American Journal of Epidemiology
Published by Oxford University Press on behalf of the Johns Hopkins Bloomberg School of Public Health 2022.

Vol. 191, No. 5
https://doi.org/10.1093/aje/kwac020
Advance Access publication:
February 2, 2022

Practice of Epidemiology

Evaluating Confounding Control in Estimations of Influenza Antiviral Effectiveness in Electronic Health Plan Data

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Initially submitted April 18, 2021; accepted for publication January 28, 2022.

Observational studies of oseltamivir use and influenza complications could suffer from residual confounding. Using negative control risk periods and a negative control outcome, we examined confounding control in a health-insurance-claims–based study of oseltamivir and influenza complications (pneumonia, all-cause hospitalization, and dispensing of an antibiotic). Within the Food and Drug Administration's Sentinel System, we identified individuals aged ≥18 years who initiated oseltamivir use on the influenza diagnosis date versus those who did not, during 3 influenza seasons (2014–2017). We evaluated primary outcomes within the following 1–30 days (the primary risk period) and 61–90 days (the negative control period) and nonvertebral fractures (the negative control outcome) within days 1–30. We estimated propensity-score–matched risk ratios (RRs) per season. During the 2014–2015 influenza season, oseltamivir use was associated with a reduction in the risk of pneumonia (RR = 0.72, 95% confidence interval (CI): 0.70, 0.75) and all-cause hospitalization (RR = 0.54, 95% CI: 0.53, 0.55) in days 1–30. During days 61–90, estimates were near-null for pneumonia (RR = 1.04, 95% CI: 0.95, 1.15) and hospitalization (RR = 0.94, 95% CI: 0.91, 0.98) but slightly increased for antibiotic dispensing (RR = 1.14, 95% CI: 1.08, 1.21). The RR for fractures was near-null (RR = 1.09, 95% CI: 0.99, 1.20). Estimates for the 2016–2017 influenza season were comparable, while the 2015–2016 season had conflicting results. Our study suggests minimal residual confounding for specific outcomes, but results differed by season.

antiviral agents; bias; confounding factors; epidemiologic methods; health-care administrative claims; human influenza; oseltamivir; pneumonia

Abbreviations: CI, confidence interval; ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*; ICD-10-CM, *International Classification of Diseases, Tenth Revision, Clinical Modification*; PS, propensity score; RR, risk ratio.

Oseltamivir is an antiviral agent recommended for influenza types A and B and has been shown to reduce time to symptom relief (<1–1.5 days) (1–4). Its effects on influenza complications are less certain. In observational studies, researchers evaluating the association between oseltamivir use and influenza complications have reported conflicting findings (5–14), and these studies probably suffered from confounding by indication, in which oseltamivir users are at an earlier disease stage than non–oseltamivir users and therefore appear to have better outcomes (15). Underlying health status (frailty or functional limitation) could also explain these findings, since oseltamivir users are more likely to be healthier than nonusers, potentially explaining the reduction in risk of influenza complications with oseltamivir use (16, 17).

Influenza vaccine studies in older adults have been shown to suffer from residual confounding due to underlying frailty (18–21). Evidence of residual confounding has not been evaluated in observational studies of influenza antiviral treatment. We aimed to examine evidence of residual confounding in the association between oseltamivir and influenza complications (hospitalized pneumonia, all-cause hospitalization, and dispensing of antibiotics as an indicator of secondary bacterial infection) and determine whether we could adequately adjust for confounding.

We assessed windows of time in which oseltamivir is expected to have no biological effects on these complications as negative control risk periods, since initiation of oseltamivir is indicated within 2 days after symptom

onset and its effectiveness is short-lived (22). We evaluated nonvertebral fractures as a negative control outcome (i.e., an outcome not directly affected by oseltamivir) (23). We expected that if our confounding control was sufficient, we would observe null associations in these negative control analyses, with the assumption that such negative control risk periods and outcomes shared similar sources of bias with our primary risk periods and outcomes (17, 23–25). We studied 3 separate influenza seasons with varying degrees of severity and vaccine effectiveness to assess whether findings varied by these attributes.

METHODS

We developed a propensity score (PS)-matched, new-user cohort study.

Data source

We conducted this project within the Sentinel System, an active surveillance system funded by the Food and Drug Administration to monitor regulated medical products (26). The Sentinel System is a network of data partners who store curated health insurance claims and electronic health record data within their individual sites using a standardized and quality-checked data format, the Sentinel Common Data Model. Analyses were carried out using the Cohort Identification and Descriptive Analysis tool, version 7.3.4 (27, 28). We included 13 Sentinel Data Partners: national health plans, 100% Medicare fee-for-service data, and integrated health-care delivery systems.

Study cohorts

We examined 3 influenza seasons (October 1–April 30) separately: one that was relatively severe (2014–2015), one that was mild (2015–2016), and one that was moderate (2016–2017), per the Centers for Disease Control and Prevention's definition of severity, which is based on volume of outpatient care, hospitalization rates, and mortality (29). Within each season, we identified new influenza diagnoses using influenza-specific diagnosis codes in the outpatient, emergency, or ambulatory-care setting, after a 90-day washout in which no influenza diagnosis was documented (*International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) and *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM); see Web Table 1, available at https://doi.org/10.1093/aje/kwac020, for codes). Individuals with more than 1 eligible influenza diagnosis per season contributed only the first diagnosis to the analysis. We identified persons who began using oseltamivir on the date of influenza diagnosis, with no history of influenza antiviral use in the prior 90 days, via National Drug Codes in the outpatient or ambulatory-care setting. Those who did not fill oseltamivir prescriptions on the diagnosis date were defined as noninitiators.

We restricted the study to persons aged 18 years or more at the time of influenza diagnosis who had at least 365 days of medical and pharmacy insurance coverage prior to that, with a 45-day allowable coverage gap. We excluded individuals with any of the following during the 90 days prior to influenza diagnosis: dispensing of any outpatient influenza antiviral medication (National Drug Codes for oseltamivir, zanamivir, peramivir, amantadine, or rimantadine and Healthcare Common Procedure Coding System codes for peramivir (codes C9451 and J2547)); a pneumonia diagnosis in any care setting; a diagnosis code indicating severe chronic kidney disease, end-stage renal disease, or cirrhosis of the liver; and any inpatient encounters. For the respiratory antibiotic outcome and nonvertebral fractures, we also excluded patients who had these occurrences within the 90-day baseline window, ensuring that the outcomes were incident (see Web Table 2 for codes).

Since we did not have laboratory data with which to identify confirmed influenza infection, to reduce misclassification of influenza we excluded persons with season-specific influenza vaccination codes on the influenza diagnosis date (to exclude those with likely rule-out diagnosis codes) and those with select acute respiratory tract symptoms (e.g., bronchitis, sinusitis, otitis media) in any care setting within the 14 days prior to influenza diagnosis or on the day of influenza diagnosis (to ensure that influenza diagnoses were incident and not a differential diagnosis). The study design is depicted graphically in Figure 1.

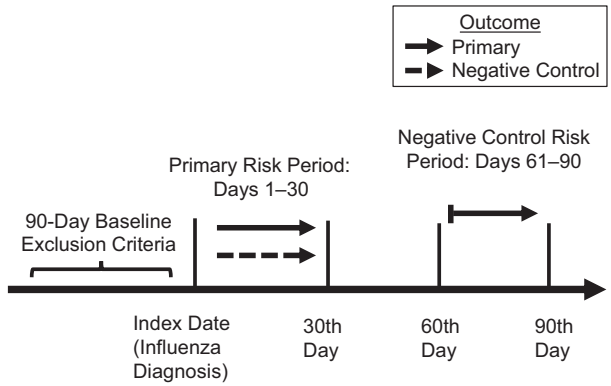

Figure 1. Study design for new influenza patients in the Sentinel System, 2014–2017. Exclusion criteria were applied in the prior 90 days unless otherwise specified. The criteria included an influenza diagnosis in any health-care setting, no use of influenza antiviral agents, no influenza vaccine on the index date, no pneumonia diagnoses (any care setting) or hospitalizations, and no acute respiratory infections for −14 to 0 days from the index date. The analyses for the antibiotic dispensing outcome also excluded persons with such a dispensing in the prior 90 days; the analyses for the fracture outcome also excluded those with a fracture diagnosis in the prior 90 days.

Outcome assessment

We assessed the following influenza complications: pneumonia hospitalization, all-cause hospitalization, and outpatient dispensing of antibiotics for respiratory infection. We defined pneumonia hospitalization on the basis of any

pneumonia-related ICD-9-CM or ICD-10-CM codes in the inpatient setting (principal or secondary discharge diagnoses; see Web Table 3 for codes). Prior literature shows high positive predictive values (88%) for inpatient pneumonia diagnosis codes in claims data (30).

To identify respiratory antibiotic dispensings, we used a combination of a dispensing for cephalosporin, macrolide, penicillin, tetracycline, quinolone, or sulfonamide (via National Drug Codes in the outpatient or ambulatory setting; see Web Table 4) and a diagnosis code for a respiratory complication (i.e., bronchitis, lower respiratory tract infection, or pneumonia) within (±) 2 days of the dispensing, following a previously published algorithm (31, 32).

For the negative control outcome during the primary risk period, we identified nonvertebral and compression-/osteoporosis-related fractures using ICD-9-CM and ICD-10-CM diagnosis codes in the emergency or inpatient setting (inpatient principal or secondary discharge diagnoses; see Web Table 3 for codes) (33–36). We chose fractures because they were not expected to be affected by oseltamivir use but are related to frailty. Therefore, we reasoned that if our confounding control for frailty was adequate, we should observe null effect estimates.

Primary and negative control risk periods

Given that oseltamivir is generally recommended for use within 48 hours of symptom onset, we conducted intention-to-treat analyses, per season, allowing treatment changes during follow-up, such that only patients who initiated oseltamivir use on the date of influenza diagnosis were considered oseltamivir initiators (i.e., those who began using oseltamivir after the date of their diagnosis were considered noninitiators) (37). We conducted sensitivity analyses to examine the impact of misclassification of our exposure assignment. The primary risk period for assessing complications was days 1–30 following influenza diagnosis.

We defined a negative control risk period as one during which there was no expected biological effect of oseltamivir on influenza complications. We followed individuals from the 61st day after the date of influenza diagnosis to the 90th day after diagnosis, using the same censoring criteria as for the primary risk period. In the negative control analyses, individuals with an outcome occurring before day 61 were included (i.e., allowing recurrent outcomes) so that persons in the negative control risk period would be as similar as possible to those in the primary risk period (23), minimizing selection bias (38). Individuals lost to follow-up prior to day 61 due to disenrollment from medical or drug coverage or death were excluded from these analyses. If an individual was diagnosed with influenza towards the end of each season, follow-up continued past the season's end date. We chose a buffer period of 30 days between primary risk periods (days 1–30) and negative control risk periods (days 61–90) to avoid potential carryover of oseltamivir action.

We ended follow-up on the earliest of the following: the end of the risk period, disenrollment from medical or pharmacy coverage, or death.

Confounding control

For each seasonal cohort, we estimated propensity scores separately using multivariable logistic regression, predicting oseltamivir initiation (versus noninitiation) based on measured confounders (39). Our aim was to include in the model conditions that are associated with a high risk of influenza complications, as defined by the Infectious Diseases Society of America (22). Covariates we included for the primary and negative control risk periods were demographic characteristics, calendar year of cohort entry, chronic comorbid conditions, concomitant medications, immunosuppression (use of steroids or immunosuppressive drugs or human immunodeficiency virus/acquired immunodeficiency syndrome), smoking, obesity, frailty indicators (to account for functional decline in older adults) (40), score on a Charlson/Elixhauser combined comorbidity index (41), and measures of healthcare utilization (mean number of ambulatory, emergency room, inpatient, and non–acute-care institutional encounters; medication dispensings). We defined these confounders on the basis of at least 1 relevant diagnosis, procedure, or dispensing during the 365 days prior to and including the influenza diagnosis date (see Web Tables 5 and 6).

Statistical analyses

We matched oseltamivir initiators and noninitiators one-to-one by PS using nearest-neighbor matching within the specified caliper of 0.01 on the probability scale of the PS (42). The balance of measured covariates between the exposed and unexposed was assessed by standardized mean differences; a value less than 0.1 was considered adequate balance (42). We examined plots of the PS distributions between the exposed and unexposed before and after matching.

Crude (unmatched) and PS-matched risk ratios (RR) comparing oseltamivir initiators with noninitiators were estimated via log-binomial regression. We estimated the cumulative incidence of the outcome from day 1 of follow-up to day 90, using the Kaplan-Meier estimator within the PS-matched population.

We studied the potential impact of exposure misclassification on our estimates using quantitative bias analysis for nondifferential and differential misclassification (43, 44). We estimated expected RRs that would be obtained if misclassification error was corrected based on presumed bias parameters (sensitivity and specificity of misclassification). We used study data to inform the parameters by examining the proportion of patients identified as noninitiators who initiated oseltamivir use after their index date.

To increase the precision of estimates, we examined the negative control outcome of fracture over 90 days following influenza diagnosis. We also examined heterogeneity of RRs by age group (18–49, 50–64, or ≥65 years) and by having an influenza test (for hospitalization and fracture outcomes only) within 7 days prior to or on the date of influenza diagnosis. In all subgroup analyses, we used the PS estimated in the whole cohort, but matching was re-performed within each subgroup (45, 46).

RESULTS

Before PS matching, we identified 206,238 oseltamivir initiators and 160,929 noninitiators during the 2014–2015 influenza season for the pneumonia hospitalization outcome (Table 1). During the later seasons with milder severity, there were fewer numbers: 95,962 oseltamivir initiators and 88,246 noninitiators for the 2015–2016 season and 197,632 oseltamivir initiators and 152,848 noninitiators for the 2016–2017 season. The number of individuals identified per cohort, per season, varied by outcome because of differences in eligibility/washout criteria (Tables 2–4). (The number of Sentinel Data Partners contributing to each season varied because the PS models did not converge at some sites. Eleven Data Partners contributed to the 2014–2015 season, 9 to the 2015–2016 season, and 12 to the 2016–2017 season.)

The mean age of individuals in the cohorts was 49–56 years (standard deviations, 14–15) across the seasons. The proportion of older patients (age ≥65 years) was 32%–40% before PS matching. Across seasons and risk periods, before PS matching, oseltamivir initiators (as compared with noninitiators) tended to be younger, to have a lower burden of cardiovascular and chronic pulmonary disorders, to have lower combined comorbidity scores, to have less prior use of an ambulance service or life support (an indicator of frailty), and to have more prior vaccination and influenza testing. Characteristics of the cohorts varied by season before PS matching. Prior to PS matching, the average age of the oseltamivir initiators was younger in the later, milder seasons than in 2014–2015. Patients in the later seasons were also less likely to be White and tended to have lower prevalence of selected comorbid conditions (e.g., cardiovascular disease, diabetes) prior to matching.

Covariate differences were reduced after PS matching, with all standardized differences being less than 0.1 across seasons, risk periods, and outcomes. Tables of baseline characteristics were generated for each outcome, season, and risk period. An example of the baseline characteristics before and after PS matching for one of the analyses is shown in Table 1. Distribution patterns of baseline covariates before and after matching among persons remaining at the start of the negative control period were similar to those at the beginning of the primary risk period. Web Figures 1–6 show the standardized differences for the covariates for all analyses.

Table 2 shows the results for the 2014–2015 influenza season. We observed a decreased risk of pneumonia among oseltamivir initiators versus noninitiators in 2014–2015, with an adjusted RR of 0.72 (95% confidence interval (CI): 0.70, 0.75). During the negative control risk period, the RR was near-null (RR = 1.04, 95% CI: 0.95, 1.15). We observed a reduced risk of all-cause hospitalization events among oseltamivir users versus non–oseltamivir users, with an adjusted RR of 0.54 (95% CI: 0.53, 0.55), which was null in the negative control risk period (RR = 0.94, 95% CI: 0.91, 0.98). The adjusted RR for the antibiotics outcome was 1.03 (95% CI: 1.00, 1.05) in the primary risk period, though it was further from the null in the negative control period (RR = 1.14, 95% CI: 1.08, 1.21). The adjusted RR for fracture in days 1–30 was 1.09 (95% CI: 0.99, 1.20).

The 2015–2016 season had similar though attenuated results for the primary risk period (Table 3). The negative control risk period estimates during this mild season were generally biased away from the null, though they were based on smaller numbers: RR = 0.89 (95% CI: 0.66, 1.20) for pneumonia and RR = 0.70 (95% CI: 0.64, 0.77) for hospitalization. The 2016–2017 season results (Table 4) were more similar to those of 2014–2015 in the primary risk period and the negative control risk period, with the exception being the PS-matched RR for pneumonia in the negative control risk period, which was 0.74 (95% CI: 0.65, 0.85). Associations for fractures were consistently near the null across all seasons for both the day 1–30 and day 1–90 analyses. Kaplan-Meier cumulative risk functions were consistent with these findings for all analyses (Web Figures 7–13).

Results of the subgroup analyses stratified by age varied according to season and7 outcome (data not shown). The 2014–2015 results were generally similar across age groups. For fractures, results were null in the oldest age group (≥65 years), which is the subgroup most likely to experience fractures. For the other 2 seasons, results varied more by age and outcome.

The subgroup analysis for persons with and without an influenza test—performed for all-cause hospitalization and fractures only—also yielded results that varied by season and outcome and by test status (Web Tables 7–12). We hypothesized that persons treated with oseltamivir and those not treated would be more comparable among the untested, since other investigators have reported that among those tested for influenza, people who were not treated were more likely to have tested negative or to have had a later symptom onset (47). Among persons not tested, the results were similar to the main analyses for the 2014–2015 and 2016–2017 seasons.

Assuming nondifferential exposure misclassification and assuming that 15% of the unexposed were in fact exposed, we estimated expected RRs similar to those originally observed (Web Table 13). Estimates were similar even when assuming 10% misclassification among the exposed concurrently with 15% misclassification among the unexposed (Web Table 14). When we assumed that such exposure misclassification occurred only among persons who developed the outcomes or those who did not have an outcome—for example, patients who had such misclassification were at higher risk of the outcomes than those who did not and vice versa—some meaningful differences were found between observed and expected estimates, though they were not consistently seen across the outcomes by risk window and season (Web Tables 15 and 16).

DISCUSSION

The negative control results from this study suggested minimal residual confounding for pneumonia and all-cause hospitalization outcomes during the relatively severe 2014–2015 season, while associations during the mildest season studied, 2015–2016, suggested residual confounding or potential modification of effect estimates by influenza season. The negative control outcome of fractures suggested adequate control of confounding from sources related to

Table 1. Distribution of Selected Baseline Characteristics of Oseltamivir Initiators Versus Noninitiators Among Newly Diagnosed Influenza Patients, Sentinel System, October 2014–April 2015

Characteristic	Before Matching					After Matching				
	Treated on Day of Diagnosis (n = 206,238)		Not Treated on Day of Diagnosis (n = 160,929)		Covariate Balance (SMD)	Treated on Day of Diagnosis (n = 119,453)		Not Treated on Day of Diagnosis (n = 119,453)		Covariate Balance (SMD)
	No.	%	No.	%		No.	%	No.	%	
Demographic Characteristics										
Age, years[a]	54.9 (14.2)		56.4 (15.6)		−0.099	56.1 (14.5)		55.9 (14.9)		0.015
18–49	87,074	42.2	63,675	39.6	0.054	47,953	40.1	47,925	40.1	0
50–64	40,041	19.4	31,600	19.6	−0.006	22,436	18.8	23,302	19.5	−0.018
≥65	79,123	38.4	65,654	40.8	−0.05	49,064	41.1	48,226	40.4	0.014
Male sex	86,669	42.0	64,039	39.8	0.045	47,795	40.0	49,246	41.2	−0.025
Race/ethnicity[b]										
White	90,091	43.7	74,312	46.2	−0.05	55,451	46.4	55,494	46.5	−0.001
African-American	8,038	3.9	10,595	6.6	−0.121	6,318	5.3	6,222	5.2	0.004
Asian	4,366	2.1	4,116	2.6	−0.029	3,033	2.5	3,002	2.5	0.002
Unknown	102,665	49.8	70,772	44.0	0.116	53,940	45.2	54,056	45.3	−0.002
Hispanic origin	4,240	2.1	4,633	2.9	−0.053	3,059	2.6	3,031	2.5	0.001
Year										
2014	81,418	39.5	60,501	37.6	0.039	45,083	37.7	45,316	37.9	−0.004
2015	124,820	60.5	100,428	62.4	−0.039	74,370	62.3	74,137	62.1	0.004
Recorded History of Comorbid Conditions, Frailty-Related Conditions, and Other Health-Related Behaviors										
Combined comorbidity score[a]	0.7 (1.6)		1.1 (1.9)		−0.223	0.8 (1.8)		0.8 (1.7)		0.007
Asthma	21,662	10.5	19,754	12.3	−0.056	13,544	11.3	13,226	11.1	0.008
Cardiovascular disease	48,618	23.6	45,989	28.6	−0.114	31,531	26.4	31,102	26.0	0.008
Cerebrovascular disease	13,953	6.8	14,700	9.1	−0.088	9,470	7.9	9,390	7.9	0.002
Chronic pulmonary disorder	24,742	12.0	26,688	16.6	−0.131	17,281	14.5	16,991	14.2	0.007
Developmental delay	340	0.2	374	0.2	−0.015	250	0.2	235	0.2	0.003
Diabetes	37,321	18.1	34,734	21.6	−0.088	24,243	20.3	23,787	19.9	0.01
Evidence of pregnancy	7,918	3.8	7,557	4.7	−0.042	5,117	4.3	4,950	4.1	0.007

Table continues

Table 1. Continued

Characteristic	Before Matching					After Matching				
	Treated on Day of Diagnosis (*n* = 206,238)		Not Treated on Day of Diagnosis (*n* = 160,929)		Covariate Balance (SMD)	Treated on Day of Diagnosis (*n* = 119,453)		Not Treated on Day of Diagnosis (*n* = 119,453)		Covariate Balance (SMD)
	No.	%	No.	%		No.	%	No.	%	
Frailty										
Ambulance/life support	12,937	6.3	22,274	13.8	−0.254	11,045	9.2	10,798	9.0	0.007
Coagulopathy	3,031	1.5	3,378	2.1	−0.048	2,111	1.8	2,098	1.8	0.001
Dementia	10,437	5.1	13,603	8.5	−0.135	7,978	6.7	7,882	6.6	0.003
Difficulty walking	12,059	5.8	14,776	9.2	−0.127	8,753	7.3	8,679	7.3	0.002
Home hospital bed	42	0.0	77	0.0	−0.015	28	0.0	22	0.0	0.003
Home oxygen use	667	0.3	649	0.4	−0.013	399	0.3	376	0.3	0.003
Paralysis	1,024	0.5	1,508	0.9	−0.052	804	0.7	802	0.7	0
Parkinson disease	1,135	0.6	1,527	0.9	−0.046	879	0.7	854	0.7	0.002
Rehabilitation care	8,398	4.1	8,763	5.4	−0.065	5,680	4.8	5,588	4.7	0.004
Sepsis	4,425	2.1	6,115	3.8	−0.098	3,280	2.7	3,311	2.8	−0.002
Stroke/brain injury	5,174	2.5	6,501	4.0	−0.086	3,792	3.2	3,713	3.1	0.004
Wheelchair use	316	0.2	493	0.3	−0.032	234	0.2	238	0.2	−0.001
HIV/AIDS	718	0.3	771	0.5	−0.020	488	0.4	490	0.4	0
Hematological disorder	25,158	12.2	25,659	15.9	−0.108	16,983	14.2	16,728	14.0	0.006
Hepatic disorder	4,228	2.1	3,777	2.3	−0.020	2,647	2.2	2,585	2.2	0.004
Immune disorder	3,381	1.6	2,999	1.9	−0.017	2,098	1.8	2,042	1.7	0.004
Influenza test	133,124	64.5	81,134	50.4	0.289	65,555	54.9	67,855	56.8	−0.039
Institutional stay	1,954	0.9	2,595	1.6	−0.059	1,459	1.2	1,437	1.2	0.002
Malignant neoplasm	19,220	9.3	14,666	9.1	0.007	11,193	9.4	11,076	9.3	0.003
Metabolic disorder	110,140	53.4	89,551	55.6	−0.045	65,777	55.1	64,950	54.4	0.014
Musculoskeletal disorder	112,202	54.4	93,841	58.3	−0.079	68,071	57.0	66,955	56.1	0.019
Nervous system disorder	46,166	22.4	42,224	26.2	−0.090	29,023	24.3	28,401	23.8	0.012
Nutritional disorder	30,329	14.7	24,780	15.4	−0.019	18,290	15.3	17,928	15.0	0.008
Obesity or related surgery	24,108	11.7	20,896	13.0	−0.039	14,811	12.4	14,496	12.1	0.008
Other respiratory disorder	628	0.3	619	0.4	−0.014	413	0.3	419	0.4	−0.001
Pneumococcal vaccination status	41,648	20.2	32,574	20.2	−0.001	24,743	20.7	24,509	20.5	0.005

Table continues

Table 1. Continued

Characteristic	Before Matching					After Matching				
	Treated on Day of Diagnosis (*n* = 206,238)		Not Treated on Day of Diagnosis (*n* = 160,929)		Covariate Balance (SMD)	Treated on Day of Diagnosis (*n* = 119,453)		Not Treated on Day of Diagnosis (*n* = 119,453)		Covariate Balance (SMD)
	No.	%	No.	%		No.	%	No.	%	
Pneumonia	5,132	2.5	5,560	3.5	−0.057	3,462	2.9	3,449	2.9	0.001
Renal disorder	24,379	11.8	23,486	14.6	−0.082	15,897	13.3	15,680	13.1	0.005
Spinal cord injury	326	0.2	413	0.3	−0.022	220	0.2	236	0.2	−0.003
Tobacco use	13,389	6.5	16,090	10.0	−0.128	9,686	8.1	9,441	7.9	0.008
Influenza vaccination	74,859	36.3	52,741	32.8	0.074	41,825	35.0	41,596	34.8	0.004
History of Medication Dispensings										
Corticosteroids	77,744	37.7	54,991	34.2	0.074	42,862	35.9	42,099	35.2	0.013
Immunosuppressive agents	36,613	17.8	26,993	16.8	0.026	20,825	17.4	20,507	17.2	0.007
Intensity of Health-Care Service Utilization[a]										
No. of ambulatory health-care encounters	15.2 (14.4)		15.7 (16.0)		−0.031	15.5 (15.1)		15.2 (14.5)		0.017
No. of emergency room encounters	0.5 (1.3)		0.9 (2.2)		−0.235	0.7 (1.6)		0.7 (1.5)		−0.014
No. of inpatient hospital encounters	0.1 (0.4)		0.1 (0.5)		−0.103	0.1 (0.4)		0.1 (0.4)		0.002
No. of nonacute institutional encounters	0 (0.3)		0.1 (0.4)		−0.082	0 (0.4)		0 (0.4)		0.001
No. of other ambulatory encounters	3.3 (8.7)		5 (12.6)		−0.157	4 (10.7)		4 (10.4)		−0.001
No. of unique drug classes	8.3 (4.9)		7.2 (5.2)		0.220	7.8 (4.7)		7.6 (5.2)		0.025
No. of unique generics	9 (5.6)		7.9 (6.0)		0.186	8.5 (5.5)		8.3 (5.9)		0.023
No. of filled prescriptions	28.7 (28.7)		30.1 (33.9)		−0.046	29.7 (31.5)		29.4 (30.6)		0.008

Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; SMD, standardized mean difference.
[a] Values are expressed as mean (standard deviation).
[b] Race/ethnicity data are not completely populated at all Sentinel Data Partner sites; therefore, data on race/ethnicity are incomplete.

Table 2. Propensity-Score–Matched Risk Ratios for Influenza Complications and Fracture Among Oseltamivir Initiators Versus Noninitiators, Sentinel System, October 2014–April 2015

Outcome	Before PS Matching						After PS Matching				
	Oseltamivir Initiators		Oseltamivir Noninitiators		RR	95% CI	No. of Events		No. of Matched Pairs	RR	95% CI
	No. of Events	No. of Patients	No. of Events	No. of Patients			Oseltamivir Initiators	Oseltamivir Noninitiators			
Primary Risk Period											
Pneumonia	1,467	206,238	2,258	160,929	0.51	0.49, 0.52	1,021	1,411	119,453	0.72	0.70, 0.75
Hospitalization	4,352	206,238	9,434	160,919	0.36	0.35, 0.37	2,994	5,561	119,448	0.54	0.53, 0.55
Antibiotics	5,536	139,373	3,869	111,566	1.15	1.12, 1.17	3,024	2,943	77,363	1.03	1.00, 1.05
Negative Control Risk Period											
Pneumonia	239	197,917	283	153,820	0.66	0.61, 0.71	174	167	114,587	1.04	0.95, 1.15
Hospitalization	1,905	197,917	2,136	153,810	0.69	0.67, 0.71	1,263	1,339	114,583	0.94	0.91, 0.98
Antibiotics	1,029	133,515	669	106,408	1.23	1.17, 1.28	561	490	74,077	1.14	1.08, 1.21
Negative Control Outcome											
Fracture	262	203,790	259	158,245	0.79	0.73, 0.85	176	162	117,730	1.09	0.99, 1.20

Abbreviations: CI, confidence interval; PS, propensity score; RR, risk ratio.

Table 3. Propensity-Score–Matched Risk Ratios for Influenza Complications and Fracture Among Oseltamivir Initiators Versus Noninitiators, Sentinel System, October 2015–April 2016

Outcome	Before PS Matching						After PS Matching				
	Oseltamivir Initiators		Oseltamivir Noninitiators		RR	95% CI	No. of Events		No. of Matched Pairs	RR	95% CI
	No. of Events	No. of Patients	No. of Events	No. of Patients			Oseltamivir Initiators	Oseltamivir Noninitiators			
Primary Risk Period											
Pneumonia	632	95,962	988	88,246	0.59	0.56, 0.61	477	555	59,247	0.86	0.81, 0.91
Hospitalization	1,761	95,962	3,920	88,242	0.41	0.40, 0.42	1,330	1,992	59,246	0.67	0.65, 0.69
Antibiotics	2,571	65,956	2,046	62,594	1.19	1.16, 1.22	1,546	1,419	38,649	1.09	1.06, 1.12
Negative Control Risk Period											
Pneumonia	20	93,601	59	85,462	0.31	0.25, 0.39	16	18	57,574	0.89	0.66, 1.20
Hospitalization	205	93,601	435	85,458	0.43	0.40, 0.46	153	219	57,576	0.70	0.64, 0.77
Antibiotics	116	64,299	144	60,575	0.76	0.68, 0.85	77	66	37,566	1.17	1.01, 1.35
Negative Control Outcome											
Fracture	70	95,230	108	87,384	0.59	0.52, 0.68	51	54	58,739	0.94	0.80, 1.12

Abbreviations: CI, confidence interval; PS, propensity score; RR, risk ratio.

Table 4. Propensity-Score–Matched Risk Ratios for Influenza Complications and Fracture Among Oseltamivir Initiators Versus Noninitiators, Sentinel System, October 2016–April 2017

Outcome	Before PS Matching						After PS Matching				
	Oseltamivir Initiators		Oseltamivir Noninitiators				No. of Events				
	No. of Events	No. of Patients	No. of Events	No. of Patients	RR	95% CI	Oseltamivir Initiators	Oseltamivir Noninitiators	No. of Matched Pairs	RR	95% CI
Primary Risk Period											
Pneumonia	1,275	197,632	2,163	152,848	0.46	0.44, 0.47	898	1,237	110,347	0.73	0.70, 0.75
Hospitalization	3,928	197,632	9,048	152,840	0.34	0.33, 0.34	2,626	4,993	110,347	0.53	0.52, 0.54
Antibiotics	4,862	134,501	3,623	109,443	1.09	1.07, 1.11	2,751	2,676	73,095	1.03	1.00, 1.05
Negative Control Risk Period											
Pneumonia	104	192,560	167	147,675	0.48	0.43, 0.53	73	98	107,152	0.74	0.65, 0.85
Hospitalization	931	192,560	1,165	147,668	0.61	0.59, 0.64	637	678	107,151	0.94	0.90, 0.99
Antibiotics	470	130,912	326	105,592	1.16	1.09, 1.24	278	224	70,929	1.24	1.15, 1.34
Negative Control Outcome											
Fracture	198	196,019	230	151,097	0.66	0.61, 0.72	127	125	109,259	1.02	0.91, 1.13

Abbreviations: CI, confidence interval; PS, propensity score; RR, risk ratio.

frailty (16, 17). Associations for antibiotic dispensings, on the other hand, suggested potential residual confounding by indication due to respiratory tract infections or influenza disease severity. The 2016–2017 season results were similar to those of 2014–2015 except for evidence of residual confounding for the pneumonia outcome. Our study highlights how negative control analyses could be used to evaluate confounding control in observational studies based on electronic health-care data, especially when there is no suitable active comparator.

Our findings in the primary risk periods were consistent with meta-analyses and pooled analyses of randomized clinical trials, which reported RR estimates of 0.5–0.7 for pneumonia and 0.3–0.9 for hospitalization in both total trial populations and influenza-infected populations of oseltamivir use versus placebo (3, 32, 48). The population captured within Sentinel is more diverse and inclusive of patients with high-risk conditions and severe comorbidity—patients typically excluded from clinical trials. Pneumonia and lower respiratory tract complications in trials were mostly self-reported and not clinically confirmed, while our claims-based outcomes were specified on the basis of definitions with high reported specificity, which reduces misclassification bias (44).

Researchers in prior observational, claims-based studies also reported protective associations between oseltamivir and these outcomes, although with higher variability: RRs for pneumonia ranged from 0.5 to 0.8 and those for hospitalization ranged from 0.3 to 0.7 (5–11, 13). Several studies utilized a never-user comparison group and were susceptible to healthy-user bias or confounding due to underlying indications or frailty (15–17, 49).

Evaluating confounding control

To our knowledge, our study is the first to have evaluated confounding control in estimation of influenza antiviral effectiveness by utilizing negative control risk periods. A study by Jackson et al. (19) showed that influenza vaccine studies suffer from confounding due to underlying frailty/health status, since the vaccine appeared to reduce mortality risk outside of the influenza seasons, especially in older adults.

In the negative control period analyses, we conducted analyses in the same individuals but during periods when the exposure was not expected to biologically alter the outcome risk. Therefore, if confounding control in the primary risk periods was sufficient, we should have observed null estimates in the negative control periods. Given our relatively young (mean age = 40–50 years) and healthy populations with outpatient influenza diagnoses, time-varying confounding over 3 months with respect to frailty, behavioral risk factors, or comorbidity is likely to have been minimal (40, 50, 51).

One potential limitation of the use of negative control risk periods is the dropout of people prior to the start of the negative control period due to death or health-plan disenrollment. We retained people who had an earlier event in our negative control analyses, since excluding them could have introduced selection bias. Our findings indicated that approxi-

mately 5% of the original cohort died or disenrolled from their health plans prior to the beginning of negative control periods (days 61–90), and the distributions of baseline characteristics of patients at the beginning of the negative control period were very similar to those in the original cohort. One downside of including recurrent outcomes (i.e., not excluding patients with events prior to the negative control period) is that risk factors for recurrent outcomes versus first-time outcomes might be different. We used a buffer period of 30 days between the primary (days 1–30) and negative control (days 61–90) periods to reduce any potential downstream effect of interventions during the primary risk period.

Seasonal variation in estimates

We adjusted for confounding separately within each season. During milder influenza seasons, particularly 2015–2016, the adjusted RRs for pneumonia and hospitalization did not reach the null in the negative control period, which could indicate heterogeneity of effect estimates due to influenza severity or increased potential for bias during milder seasons. In milder seasons, influenza patients might be more selectively prescribed oseltamivir, such that underlying differences between the cohorts with respect to disease severity or underlying health status might be greater for milder seasons (24, 49).

The standardized mean differences prior to matching for age, White race, and some major comorbid conditions were indeed larger in the later seasons (Web Figures 1–6). This larger degree of measured confounding might imply larger unmeasured confounding, perhaps explaining some of the negative control estimates in the later seasons' being away from the null. Propensity scores were generally higher in the 2014–2015 season, but the degree of overlap between the prematched cohorts was approximately similar across the seasons (Web Figures 14–16). Smaller cohort sizes in milder seasons are yet another factor that could explain the findings. Alternatively, misclassification of cohort identification may have been higher during the mild seasons.

Estimates for the antibiotic dispensing outcome showed less seasonal variation and were consistently near-null across seasons for the primary risk period. Estimates during the negative control periods were slightly biased away from the null, suggesting slight confounding by indication. In a prior study, Nordstrom et al. (6) reported an RR of 0.9 for the impact of oseltamivir treatment on antibiotic dispensings, which was close to our results. We used a combination algorithm of a symptom for lower respiratory tract infection and an antibiotic dispensing to define the outcome, though we may have captured some prophylactic antibiotic use, since antibiotic dispensings might reflect provider and patient preferences (17, 49). Results for the negative control outcome of fracture were consistently near-null, suggesting that frailty was not likely to be a major source of residual confounding in our primary outcome estimates.

Other strengths and limitations

Strengths of our large-scale study include the use of real-world populations from diverse health-care settings and data sources. We employed multiple negative control analyses to examine the ability to detect residual confounding in studies of antiviral drug use in electronic health-care data, which is especially relevant in times of epidemics and pandemics. Our utilization of a new-user study design avoided selection bias due to left-truncation and the healthy user bias that might occur with other study designs, and restriction to new influenza diagnoses also probably reduced the potential for confounding by influenza disease severity (17, 52, 53).

Our findings should be interpreted in the context of the study's limitations. Date of symptom onset is not captured in health insurance claims data (or structured medical record data). Therefore, the noninitiators may have had a longer duration of illness prior to the health-care visit at which they were diagnosed, since oseltamivir initiation is generally indicated within 2 days after symptom onset. Given that oseltamivir is most effective within 2 days of symptom onset, our intention was to identify initiation as close to symptom onset as possible; we used an intention-to-treat exposure definition, in which only those who were dispensed oseltamivir on the day of diagnosis were considered initiators (37). We found that up to 15% of noninitiators eventually initiated oseltamivir after the index date in our data, and our bias analyses (Web Tables 13 and 14) showed that the RRs that were adjusted for this potential exposure misclassification were close to the primary RRs. We additionally examined the scenarios in which exposure misclassification was differential: 1) only among patients who developed the outcome and 2) only among those who did not develop the outcome. While such scenarios showed different expected estimates from the observed ones (Web Tables 15 and 16), these scenarios were relatively extreme and may not have reflected the real-world scenarios.

We used influenza-specific diagnosis codes to identify cohorts, and a prior Sentinel study demonstrated that trends in the dispensing of influenza antiviral agents align well with Centers for Disease Control and Prevention influenza surveillance data (54). By relying on diagnosis codes, we may have captured some people without true influenza infection and may have missed some who did have true infection. Perhaps because of the specific nature of the influenza codes we used, a large proportion (50%–55%) of patients in our study were prescribed oseltamivir—a much higher proportion than previously reported (approximately 10%–30%) (4–6, 8, 10, 11).

We used very specific definitions to identify influenza complication outcomes, since highly specific outcomes have been shown to have less biased RR estimates with respect to misclassification (30, 36, 44). We examined the trends in ICD-9-CM and ICD-10-CM diagnosis codes over time to examine whether coding changes affected the validity of outcome assessment and did not detect any significant changes in these trends across the coding transition (data not shown).

Conclusion

Our multidatabase cohort study suggests adequate confounding control for some but not all outcomes in an evaluation of the association between oseltamivir use and influenza

complications, with variation by influenza season. Negative controls should be used to evaluate the presence of confounding in observational studies of drug safety and effectiveness when there is a high potential for unmeasured confounding.

ACKNOWLEDGMENTS

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This work was funded by the Food and Drug Administration (FDA) through the US Department of Health and Human Services (contract HHSF223201400030I).

The FDA Sentinel System does not allow the public release of individual-level data.

We thank the Sentinel Data Partners who provided the data used in the analysis: CVS Health Clinical Trial Services (an affiliate of Aetna, a CVS Health Company), Blue Bell, Pennsylvania; Department of Population Health Sciences, Duke University School of Medicine, Durham, North Carolina (through the Centers for Medicare and Medicaid Services, which provided the data); Harvard Pilgrim Health Care, Boston, Massachusetts; HealthCore/Anthem, Wilmington, Delaware; HealthPartners Institute, Minneapolis, Minnesota; Humana Healthcare Research Inc., Louisville, Kentucky; Kaiser Permanente Hawai'i Center for Integrated Health Care Research, Honolulu, Hawaii; Kaiser Permanente Northern California Division of Research, Oakland, California; Kaiser Permanente Northwest Center for Health Research, Portland, Oregon; Kaiser Permanente Washington Health Research Institute, Seattle, Washington; Marshfield Clinic Research Institute, Marshfield, Wisconsin; OptumInsight Life Sciences Inc., Boston, Massachusetts; and Department of Health Policy, Vanderbilt University Medical Center, Nashville, Tennessee (through the TennCare Division of the Tennessee Department of Finance and Administration, which provided the data).

An earlier version of this work was presented at the 35th Annual International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Philadelphia, Pennsylvania, August 24–28, 2019.

This article reflects the views of the authors and should not be construed as representing the views or policies of the FDA.

Harvard Pilgrim Health Care Institute is a nonprofit organization that conducts work for government and private organizations, including pharmaceutical companies. The authors have no individual conflicts of interest to declare.

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