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ORIGINAL ARTICLE

Effects of antiviral treatment on influenza-related complications over four influenza seasons: 2006–2010

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ABSTRACT

Purpose: The objective of the study is to evaluate the effect of antiviral treatment, pre-existing diseases, and sociodemographic factors on the risk of influenza-related complications and healthcare utilization.

Methods: Case data was obtained from U.S. MarketScan Research Databases. Cases had a clinical diagnosis of influenza between 2006 and 2010 and continuous healthcare insurance from 90 days before to 30 days after diagnosis. Logistic regression models were applied to explore the impact of antiviral treatment on complications and healthcare utilization. Modified generalized estimating equation regression models in propensity score matched samples were used to address the robustness of the study.

Results: Analyses included 1,557,437 cases from four influenza seasons. In each season, 34.82%–43.42% of patients received antiviral treatment, mostly oseltamivir. On average, 1.86% of patients were hospitalized, 9.56% visited the emergency room and 41.14% made $\geq$2 outpatient visits. The incidence of complications ranged from 17.62 to 19.67 per 100 patient-months. The relative risk of complications was increased in patients aged 0–4 years and those with pre-existing diseases, including asthma, Parkinson's disease, and cystic fibrosis. Overall, patients receiving antiviral treatment had an 11% reduction in the risk of complications. Among oseltamivir-treated patients, the risk of complications was significantly reduced by 81% in those treated $\leq$2 days after diagnosis compared with later. Antiviral treatment significantly reduced the risk of hospitalization, emergency room visits and need for $\geq$2 outpatient visits by 29%, 24% and 11%, respectively. The propensity score matching method improved the strength of the study.

Conclusions: Early treatment with antivirals, and specifically oseltamivir, significantly reduced the risk of influenza-related complications and healthcare utilization. However, lacking information about disease severity and the time from onset of symptoms to fulfillment of a prescription may bias the outcomes.

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Introduction

Influenza outbreaks follow seasonal patterns that vary in distribution and severity from year to year. The Centers for Disease Control and Prevention of the United States (the U.S. C.D.C.) estimates that influenza results in approximately 200,000 hospitalizations and 3000 to 49,000 deaths yearly, depending on the severity of the season[1]. Individuals with pre-existing chronic diseases are more at risk of severe disease and development of complications[2–4]. Worldwide pandemics occur rarely, but result in excess morbidity and mortality in previously healthy individuals as a result of the new circulating strain to which there is no, or extremely limited, group immunity. In 2009, a novel influenza A (2009 H1N1) virus, which spread to more than 200 countries, posed a major challenge for health systems globally[5]. Despite major investments in seasonal and pandemic influenza preparedness in recent years, influenza prevention and control continue to represent a major challenge for public health systems worldwide[6–10]. Influenza is a substantial economic burden for society in terms of direct medical costs, e.g. increases in outpatient visits, hospitalizations and the management of clinical complications. In addition, the indirect costs of influenza are considerable and stem largely from absenteeism and loss of work productivity[11,12].

With reviewing worldwide studies, treatment with neuraminidase inhibitors has been shown to reduce both the severity and duration of influenza symptoms in randomized clinical trials in both adults and children[13–17]. The effect of neuraminidase inhibitors on the reduction of complications and improvement of health outcomes is controversial. Evidence demonstrating a reduced rate of complications in patients treated with antivirals has been provided by several meta-analyses of randomized clinical trials[18–20]. Previous claims database analyses have also demonstrated a reduction in the risk of influenza complications following oseltamivir treatment[21–25]. Although the U.S. C.D.C. and other health authorities remain convinced that the body of evidence clearly indicates a positive impact of antivirals on the reduction of complications

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and hospitalizations in susceptible individuals[26], a recent publication from the Cochrane Collaboration has questioned the validity of these studies[27].

To bridge the gap, this paper reports a retrospective claims-based cohort analysis in participants with outpatient clinical diagnosed influenza. The objectives of the study were to compare the incidence of influenza-related complications among a large cohort of patients with a clinical diagnosis of influenza during four influenza seasons (2006–2010) in the U.S. We also sought to describe the clinical complications associated with influenza and determine risk factors for their occurrence. Finally, we analyzed influenza treatment and its initiation time from the diagnosis to determine the effects of antivirals on the risk of influenza-related complications and healthcare resource utilization, as assessed by hospitalization, emergency room visits, and repeated visits to the clinic or physician.

Patients and methods

Data source

Data were extracted from the MarketScan Commercial Claims and Encounters Database and the MarketScan Medicare Supplemental and Coordination of Benefits Database (Thomson Reuters, Cambridge, MA, U.S.A.). The databases include employees, dependents and retirees insured by employer-sponsored commercial and Medicare insurance[28]. The claims files capture inpatient and outpatient care and use of facilities and services, including the date and place of service, provider type, and payment information. Each medical claim is associated with up to 15 International Classifications of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes and up to 15 ICD-9-CM procedure codes. Pharmacy claims record the National Drug Code (N.D.C.), dispense date, quantity and days supplied, and payments[28]. Under a user agreement with the data owner, this licensed data consist of patients with influenza between 2006 and 2010, during the influenza season. The participants were initially identified from outpatient claims data. Once the cases and their index date had been identified, outpatient, inpatient, and emergency claims that linked to the cases were extracted.

The index date was defined as the date of the first influenza diagnosis in an influenza season. The study period for each patient included a 3 month (90 day) baseline period before the index date, during which baseline characteristics were summarized, and a 1 month (30 day) follow-up period after the index date. We extracted the study sample from patients with a billed diagnosis of influenza (ICD9-code: 487.xx, 488.xx) during four influenza seasons: 1 October 2006 through 31 March 2007 for season 1 (2006–2007); 1 October 2007 through 31 March 2008 for season 2 (2007–2008); 1 October 2008 through 31 March 2009 for season 3 (2008–2009); and 1 April 2009 through 31 March 2010 for season 4 (2009–2010, the H1N1 pandemic season). The following exclusion criteria were applied: (1) influenza diagnosis on the same day as influenza vaccination; (2) cases had less than 90 days of pre-index healthcare insurance; (3) cases had less than 30 days of post-index healthcare insurance.

Antiviral treatment

Licensed antiviral agents in the United States are adamantanes (amantadine and rimantadine) and neuraminidase inhibitors (oseltamivir and zanamivir). The study included the neuraminidase inhibitors as antivirals due to the high level resistance of adamantane treatment to the seasonal influenza A viruses and the 2009 H1N1 virus[29,30]. Since early treatment (less than 48 hours) was recommended, the antiviral treatment in our study was categorized into overall antiviral treatment, antiviral treatment within 2 days after influenza diagnosis, and oseltamivir treatment within 2 days[29]. Due to the high percentage of oseltamivir prescription (>90%), a subgroup analysis was conducted including only oseltamivir as the treatment. For cases treated with antivirals, the time between the initiation of therapy was defined as the date from clinical diagnosis to prescription fulfillment, measured in days.

Outcomes

The main outcomes of the study are influenza-related complications and healthcare utilizations. Any newly diagnosed influenza-related complications occurring during the follow-up window (1–30 days after the index date) were defined as complications. Complications including acute respiratory infections (acute sinusitis, acute bronchitis and bronchiolitis, acute pneumonia, nasopharyngitis, pharyngitis, tonsillitis, laryngitis and tracheitis, upper respiratory infection, influenza with other respiratory manifestations), asthma, acute otitis media, renal disease, acute pericarditis or myocarditis (pericarditis, myocarditis), heart failure, nervous symptoms (febrile convulsions, ataxia, myositis and myoglobinuria, Guillain–Barré syndrome, Reye's syndrome, and encephalopathy) were identified by sets of ICD-9 codes utilized in previous studies (Appendix Table 2)[31–33]. Healthcare utilization was identified if patients experienced hospitalization, emergency room use, or return to hospital visit to outpatient department, during the follow-up window.

Covariates

Covariates were chosen based on a review of the medication literature, author's clinical experience, and limited to variables that were available in the databases. The included covariates are gender (male, female), age (0–4, 5–17, 18–49, 50–64 and ≥65 years), geographic region, types of health insurance plan, other treatments (antipyretics, nasal decongestants, ear drops, cough medication or throat preparation), and influenza-related pre-existing disease.

We defined pre-existing disease as occurring within the 90 days prior to the first influenza diagnosis. The pre-existing diseases included chronic respiratory disease (asthma, chronic obstructive pulmonary disease [C.O.P.D.], chronic pulmonary heart disease and cystic fibrosis), heart disease (congestive heart failure and ischemic heart disease), renal disease, diabetes mellitus, Parkinson's disease, rheumatoid arthritis, or immunocompromised disease (malignancy tumor, acquired immune deficiency syndrome [A.I.D.S.], transplant organ,

other lymphatic and hematopoietic tissues) (Appendix Table 1)[4,31,32,34].

The complex nature of health care systems in the U.S. emphasize that the healthcare coverage and service significantly affects health outcomes[35]. To control this impact, we categorized health insurance by various health plan types, including Exclusive Provider Organization (E.P.O.), Health Maintenance Organization (H.M.O.), Point-Of-Service plan (P.O.S.), Preferred Provider Organization (P.P.O.), Consumer-Driven Health Plans (C.D.H.P.), High Deductible Health Insurance (H.D.H.P.), comprehensive, and unknown insurance providers. Influenza immunization status was identified by sets of Current Procedural Terminology (C.P.T.) codes. All influenza vaccination related C.P.T. codes across 2006 to 2010 were included.

Data analysis

The incidence of complications was calculated as the number of complication cases over the total person-months of influenza cases in the MarketScan database during each influenza season.

Crude and multivariate logistic regression models were applied to evaluate the impact of antiviral treatment on the risk of developing clinical complications and seeking healthcare service. Odds ratios and 95% confidence intervals were used to assess the risk factors for influenza-related complications and healthcare utilizations.

To address the robustness of our study, sensitivity analyses were conducted by modified generalized estimating equation (G.E.E.) regression models in a propensity score matched sample.

In the influenza cases, their health-seeking behavior and influenza severity could be impacted by age and gender, as well as medical and treatment history. This selection bias could further impact the antiviral treatment effectiveness for complications and healthcare utilization. Propensity score matching methods could reduce this bias by formatting an appropriate comparator group of untreated patients who are similar to the treated patients. The probability of using antiviral treatment was estimated by considering the impact of age, gender, region, health insurance plan, immunization status, pre-existing diseases, and other treatment in each flu season using logistic regression model. The treated and untreated cases were 1:1 matched using the nearest neighbor matching method with a caliper width of 0.005 by season. The matching process is presented in Figure 1.

Although the odds ratio is a popular estimation in epidemiology and medical research, when prevalence or incidence of an outcome is high (>10%), the odds will overestimate or underestimate the risk ratio[36,37]. A modified Poisson approach with G.E.E. estimation was recommended to address this bias for the binary outcomes[38]. In S.A.S. codes, the robust variance estimator is provided by the REPEATED statement in PROC GENMOD, which gives a proper estimate of the standard error of the relative risk. Modification is applied by using the LSMEANS statement in S.A.S.[38].

S.A.S. version 9.2 was used to perform the data analyses. The significance level was set at a two-tailed alpha = 0.05.

Results

De-identified data from the MarketScan database included covered lives of 124,096,527 individuals. Of these, 4,540,965 cases were identified with influenza diagnosis codes (ICD-9-CM: 487.xx, 488.xx) during the four influenza seasons. After applying the exclusion criteria listed previously and eliminating duplicates, we identified a total of 1,557,437 eligible cases, which included 22,017 cases with recurrent influenza diagnoses. The total numbers of influenza episodes (single or recurrent) in each of the four influenza seasons were: 177,959 episodes in season 1 (2006–2007), 377,278 episodes in season 2 (2007–2008), 224,791 episodes in season 3 (2008–2009) and 777,409 episodes in season 4 (2009–2010) (Figure 1).

Baseline characteristics of the study population are outlined in Table 1. Over the four seasons, the largest number of cases was identified during the pandemic H1N1 (2009) influenza season from April 2009 to March 2010; this accounted for approximately half of all cases. The age and gender distribution did not differ significantly from season to season. Approximately one-half of patients were aged 17 years or younger and 52.83% of cases occurred in females. The prevalence of pre-existing diseases ranged from 15.62% to 24.35% across the four seasons. The most common underlying diseases included asthma, chronic obstructive pulmonary disease, diabetes mellitus, and cardiovascular disease. Influenza vaccine coverage ranged from 20.95% (2006) to 47.32% (2009). For all four seasons, approximately 2% of patients were hospitalized, 10% used the emergency department and 41% made two or more outpatient visits during the 30 days post-index date.

Notably, the regional distribution of our study sample was significantly concentrated in the Southern region of the U.S., which accounted for 59% to 69% of cases over the four seasons. Almost 70% of patients with influenza episodes had preferred provider organization (P.P.O.) health plans, and approximately 10% and 13% of those had point of service (P.O.S.) and health maintenance organization (H.M.O.), respectively.

The incidence of clinical complications varied from 17.62 to 19.67 per 100 person-months across the four seasons, with the highest rate seen during the pandemic H1N1 (2009) season, 2009–2010 (Table 2). For all four seasons, the most common complications were acute respiratory disease (13.78%), acute otitis media (2.34%) and asthma (1.80%).

We next examined the relative risk of complications in different patient groups (Table 3). Among the different age groups, patients aged 0–4 years had the highest risk of complications and those aged 18–49 years had the lowest risk of complications. Patients aged ≥65 years maintained an 8% lower risk than the 0–4 year group. Females were slightly more at risk of influenza complications than males. Pre-existing diseases that were associated with statistical significant increases in relative risk of complications were asthma (O.R. = 1.90; 95% C.I., 1.88–1.93), Parkinson's disease (O.R. = 1.63; 95% C.I., 1.38–1.93), and cystic fibrosis (O.R. = 1.67; 95% C.I., 1.42–1.96) (Table 3). C.O.P.D., cardiovascular disease, rheumatoid arthritis, diabetes and immunocompromised disease status also demonstrated increased risk. In addition, we noted an increased risk of complications in patients who had

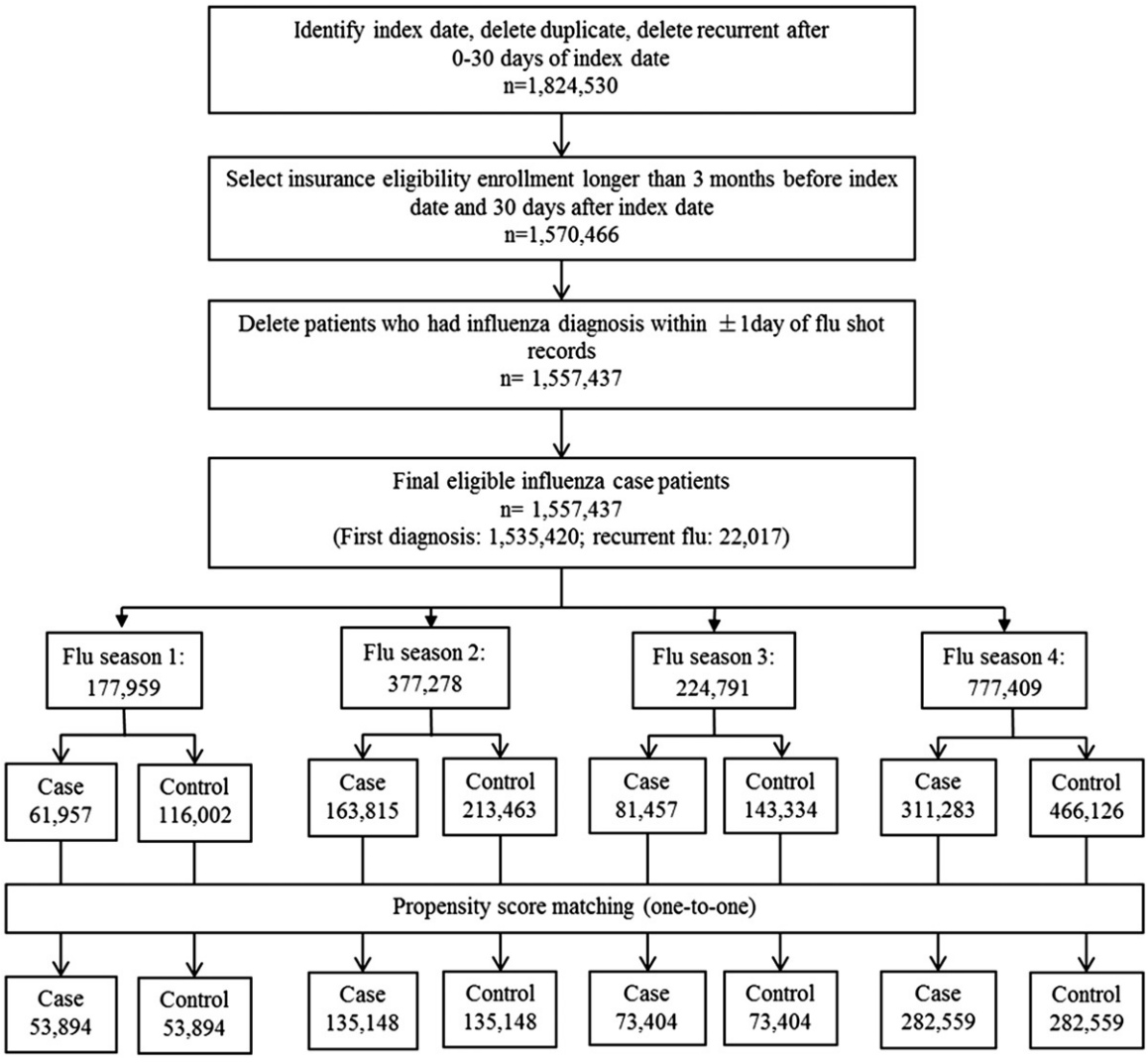

Figure 1. Flow chart of study enrollment.

received an influenza immunization during the 90 days prior to the index date.

On average, 60.29% of all patients diagnosed with influenza did not receive any influenza-related treatment in the four seasons (Table 4). Over the four seasons, between 34.82% and 43.42% of individuals with influenza were treated with antiviral agents. Oseltamivir accounted for over 95% of treatment courses with the exception of the 2008–2009 seasons, when oseltamivir accounted for 74% of treatment courses. Nearly all (99%) oseltamivir use occurred within 2 days of influenza diagnosis across years.

Next, we examined the effects of antiviral treatment on the risk of complications using multivariate logistic regression models. Compared with the reference population of patients that did not receive antivirals, the risk of complications was reduced by 11% in patients who received antivirals (Table 5). The relative risk of the most common complications (respiratory infections, acute otitis media and exacerbation of asthma) was reduced by 10%, 19% and 13%, respectively with antiviral treatment. The complication with the greatest reduction in relative risk was heart failure (43% reduction).

More than 98% of antiviral use occurred within 2 days of diagnosis. Among the patients who had antiviral treatment, there was a significant 74% reduction in relative risk of overall complications in patients who took antivirals within 2 days compared with the reference group who took antivirals after 2 days (Table 5). Furthermore, when the analysis was restricted to patients who received oseltamivir, patients who took oseltamivir within 2 days of influenza diagnosis showed an 81% reduction in relative risk of overall complications compared with patients who took oseltamivir after two days (Table 5). Similar reductions in relative risk were observed for each individual complication with the exception of acute otitis media.

Using similar reference groups and the same model, we examined the impact of antiviral treatment on healthcare utilization, assessed by the risk of hospitalization, emergency room visit, and need for $\geq$2 outpatient visits. Compared with no antiviral treatment, treatment reduced the relative risk of hospitalization by 29%, emergency room use by 24% and need for $\geq$2 outpatient visits by 11% (Table 6). When initiated within 2 days of influenza diagnosis, any antiviral treatment, and specifically oseltamivir, reduced the relative risk of these same measures of healthcare utilization by 90%, 50%, and 70%, respectively, compared with treatment more than 2 days after influenza diagnosis.

The sensitivity analyses using modified G.E.E. regression models in propensity score matched samples confirmed the

Table 1. Demographic characteristics, pre-existing conditions, and healthcare utilizations by influenza season.

	Total 2006–2010	Season 1 2006–2007	Season 2 2007–2008	Season 3 2008–2009	Season 4 2009–2010
Number of episodes	1,557,437	177,959	377,278	224,791	777,409
Age (years), mean ± SD	23 ± 19.0	22.7 ± 19.3	28.7 ± 19.7	22.6 ± 18.4	22.3 ± 18.1
Age group, *n* (%)					
0–4 years	187,903 (12.06)	25,195 (14.16)	42,595 (11.29)	25,673 (11.42)	94,440 (12.15)
5–17 years	609,381 (39.13)	74,091 (41.63)	100,083 (26.53)	97,940 (43.57)	337,267 (43.38)
18–49 years	562,944 (36.15)	56,794 (31.91)	168,136 (44.57)	76,653 (34.10)	261,361 (33.62)
50–64 years	171,238 (10.99)	18,603 (10.45)	58,349 (15.47)	20,898 (9.30)	73,388 (9.44)
≥65 years	25,971 (1.67)	3276 (1.84)	8115 (2.15)	3627 (1.61)	10,953 (1.41)
Gender, *n* (%)					
Male	734,568 (47.17)	85,388 (47.98)	176,666 (46.82)	107,572 (47.85)	364,942 (46.94)
Female	822,869 (52.83)	92,571 (52.02)	200,612 (53.18)	117,219 (52.15)	412,467 (53.06)
Region, *n* (%)					
Northeast[a]	114,240 (7.34)	7832 (4.40)	18,383 (4.87)	17,259 (7.68)	70,766 (9.10)
North Central[b]	312,843 (20.09)	32,914 (18.50)	91 252 (24.19)	37,549 (16.70)	151,128 (19.44)
South[c]	969,412 (62.24)	123,089 (69.17)	237,490 (62.95)	153,671 (68.36)	455,162 (58.55)
West[d]	156,036 (10.02)	13,169 (7.40)	28,699 (7.61)	15,740 (7.00)	98,428 (12.67)
Unknown	4906 (0.32)	955 (0.54)	1454 (0.39)	572 (0.25)	1925 (0.25)
Health plan, *n* (%)					
E.P.O.[e]	12,403 (0.8)	891 (0.50)	2585 (0.68)	1845 (0.82)	7082 (0.91)
H.M.O.[f]	206,198 (13.24)	21,811 (12.26)	49,272 (13.06)	28,885 (12.85)	106,230 (13.66)
P.O.S.[g]	141,701 (9.1)	19,179 (10.78)	37,809 (10.02)	20,525 (9.13)	64,188 (8.26)
P.P.O.[h]	1,076,510 (69.12)	123,844 (69.60)	257,173 (68.17)	157,212 (69.94)	538,281 (69.24)
P.O.S. with capitation	7995 (0.51)	832 (0.47)	1710 (0.45)	1358 (0.60)	4095 (0.53)
C.D.H.P.[i]	34,813 (2.24)	3691 (2.07)	9168 (2.43)	4504 (2.00)	17,450 (2.25)
H.D.H.P.[j]	7712 (0.5)	0 (0.00)	1398 (0.37)	1134 (0.50)	5180 (0.67)
Comprehensive[k]	27,945 (1.79)	4727 (2.66)	8586 (2.28)	3806 (1.69)	10,826 (1.39)
Unknown[l]	42,160 (2.71)	2984 (1.68)	9577 (2.54)	5522 (2.46)	24,077 (3.10)
Pre-existing diseases, *n* (%)	346,008 (22.22)	27,800 (15.62)	78,040 (20.69)	48,003 (21.35)	189,269 (24.35)
Asthma	158,576 (10.18)	11,380 (6.40)	28,048 (7.43)	22,652 (10.1)	96,496 (12.4)
Renal[m]	17,621 (1.13)	1166 (0.66)	3825 (1.01)	2612 (1.17)	10,009 (1.29)
C.O.P.D.[n]	90,540 (5.81)	6947 (3.90)	20,867 (5.53)	13,090 (5.82)	49,636 (6.39)
Diabetes mellitus	91,926 (5.9)	7520 (4.23)	24,210 (6.42)	12,237 (5.44)	47,959 (6.17)
Cardiovascular disease	39,454 (2.53)	3600 (2.02)	11,190 (2.97)	5462 (2.43)	19,202 (2.47)
Parkinson's disease	665 (0.04)	65 (0.04)	190 (0.05)	97 (0.04)	313 (0.04)
Rheumatoid arthritis	7208 (0.46)	573 (0.32)	1845 (0.49)	969 (0.43)	3821 (0.49)
Cystic fibrosis	753 (0.05)	52 (0.03)	124 (0.03)	102 (0.05)	475 (0.06)
Immunocompromise[o]	46,374 (2.98)	3418 (1.92)	11,720 (3.11)	5885 (2.62)	22,455 (2.89)
Vaccination before influenza, *n* (%)	602,586 (38.69)	37,281 (20.95)	271,707 (27.98)	132,900 (40.88)	409,566 (47.32)
Healthcare utilization, *n* (%)					
Hospitalization	28,986 (1.86)	3372 (1.90)	6745 (1.79)	4114 (1.83)	14,755 (1.90)
Emergency department	148,884 (9.56)	13,824 (7.77)	32,120 (8.51)	17,817 (7.93)	85,123 (11.0)
Outpatient visits ≥2	640,747 (41.14)	69,525(39.07)	149,859 (39.72)	89,791 (39.94)	331,572 (42.65)

[a]Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, New Jersey, and Pennsylvania.
[b]Illinois, Indiana, Michigan, Ohio, Wisconsin, Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, and South Dakota.
[c]Alabama, Arkansas, Florida, Georgia, Kentucky, Louisiana, Mississippi, Missouri, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia.
[d]Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, and Wyoming.
[e]Exclusive Provider Organization.
[f]Health Maintenance Organization.
[g]Point-Of-Service plan.
[h]Preferred Provider Organization.
[i]Consumer-Driven Health Plans.
[j]High Deductible Health Insurance.
[k]Comprehensive Health Insurance.
[l]Participants did not provide health plan information.
[m]Acute glomerulonephritis, chronic glomerulonephritis, nephrotic syndrome, chronic kidney disease, nephritis and nephropathy (not specified as acute or chronic), unspecified renal failure, dialysis, and infections of kidney.
[n]Asthma excluded, chronic pulmonary heart disease included.
[o]Malignancy tumor, acquired immune deficiency syndrome (A.I.D.S.), transplant organ, other lymphatic and hematopoietic tissue.

impacts of antiviral treatment on complications (O.R. = 0.91 vs. O.R. = 0.89), hospitalization (O.R. = 0.72 VS. O.R. = 0.71), ≥2 outpatient visits (O.R. = 0.93 VS. O.R. = 0.89), and emergency room use (O.R. = 0.77 VS. O.R. = 0.76), compared to logistic regression models (Table 7).

Discussion

We analyzed the risk of complications and healthcare utilization in patients with a clinical diagnosis of influenza during the four influenza seasons from 2006 to 2010. This study represents the largest claims analysis of influenza cases reported to date for the U.S., with a database of over 124 million beneficiaries. Our results indicate that major predictors of the risk of influenza complications included the pre-existing conditions asthma, Parkinson's disease and cystic fibrosis. Other risk factors included younger age, being female, C.O.P.D., rheumatoid arthritis, cardiovascular disease and immunocompromised disease states. We also observed an increased relative risk of complications in patients who had an influenza

Table 2. Clinical complications in influenza cases by influenza season.

	Total	Season 1 2006–2007	Season 2 2007–2008	Season 3 2008–2009	Season 4 2009–2010
Number of influenza episodes	1,557,437	177,959	377,278	224,791	777,409
Overall complications	259,187	29,350	59,023	36,896	133,918
Person months	1,372,108.60	157,774.43	335,040.80	198,630.17	680,663.20
Incidence rate per 100 person-months[a]	18.90	18.60	17.62	18.58	19.67
Acute respiratory infection, *n* (%)	214,698 (13.78)	23,951 (13.46)	49,016 (12.99)	30,264 (13.46)	111,467 (14.34)
Acute otitis media, *n* (%)	36,434 (2.34)	5050 (2.84)	9182 (2.43)	6021 (2.68)	16,181 (2.08)
Asthma, *n* (%)	28,006 (1.80)	2396 (1.35)	4759 (1.26)	3721 (1.66)	17,130 (2.20)
Myositis and myoglobinuria, *n* (%)	3832 (0.25)	339 (0.19)	844 (0.22)	558 (0.25)	2091 (0.27)
Heart failure, *n* (%)	2502 (0.16)	310 (0.17)	635 (0.17)	402 (0.18)	1155 (0.15)
Renal[b], *n* (%)	1335 (0.09)	143 (0.08)	305 (0.08)	197 (0.09)	690 (0.09)
Febrile convulsions, ataxia, *n* (%)	1631 (0.11)	182 (0.10)	339 (0.09)	277 (0.12)	833 (0.11)
Acute pericarditis or myocarditis, *n* (%)	110 (0.00)	22 (0.01)	27 (0.00)	15 (0.00)	46 (0.00)
Guillain–Barré syndrome, *n* (%)	58 (0.00)	7 (0.00)	15 (0.00)	6 (0.00)	30 (0.00)

[a]Incidence rate per 100 person-months = number of complications/person months.
[b]Acute glomerulonephritis, nephrotic syndrome, nephritis and nephropathy (not specified as acute or chronic), acute kidney failure, unspecified renal failure, infections of kidney.

Table 3. Predictors of complications in influenza cases[a].

	O.R.	Lower 95% C.L.	Upper 95% C.L.	*p* values
Age group				
0–4 years	Reference group			
5–17 years	0.46	0.46	0.47	<0.0001
18–49 years	0.48	0.47	0.48	<0.0001
50–64 years	0.57	0.56	0.58	<0.0001
≥65 years	0.89	0.86	0.92	<0.0001
Gender				
Male	Reference group			
Female	1.08	1.07	1.089	<0.0001
Pre-existing diseases				
None	Reference group			
Renal	1.49	1.43	1.54	<0.0001
Asthma	1.90	1.88	1.93	<0.0001
C.O.P.D.[b]	1.33	1.31	1.35	<0.0001
Diabetes mellitus	1.18	1.16	1.21	<0.0001
Cardiovascular disease	1.29	1.26	1.33	<0.0001
Rheumatoid arthritis	1.30	1.23	1.37	<0.0001
Parkinson's disease	1.63	1.38	1.93	<0.0001
Cystic fibrosis	1.67	1.42	1.96	<0.0001
Immunocompromise[c]	1.14	1.11	1.17	<0.0001
Vaccination before influenza				
No	Reference group			
Yes	1.21	1.20	1.22	<0.0001

[a]Complications were an aggregate of those reported in Appendix Table 2.
[b]Asthma excluded, chronic pulmonary heart disease included.
[c]Malignancy tumor, acquired immune deficiency syndrome (A.I.D.S.), transplant organ, other lymphatic and hematopoietic tissues.
C.L., confidence limit; O.R., odds ratio.

immunization. This could be the selection bias that people who are at risk of having influenza or related complications are more willing to take influenza vaccine[29].

In our study population, antiviral treatment reduced the overall risk of complications by 11%. Antiviral treatment also reduced the risk of the most common complications (respiratory infections, otitis media and newly diagnosed asthma) by 10% to 19%. Our data also indicates that antiviral treatment reduced the risk of excess healthcare resource utilization, assessed by claims for hospitalization, emergency room usage and ≥2 visits to a physician or clinic during follow-up.

We also documented a marked reduction in the risk of secondary complications and healthcare resource utilization when antiviral treatment was initiated within 2 days of diagnosis compared with initiation after 2 days. In the sensitivity analysis, the propensity score matching removes the effects of confounders in exploring the causal effects of antiviral treatment on the results. The similar results of G.E.E. models and logistic regression models approved the strength of the study.

Our data are in agreement with other recent studies evaluating oseltamivir treatment and its effects on influenza complications. A study that examined the effect of oseltamivir treatment, using pooled data from ten placebo-controlled randomized trials, demonstrated a 55% reduction in lower respiratory tract complications in oseltamivir-treated patients with confirmed influenza versus placebo[18]. This study also demonstrated a 59% reduction in hospitalization for any cause in oseltamivir-treated patients compared with placebo patients[18]. A second meta-analysis of these same clinical trials by a different group of investigators confirmed these results[19]. Previous trials also indicated that early initiation of oseltamivir treatment for influenza improves influenza-related complications and duration of hospitalization[13,39,40]. Several claims database analyses have also demonstrated similar results to ours. A study using the Ingenix Research Database examined complications of influenza in eight million United Healthcare members between December 1999 and the end of March 2002[24]. This analysis demonstrated a 28% reduction in the risk of pneumonia in oseltamivir-treated patients with influenza-like illness compared with untreated patients[24]. These investigators also demonstrated a 26% reduction in risk of hospitalization for any cause in the 30 days following the index date for oseltamivir-treated patients compared with untreated patients[24]. Similar reductions in the risk of influenza complications and hospitalization in oseltamivir-treated adults and children with influenza-like illness were seen using other claims databases, including the Thomson MarketScan Database for the six influenza seasons from 2000 to 2006 and the PharMetrics Patient-Centric Database for the five influenza seasons from 2001 to 2006[21,23]. In a separate claims database analysis of children with chronic medical conditions, oseltamivir was shown to reduce the risk of respiratory complications other than pneumonia, otitis media and hospitalization in the 30 days following clinical diagnosis of influenza[22]. Detailed information in children (0–17 years of age) was published by

Table 4. Treatment patterns in influenza cases by influenza season.

	Total	Season 1 2006–2007	Season 2 2007–2008	Season 3 2008–2009	Season 4 2009–2010
Number of episodes	1,557,437	177,959	377,278	224,791	777,409
Antiviral drugs, *n* (%)					
Treated, *n* (%)	618,512 (39.71)	61,957 (34.82)	163,815 (43.42)	81,457 (36.24)	311,283 (40.04)
Oseltamivir, *n* (%)	575,520 (93.05)	59,282 (95.68)	157,829 (96.35)	60,286 (74.01)	298,123 (95.77)
Oseltamivir initiation within 2 days, *n* (%)	568,461 (98.77)	58,755 (99.11)	156,330 (99.05)	59,691 (99.01)	293,685 (98.51)
Other treatments[a]	276,332 (17.74)	30,797 (17.30)	85,624 (22.70)	39,177 (17.43)	120,734 (15.53)
Antibiotics, *n* (%)	358,261 (23.00)	37,917 (21.31)	88,878 (23.56)	54,437 (24.22)	177,029 (22.77)
Time to initiate antiviral treatment[b] (days), mean ± SD	0.24 ± 1.76	0.2 ± 1.61	0.21 ± 1.66	0.23 ± 1.78	0.27 ± 1.83
Duration of antiviral treatment[c] (days), mean ± SD	5.83 ± 5.26	5.66 ± 3.83	5.66 ± 4.72	6.47 ± 6.51	5.78 ± 5.40
Duration of antiviral treatment[c] (days), median	5	5	5	5	5

[a]Antipyretics, nasal decongestants, ear drops, cough medication or throat preparation.
[b]Time from clinical diagnosis to prescription fulfillment.
[c]Time from prescription fulfillment to end of treatment.

Table 5. Effects of antiviral treatments on the risk of complications.

	Antiviral treatment[a] (total population)				Antiviral treatment within 2 days[b] (among those who used antivirals)				Oseltamivir treatment within 2 days[c] (among those who used oseltamivir)			
	Number of events[d]	O.R.[e]	Lower 95% C.L.	Upper 95% C.L.	Number of events[d]	O.R.[e]	Lower 95% C.L.	Upper 95% C.L.	Number of events[d]	O.R.[e]	Lower 95% C.L.	Upper 95% C.L.
Complications	251,808	0.89	0.88	0.90	96,132	0.26	0.25	0.27	89,848	0.19	0.18	0.20
Acute respiratory infections[f]	208,778	0.90	0.89	0.90	80,398	0.24	0.23	0.25	75,000	0.17	0.17	0.18
Acute otitis media	35,476	0.81	0.79	0.83	12,114	0.65	0.57	0.74	11,503	0.64	0.56	0.74
Asthma	27,215	0.87	0.85	0.90	10,319	0.38	0.34	0.42	9788	0.31	0.27	0.34
Myositis and myoglobinuria	3737	0.84	0.78	0.90	1355	0.35	0.28	0.43	1248	0.29	0.23	0.38
Heart failure	2410	0.57	0.51	0.64	413	0.38	0.27	0.54	386	0.26	0.18	0.39
Renal[g]	1290	0.85	0.75	0.96	417	0.67	0.40	1.11	388	0.57	0.31	1.04

[a]Reference group: patients who did not take antivirals.
[b]Reference group: patients who took antivirals >2 days after influenza diagnosis among those who used antivirals.
[c]Reference group: patients who took oseltamivir >2 days after influenza diagnosis among those who used oseltamivir.
[d]Number of complications reported in the defined population; patients may have reported more than one complication and/or more than one event.
[e]Logistic regression models adjusted for age, gender, region, health plan, season, pre-existing diseases, immunization status, and other treatments (antipyretics, nasal decongestants, ear drops, cough medication or throat preparation).
[f]Acute sinusitis, acute bronchitis and bronchiolitis, acute pneumonia, nasopharyngitis, pharyngitis, tonsillitis, laryngitis and tracheitis, upper respiratory infection, influenza with other respiratory manifestations.
[g]Acute glomerulonephritis, nephrotic syndrome, nephritis and nephropathy (not specified as acute or chronic), acute kidney failure, unspecified renal failure, infections of kidney.
C.L., confidence limit; O.R., odds ratio.

Table 6. Effects of antiviral treatments on healthcare utilizations.

	Hospitalization				Emergency room				Outpatient visits ≥2			
	Number of events	O.R.[a]	Lower 95% C.L.	Upper 95% C.L.	Number of events	O.R.[a]	Lower 95% C.L.	Upper 95% C.L.	Number of events	O.R.[a]	Lower 95% C.L.	Upper 95% C.L.
Antiviral treatment[b]	28,052	0.71	0.69	0.73	144,294	0.76	0.75	0.77	623,604	0.89	0.89	0.90
Antiviral treatment within two days[c]	8068	0.14	0.13	0.15	48,661	0.54	0.51	0.57	237,821	0.31	0.30	0.32
Oseltamivir treatment within two days[d]	7517	0.10	0.09	0.11	45,711	0.50	0.47	0.54	221,080	0.30	0.28	0.31

[a]Logistic regression models adjusted for age, gender, region, health plan, season, pre-existing diseases, immunization status, and other treatments (antipyretics, nasal decongestants, ear drops, cough medication or throat preparation).
[b]Reference group: patients who did not take antivirals.
[c]Reference group: patients who took antivirals >2 days after diagnosis among those who used antivirals.
[d]Reference group: patients who took oseltamivir >2 days after diagnosis among those who used oseltamivir.
C.L., confidence limit; O.R., odds ratio.

Table 7. Effects of antiviral treatment on risk of complications and healthcare resource utilization after propensity score matching.

	RR[a]	Lower 95% C.L.	Upper 95% C.L.
Complications[b]	0.91	0.90	0.92
Hospitalization[b]	0.72	0.70	0.75
Outpatient visits ≥2	0.94	0.93	0.94
Emergency room[b]	0.78	0.77	0.78

[a]Participants were matched by age, gender, region, health plan, pre-existing diseases, immunization status, and other treatments (antipyretics, nasal decongestants, ear drops, cough medication or throat preparation) in each season using propensity score matching techniques.
[b]Reference group: patients who did not take antivirals.

our group in 2014 using the same database[41]. Selection bias may explain the significant increase of the risk of complications for immunized patients. For example, people who are at risk of influenza-related complications may be willing to take the influenza vaccine[29].

A claims database analysis such as ours is limited by many factors. This study was a retrospective, non-randomized study and was limited in that the clinical diagnosis of influenza could not verified by laboratory methods. Although influenza-specific ICD-9 codes are commonly used in clinical studies,

the unfavorable sensitivity and specificity of the codes may have caused the risk of influenza cases to be incorrectly estimated[42–45]. The increased risk of complications seen in those with pre-existing diseases may have been overestimated because such patients may be more likely to see a physician and be diagnosed with influenza.

A claims database analysis may also underestimate the overall incidence of complications because not all patients with influenza seek a physician's care. We may have underestimated the antiviral treatment effects, since the time from onset of symptoms to fulfillment of a prescription and influenza severity were not available in the dataset. In addition, the claims data mainly comes from large employers; medium and small employers are not represented[28]. Also, the study participants are primarily privately insured and the imbalanced geographic distribution (69.17% of the cases were from the Southern U.S.) which may also decrease the external validity.

Nonetheless, these data indicate a marked effect of antiviral treatment on influenza complications and healthcare utilization and, further, emphasizes the importance of early initiation of treatment to achieve maximum benefit.

Transparency

Declaration of funding

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Declaration of financial/other relationships

L.S. has disclosed that, in addition to funding from Veterans Affairs, National Institute of Health and National Science Foundation, he has received research funding from Eli Lilly, Takeda, B.M.S., Novartis, Daiichi, and Pfizer. L.S. has disclosed that he received funding through Tulane University from Genentech Inc. for this study. M.Z., S.L., J.L., and M.L. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article. J.H. and Y.X. have disclosed that they are current employees of Genentech. P.J.S. has disclosed that he is a former employee and consultant for Genentech.

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