disease, diabetes, renal failure, HIV/AIDS, lymphoma, metastatic cancer, rheumatoid arthritis, coagulopathy, obesity, weight loss, and fluid and electrolyte disorders (all *P* < .05; Table 2).

Discussion

We are in the midst of a pandemic that has put strain on the limited resources of our health care system. Seasonal influenza will only add to this burden. In this large, retrospective study of influenza patients, the prescription of oseltamivir, filled on the same day as an initial office visit, was associated with significantly decreased odds of hospitalization. When patients filled prescriptions within 1 to 5 days of their first office visit, and presumably started taking oseltamivir

at that point, hospitalization risk increased significantly. Moreover, as expected, age was a significant predictor of hospitalization due to influenza, as older patients were more at risk of hospitalization. Other identified factors associated with higher odds of hospitalization included male patients, patients in rural areas, various comorbidities and, specifically the 2015 to 2016 flu season. Further, as expected, prior immunization was associated with a significant reduction in the odds for hospitalization.

Our study found that filling a prescription for oseltamivir, on the same day as their initial physician visit with influenza-type symptoms, was associated with reduced odds of hospitalization, compared to patients without a prescription for oseltamivir. This has been supported by numerous studies.[10,15,16] Conversely, patients starting antiviral therapy outside this timeframe were more likely to be hospitalized.[15,16] It is likely these may have been cases with worsening symptoms that were not treated within the appropriate timeline, often due to delayed presentation and patients waiting for progression of symptoms. While prescriptions filled on the day following influenza diagnosis were associated with increased odds of hospitalization, risk of hospitalization dramatically increased when prescriptions were further delayed, filled 2 to 5 days after formal diagnosis.

In addition to the protective effect of receiving oseltamivir early in the course of the disease, having received a flu vaccine within 6 months greatly decreased the odds of hospitalization with influenza, in accordance with current literature. Meta-analyses of randomized, controlled trials involving outpatients with confirmed influenza have shown that oseltamivir shortens symptom length and decreases hospitalizations, which were also supported by our findings.[8,17] Reported influenza vaccination was low in this cohort (approximately 3.6% of all reported cases), this may a testament to the effectiveness of flu vaccination since the large majority of infected patients had not been previously vaccinated. Additionally, it may be a consequence of the growing popularity of employer-sponsored influenza vaccination clinics which would not be captured by medical records.[18]

Hospitalizations due to influenza in the 2015 to 2016 flu season were significantly more common.[19] It is possible that increased virulence of the predominant influenza strain in that particular season represents a reason for this finding. Alternatively, season-specific challenges with the vaccine may have also played a role.[20] It is also possible that this is an artifact of fewer cases being captured in our sample of the 2015 to 2016 season relative to other years, potentially a consequence of the ICD-9 to 10 coding transition in late 2015. Indeed, according to the Centers for Disease Control and Prevention, of the 4 flu seasons captured in this analysis, 2015 to 2016 was milder, with fewer hospitalizations and deaths relative to other years.[19]

Table 1. Summary of Patient Characteristics Stratified by Hospitalization Status within 30 days of First Reported Influenza Diagnosis.

	Hospitalization within 30 days	%	No hospitalization	*P*-value
Total	6441	0.27	2 389 057	
Tamiflu				<.001
Filled same day	1630	0.13	1 207 990	
Filled 1 day	400	0.67	58 985	
Filled 2-5 days	1408	11.8	10 514	
Never filled	3003	0.13	1 111 568	
Flu season				<.001
2014-2015	1265	0.19	650 999	
2015-2016	1225	0.42	292 228	
2016-2017	1306	0.27	487 835	
2017-2018	2645	0.28	957 995	
Age group				<.001
0-4	926	0.36	259 203	
5-17	899	0.12	743 832	
18-49	2084	0.21	968 078	
50-59	1505	0.5	300 789	
60+	1027	0.87	117 155	
Sex				.727
Male	2976	0.27	1 098 645	
Female	3465	0.27	1 290 412	
Location				<.001
Urban	5033	0.27	1 865 998	
Rural	974	0.29	331 636	
Unknown	434	0.27	191 423	
Median household income				.015
<$45 000	507	0.28	181 525	
$45 000-$60 000	2525	0.26	987 661	
>$60 000	433	0.28	156 355	
Unknown	2976	0.28	1 063 516	
Flu vaccine within 6 months				<.001
Yes	316	0.37	86 207	
No	6125	0.27	2 302 850	
Comorbidities				
Congestive heart failure	456	2.99	14 778	<.001
Valvular disease	472	1.06	43 952	<.001
Pulmonary circulation disorders	254	2.93	8408	<.001
Peripheral vascular disease	324	1.47	21 664	<.001
Hypertension	2125	0.66	319 310	<.001
Paralysis	117	2.66	4288	<.001
Other neurological disorders	579	1.21	47 381	<.001
Chronic pulmonary disease	2186	0.6	361 298	<.001
Diabetes	1188	0.95	124 336	<.001
Hypothyroidism	736	0.52	141 737	<.001
Renal failure	393	2.39	16 040	<.001
Liver disease	349	0.88	39 323	<.001
Peptic ulcer disease	42	0.86	4826	<.001
AIDS/HIV	43	1.17	3629	<.001
Lymphoma	96	2.16	4356	<.001
Metastatic cancer	129	2.61	4822	<.001
Solid tumor without metastasis	329	0.98	33 093	<.001
Rheumatoid arthritis	367	0.76	47 731	<.001

(continued)

Table 1. (continued)

	Hospitalization within 30 days	%	No hospitalization	P-value
Coagulopathy	404	2.07	19 115	<.001
Obesity	1205	0.55	216 259	<.001
Weight loss	316	0.94	33 246	<.001
Fluid and electrolyte disorders	1911	2.00	93 515	<.001
Anemia	764	0.79	95 351	<.001
Alcohol abuse	41	0.94	4343	<.001
Drug abuse	180	0.85	21 036	<.001
Psychoses	324	0.58	55 593	<.001
Depression	901	0.46	194 572	<.001
Sleep apnea	441	0.74	59 541	<.001

Table 2. Results from Multivariable Logistic Regression Model Predicting Hospitalization for Influenza within 30 days of First Reported Diagnosis.

	Flu hospitalization w/in 30 days (n = 6441)	
	OR [95% CI]	P-value
Tamiflu		<.001
Filled same day	0.51 [0.48, 0.55]	
Filled 1 day	2.01 [1.81, 2.24]	
Filled 2-5 days	34.1 [31.7, 36.6]	
Never prescribed	Reference	
Flu season		<.001
2014-2015	Reference	
2015-2016	1.76 [1.63, 1.91]	
2016-2017	1.15 [1.06, 1.25]	
2017-2018	1.09 [1.01, 1.17]	
Age group		<.001
0-4	1.78 [1.64, 1.94]	
5-17	0.67 [0.61, 0.72]	
18-49	Reference	
50-59	1.65 [1.53, 1.77]	
60+	2.30 [2.11, 2.51]	
Sex		<.001
Male	1.11 [1.05, 1.17]	
Female	Reference	
Location		<.001
Urban	Reference	
Rural	1.06 [0.97, 1.15]	
Unknown	0.83 [0.74, 0.93]	
Median household income		.527
<$45 000	1.05 [0.95, 1.16]	
$45 000-$60 000	Reference	
>$60 000	1.07 [0.96, 1.19]	
Unknown	1.01 [0.95, 1.08]	
Flu vaccine within 6 months comorbidities	0.84 [0.74, 0.95]	.004
Congestive heart failure	1.81 [1.58, 2.06]	<.001
Valvular disease	0.97 [0.86, 1.09]	.602
Pulmonary circulation disorders	1.45 [1.23, 1.70]	<.001
Peripheral vascular disease	0.97 [0.84, 1.11]	.628

(continued)

Table 2. (continued)

	Flu hospitalization w/in 30 days (n = 6441)	
	OR [95% CI]	*P*-value
Hypertension	1.06 [0.99, 1.14]	.12
Paralysis	1.91 [1.53, 2.39]	<.001
Other neurological disorders	1.92 [1.74, 2.13]	<.001
Chronic pulmonary disease	1.88 [1.78, 1.99]	<.001
Diabetes	1.47 [1.35, 1.59]	<.001
Hypothyroidism	0.96 [0.88, 1.05]	.341
Renal failure	1.37 [1.20, 1.57]	<.001
Liver disease	0.93 [0.81, 1.04]	.2
Peptic ulcer disease	0.73 [0.52, 1.03]	.076
AIDS/HIV	1.75 [1.26, 2.43]	.001
Lymphoma	1.68 [1.32, 2.13]	<.001
Metastatic cancer	1.75 [1.39, 2.21]	<.001
Solid tumor without metastasis	1.12 [0.97, 1.29]	.133
Rheumatoid arthritis	1.17 [1.04, 1.32]	.011
Coagulopathy	1.99 [1.76, 2.26]	<.001
Obesity	1.08 [1.00, 1.16]	.056
Weight loss	1.22 [1.07, 1.40]	.003
Fluid and electrolyte disorders	4.36 [4.08, 4.66]	<.001
Anemia	0.97 [0.89, 1.07]	.588
Alcohol abuse	1.29 [0.91, 1.81]	.153
Drug abuse	1.10 [0.93, 1.31]	.282
Psychoses	0.99 [0.87, 1.13]	.906
Depression	0.93 [0.86, 1.02]	.111
Sleep apnea	0.92 [0.82, 1.03]	.156

c-statistic: 0.819

We also found that males had higher odds of influenza-related hospitalization. While speculative, this may be due to a sex-specific differences in the willingness to seek medical care and comply with recommendations.[21] Additionally, our study found that older age and the presence of comorbidities such as immunosuppressive or cardiorespiratory disorders significantly increased the odds of hospitalization within 30 days of diagnosis, which is in agreement with previous studies.[5-7]

A third of all hospitalizations occurred in patients with hypertension, chronic pulmonary disease, and fluid and electrolyte disorders. Many of the patients had multiple comorbidities, which implies that patients with less physical reserve are the ones hospitalized. Furthermore, it appears that the urban environment, possibly due to the closer proximity of people, confers a greater risk of hospitalization and possibly severity of symptoms. The greatest risk factor included fluid and electrolyte disorders, most likely due to dehydration linked to patients feeling unwell, which increased the risk of hospitalization almost 5-fold.

Obesity has been identified as a risk factor for hospitalization and a more severe course of infection.[6,7,22] This observation reflects possibly the lack of reserve respiratory capacity among obese patients.

Higher rates of severe pandemic influenza infection have been reported in disadvantaged populations.[23,24] However, in our study, this was not shown as there was no significant association between median household income and hospitalization due to influenza. This finding might be skewed by the fact that even though lower income households have historically been shown to have reduced access to healthcare resources,[23] our sample consisted of patients that all had commercially available insurance through their employer. Thus, it is possible that monetary inequalities are negated by the presence of health insurance in this cohort.

This study has a number of limitations. The optimal prescribing window for oseltamivir is within 48 h of symptom onset. We attempted to control for this by separating prescriptions filled 0, 1, or 2 to 5 days from an initial office visit with a reported diagnosis of influenza. It is possible that patients were experiencing symptoms prior to seeking care and were thus misclassified as having received their prescription within the appropriate window. Given the stark contrast observed in the odds of hospitalization between patients prescribed

oseltamivir within on the day of diagnosis compared to 2 to 5 days, we believe our proposed classification of patients is of practical importance for clinical adoption and application. Additionally, the MarketScan database primarily consists of data from patients with employer-sponsored health insurance, failing to capture a large majority of the Medicare-aged population who are at higher risk of influenza-related complications. Further study is needed to determine if these trends persist in older populations as well as those who are uninsured or enrolled in public health insurance plans.

In conclusion, these findings are of increased importance in the context of the current COVID-19 pandemic. Drawing from our results, we would recommend that oseltamivir be prescribed to patients when they first present with influenza-like symptoms in order to reduce the burden on the healthcare system. Likewise, it is important to encourage patients to fill prescriptions promptly and not wait for worsening of symptoms. We also identified that influenza vaccination was associated with reduced odds of hospitalization, which is already well established, but particularly important this coming flu season given the reasons mentioned above. A follow-up study looking at the impact of oseltamivir therapy timing separately for those with and without previous vaccination would be a logical next step.

Declaration of Conflicting Interests

Funding

Ethics Approval

This retrospective study was approved by the Institutional Review Board (IRB# #2017-0169) of Hospital for Special Surgery.

Consent to Participate

The requirement for written informed consent was waived given the de-identified nature of the data.

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Supplemental Material

Supplemental material for this article is available online.

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