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ORIGINAL RESEARCH

Reduced mortality, complications, and economic burden among medicare beneficiaries receiving influenza antivirals

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ABSTRACT

Introduction: Antiviral therapy may be underutilized in patients at high risk for increased clinical and economic burden (e.g. older adults). We aimed to examine the benefits associated with antiviral treatment of seasonal influenza among treated and untreated Medicare beneficiaries.

Methods: This retrospective study of Medicare Claims Research Identifiable Files identified patients ≥66 years old with an influenza diagnosis in outpatient setting between October 2016–March 2019 (flu seasons 2016–2018). Index date defined as date of first claim with influenza diagnosis; baseline as the 12 months pre-index. Treated patients received antivirals ≤2 days from index. Untreated patients had no antivirals ≤6 months post-index. Treated/untreated patients were 1:1 propensity score matched. Outcomes (death, all-cause and respiratory-related healthcare resource utilization [HCRU] and costs) were assessed until death or up to 6 months post-index. Descriptive statistics were reported; Kaplan-Meier estimation was used for survival over time.

Results: Among 116,901 matched patient pairs, all-cause mortality within 6 months from index diagnosis was 1.6% among treated versus 4.3% among untreated patients. Rates (treated versus untreated) of all-cause inpatient hospitalizations during follow-up were 13.9% versus 22.7% and respiratory-related hospitalizations were 4.2% versus 9.0%. Mean (SD) total all-cause and respiratory-related costs were $9,830 ($18,616.0) and $900 ($4016.4) among the treated, respectively, versus $13,207 ($24,405.1) and $2,024 ($7,623.7) among untreated, respectively. All differences were statistically significant ($p < 0.001$).

Conclusions: Lack of antiviral treatment is associated with increased mortality, HCRU, and economic burden in older Medicare beneficiaries with seasonal influenza. Future research should investigate whether the choice of antivirals affects influenza burden.

PLAIN LANGUAGE SUMMARY

Previous studies have shown that antiviral drugs help prevent flu-related complications and lower healthcare utilization and costs. However, these previous studies have focused on working aged people with existing health problems. Our study looks at how antiviral treatment can lower the health and financial burden caused by the flu in older adults. Using a Medicare claims database from the 2016–2018 flu season, we identified 116,901 matched (treated versus untreated) patient pairs. All-cause mortality within 6 months from the index diagnosis (defined as the first claim with a flu diagnosis) was 1.6% among treated versus 4.3% among untreated patients. Rates (treated versus untreated) of all-cause inpatient hospitalizations during follow-up (defined as 6 months after the index diagnosis date) were 13.9% versus 22.7% and respiratory-related hospitalizations were 4.2% versus 9.0%. Mean total all-cause and respiratory-related costs were $9,830 and $900 among the treated, respectively, versus $13,207 and $2,024 among untreated, respectively. All differences were statistically significant ($p < 0.001$). This analysis of older adults with the flu found that prompt antiviral treatment is associated with lower rates of mortality and acute complications, reduced hospitalization, and lower healthcare costs. Use of antiviral treatment for patients at high risk of flu, such as older adults, is warranted.

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Introduction

Seasonal influenza is a major cause of morbidity and mortality in the United States (US). The Centers for Disease Control and Prevention (CDC) estimates that the 2018–2019 influenza season was associated with 380,000 influenza-related hospitalizations and 28,000 related deaths in the US[1]. Recent estimates for the total annual direct medical costs in the US range from $3.2 billion to $5.5 billion [2,3].

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Adults 65 years and older are at high risk of influenza-related complications, morbidity, and increased healthcare costs[4–6]. Indeed, in the estimates for the 2018–2019 influenza season, older adults, who made up 16% of the US population in 2018–2019[7], account for 57% of the influenza-related hospitalizations and for 75% of the influenza-related deaths[1]. Moreover, the age group with the largest share of the direct medical costs was 65 years and older (42.7% of the total), driven primarily by hospitalization costs ($1.3 billion)[2].

An important public health measure for the prevention of seasonal influenza is vaccination[8–10]. Multiple studies have shown that immunization reduces the risk of mortality, hospitalization, and complications associated with influenza[11–13]. Despite the recommendation that everyone 65 or older receive the influenza vaccine annually[8], about 25–30% of the elderly did not receive the influenza vaccine during the most recent influenza seasons[14].

Several antiviral treatment options exist for patients who become infected with influenza. Neuraminidase inhibitors (i.e. zanamivir, oseltamivir, peramivir) and the selective inhibitor of influenza cap-dependent endonuclease (i.e. baloxavir) are all active against both influenza A and B, and currently recommended by the CDC[15–21]. Clinical studies have shown that when initiated promptly (e.g. within 48 h of symptom onset), antiviral agents, as above, shorten the duration of symptoms and may reduce the incidence and severity of complications of influenza[17,22–26]. Despite evidence of potential benefits, antiviral therapy may be underutilized in patients at high risk for complications, even among those who present early for care[27].

Real world evidence on antiviral use and clinical and economic burden in influenza is scarce. Recent studies focused on commercially insured patients found that antiviral use is associated with a decrease in influenza-related complications and healthcare utilization and costs[28–30]. Another analysis investigated influenza burden for Medicare beneficiaries but treatment status was not tracked[31].

This study's aim was to broadly examine the clinical and economic benefits, including reduced acute complications, mortality, healthcare utilization, and costs, associated with antiviral treatment of seasonal influenza among a large, contemporaneous sample of Medicare beneficiaries.

Methods

Study design and data source

This retrospective cohort study examined the burden of influenza among Medicare beneficiaries in the US. The five most recent years (2015–2019) of Medicare Fee-for-Service (FFS) claims from the 100% Research Identifiable Files (RIFs) were used for the analysis. The RIF database is the most comprehensive Medicare database covering 100% of Medicare beneficiaries from all census regions and includes patient-level demographic, enrolment, and fee-for-service administrative claims data across all places of service (e.g. emergency departments, inpatient and outpatient facilities, skilled nursing and hospice facilities, and home health agencies).

Patient identification

This study included Medicare FFS beneficiaries at least 66 years of age with a diagnosis of influenza in the outpatient setting, indicated by at least one outpatient medical claim with an ICD-10-CM diagnosis code for influenza: J09.xx, J10.xx, J11.xx during the identification (ID) period of October through March of each year (seasonal influenza season) between 2016 and 2019 (i.e. three full influenza seasons). The index date for the study was defined as date of the first claim with an influenza diagnosis. If patients had multiple influenza diagnoses during the study period, one occurrence was picked randomly for identification. Patients with multiple episodes of influenza within a given season were observed for the first episode only. Patients were also required to have continuous enrollment in Medicare FFS Parts A/B and Part D during the one year prior to the index date (baseline period) and during the 6 months after index (follow-up period), or until death if occurring earlier. Thus, patients were observed from baseline until the end of follow-up or death, whichever occurred first.

Of the above patients diagnosed with influenza, two groups were created: 1) treated patients who received an approved antiviral medication for influenza (had a claim with a NDC drug code for zanamivir, oseltamivir, peramivir, or baloxavir) within 2 days after the index date; and 2) untreated patients who did not receive treatment within 6 months after the index date. Patients in either group who received antiviral medication for influenza within two months prior to the index date were excluded to ensure the exposure treatment status (i.e. initiators and nonusers of antiviral treatment). Additionally, treated patients were further excluded if they received antiviral medication for prophylaxis as indicated by a total days' supply of antiviral medication of 10 days or more, within 10 days after the first antiviral claim.

Untreated patients were matched 1:1 to treated patients using propensity score matching (greedy nearest neighbor with caliper width of 0.1 of the standard deviation of the logit of the propensity score)[32,33]. Propensity score matching allows for more balanced baseline characteristics between the cohorts and, in turn, for the antiviral treatment effect to be observed in the follow-up period with few confounding factors[34,35]. The propensity for initiating antiviral medication was estimated using logistic regression with independent variables of year of influenza season, age, gender, geographic region, race, influenza vaccine status, usual physician specialty, Charlson Comorbidity Index (CCI), number of chronic conditions, dual-eligible status, and each individual high-risk condition (asthma, chronic lung disease, heart disease, blood disorders, endocrine disorders, kidney disorders, liver disorders, metabolic disorders, extreme obesity, chronic obstructive pulmonary disease [COPD], immunosuppressive conditions [MS, HIV, RA]). In addition, patients were matched exactly on the year of influenza season and influenza vaccine status. Balance diagnostics after matching were assessed using standardized mean difference.

Measures

Disease burden was assessed during the follow-up period by observing acute complications, mortality, healthcare utilization and costs. Patients who experienced an acute complication of influenza during an inpatient hospitalization were categorized as follows: respiratory tract diagnoses, influenza with other manifestations, neurologic diagnoses, cardiovascular events, endocrine diagnoses, gastrointestinal tract diagnoses, hematologic diagnoses, and other acute diagnoses (Appendix Table 1)[36]. Mortality within 6 months from the index diagnosis was observed. Healthcare utilization was assessed by place of service, number of patients with an: inpatient, emergency department (ED), outpatient visits (excluding ED visits), skilled nursing facility, home health agency, and hospice care. Additionally, inpatient length of stay and number of office visits were calculated. Finally, total healthcare costs (all cause and respirator-related) were measured. Patients' baseline demographics (age, gender, race) were observed. To assess baseline health status of patients, comorbidities (Charlson Comorbidity Index [CCI]) and chronic conditions (as defined by the Healthcare Cost and Utilization Project [HCUP] Chronic Condition Indicator [37]) as well as conditions contributing to high influenza risk were reported (Appendix Table 2). Finally, vaccination status (assessed in the same season as and prior to the index influenza diagnosis) and year of influenza season was noted.

Statistical analysis

Descriptive statistics for all baseline and outcome measures were reported by treatment status of the matched cohorts. Means and standard deviations were reported for continuous variables; counts and percentages were reported for categorical variables. All outcome measures for matched treated and untreated patients with influenza were compared using t-tests or Chi-square tests for continuous and categorical variables, respectively.

All data transformations and statistical analyses were performed using SAS® version 9.4.

Results

During the three influenza seasons observed between 2016–2019, 335,637 patients (209,571 treated and 126,066 untreated patients) met study inclusion criteria. The final matched cohort contained 116,901 matched patient pairs (Figure 1).

Demographics and clinical characteristics

In the matched cohort, the mean (SD) age at index was 75.6 (7.2) years among both treated and untreated patients, with the greatest proportion of patients in the youngest, 66-

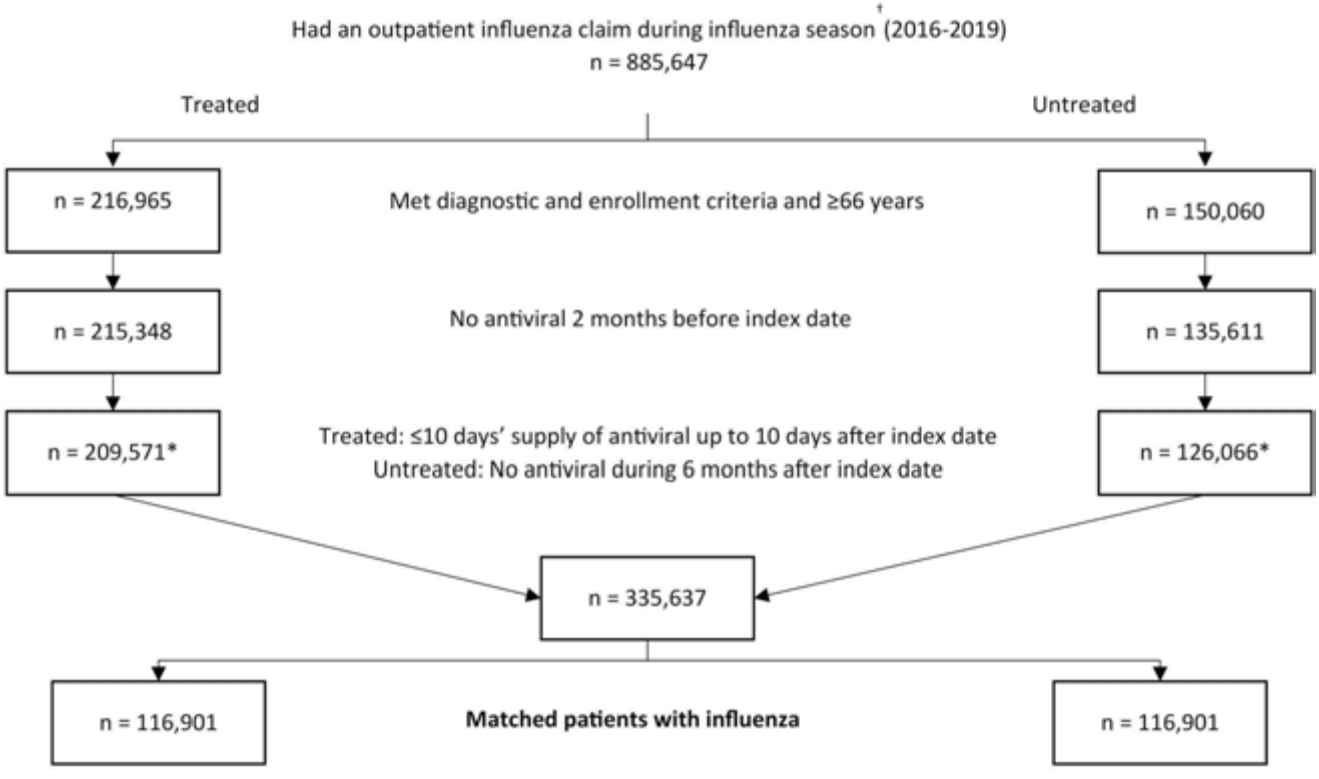

Figure 1. Patient attrition. During the three influenza seasons observed between 2016–2019, 335,637 patients (209,571 treated and 126,066 untreated patients) met study inclusion criteria. The final matched cohort contained 116,901 matched patient pairs.

74 years, age group (52.4% vs. 53.3% in the treated and untreated groups, respectively) (Table 1). The majority of patients were female (61.1% vs. 61.5% in the treated and untreated groups, respectively). In addition, at baseline, matched treated and untreated patients had on average 5.8 chronic conditions and 92.0% versus 91.6% had a high-risk condition. In each group, 61.4% received an influenza vaccine prior to influenza diagnosis, and almost 50% of influenza cases were recorded in the 2017–2018 influenza season. For patients with an antiviral, oseltamivir was most often prescribed (99.7%), followed by baloxavir (0.25%), zanamivir (0.01%), and peramivir (percentage not reported due to CMS cell suppression policy).

Acute complications and mortality

Treated patients were less likely to develop complications during the follow-up period (Figure 2). In particular, the proportion of treated patients who experienced an acute complication was nearly half that for untreated patients (8.3% vs. 15.7%). Antiviral treatment was associated with reduced complication rates across all complication categories. The most prevalent complication type, respiratory-related complications, was observed among 4.7% of treated compared to 9.6% of untreated patients. The cardiovascular event rate in the treated group was 1.3% compared to 2.6% in the untreated group. Neurologic complication rates were 0.67% and 0.97% among treated and untreated patients, respectively. The likelihood of gastrointestinal complication was also about half as much in the treated group as in the untreated group (0.27% vs. 0.45%). Furthermore, the rate of influenza with other acute manifestations was 0.07% among treated and 0.18% among untreated, while the rates of hematologic complications were 0.07% and 0.11% and of endocrine diagnoses were 0.06% and 0.11%, respectively. Other acute diagnoses were present in 4.4% of treated and 9.2% of untreated patients. Within this category, the complication rates for acute kidney failure were 3.2% vs. 6.3%, for sepsis were 2.1% vs. 4.9%, for bacteremia were 0.14% vs. 0.34%, for rhabdomyolysis were 0.09% vs. 0.29%, for complications of transplanted organ were 0.04% vs. 0.10% for treated versus untreated patients, respectively. Complication rates were statistically significantly different between the treated and untreated group in all complication categories.

Antiviral treatment was also associated with mortality benefits during the follow-up period (Figure 2). All-cause

Table 1. Baseline characteristics.

	Matched[a] treated $N = 116,901$	Matched untreated $N = 116,901$	Standardized mean difference[b]
Age, year, mean (SD)	75.6 (7.0)	75.6 (7.3)	−0.001
Age group			0.046
66-74, n (%)	61,206 (52.4)	62,325 (53.3)	
75-84, n (%)	40,715 (34.8)	38,448 (32.9)	
85+, n (%)	14,980 (12.8)	16,128 (13.8)	
Female, n (%)	71,427 (61.1)	71,904 (61.5)	−0.008
Race, n (%)			0.001
White	106,716 (91.3)	106,594 (91.2)	
Black	4,875 (4.2)	4,914 (4.2)	
Other/Unknown	5,310 (4.5)	5,393 (4.6)	
Region, n (%)			0.028
Midwest	25,343 (21.7)	25,797 (22.1)	
Northeast	21,534 (18.4)	22,012 (18.8)	
South	53,978 (46.2)	52,754 (45.1)	
West	16,046 (13.7)	16,338 (14.0)	
Year of influenza season,[c] n (%)			n/a[d]
2016	28,976 (24.8)	28,976 (24.8)	
2017	57,028 (48.8)	57,028 (48.8)	
2018	30,897 (26.4)	30,897 (26.4)	
Charlson Comorbidity Index, mean (SD)	2.4 (2.6)	2.4 (2.6)	0.014
Number of chronic conditions, mean (SD)	5.8 (2.4)	5.8 (2.5)	0.003
Received influenza vaccine for the current season prior to the index date, n (%)	71,730 (61.4)	71,730 (61.4)	n/a[d]
CDC-defined high-risk conditions, n (%)	107,564 (92.0)	107,090 (91.6)	0.015
Asthma	13,948 (11.9)	13,793 (11.8)	0.004
Chronic lung disease	35,212 (30.1)	34,663 (29.7)	0.010
Heart disease	47,970 (41.0)	47,913 (41.0)	0.001
Blood disorders	37,510 (32.1)	37,388 (32.0)	0.002
Endocrine disorders	63,060 (53.9)	63,288 (54.1)	−0.004
Kidney disorders	19,796 (16.9)	19,309 (16.5)	0.011
Liver disorders	7,287 (6.2)	7,250 (6.2)	0.001
Metabolic disorders	92,370 (79.0)	92,207 (78.9)	0.003
Extreme obesity	3,507 (3.0)	3,508 (3.0)	−0.000
COPD	19,674 (16.8)	19,135 (16.4)	0.012
Immunosuppressive conditions (MS, HIV, RA)	5,033 (4.3)	5,092 (4.4)	−0.002

[a]The propensity for initiating antiviral medication was estimated using logistic regression with independent variables of year of influenza season, age, gender, geographic region, race, influenza vaccine status, usual physician specialty, CCI, number of chronic conditions, dual-eligible status, and each individual high-risk condition (asthma, chronic lung disease, heart disease, blood disorders, endocrine disorders, kidney disorders, liver disorders, metabolic disorders, extreme obesity, COPD, immunosuppressive conditions [MS, HIV, RA]). In addition, patients were matched exactly on the year of influenza season and influenza vaccine status.

[b]The absolute value of standardized mean difference <0.2 is considered small effect size; therefore, an indicator of good match.

[c]Influenza season defined as October through March of each year (2016–2019).

[d]Matched exactly.

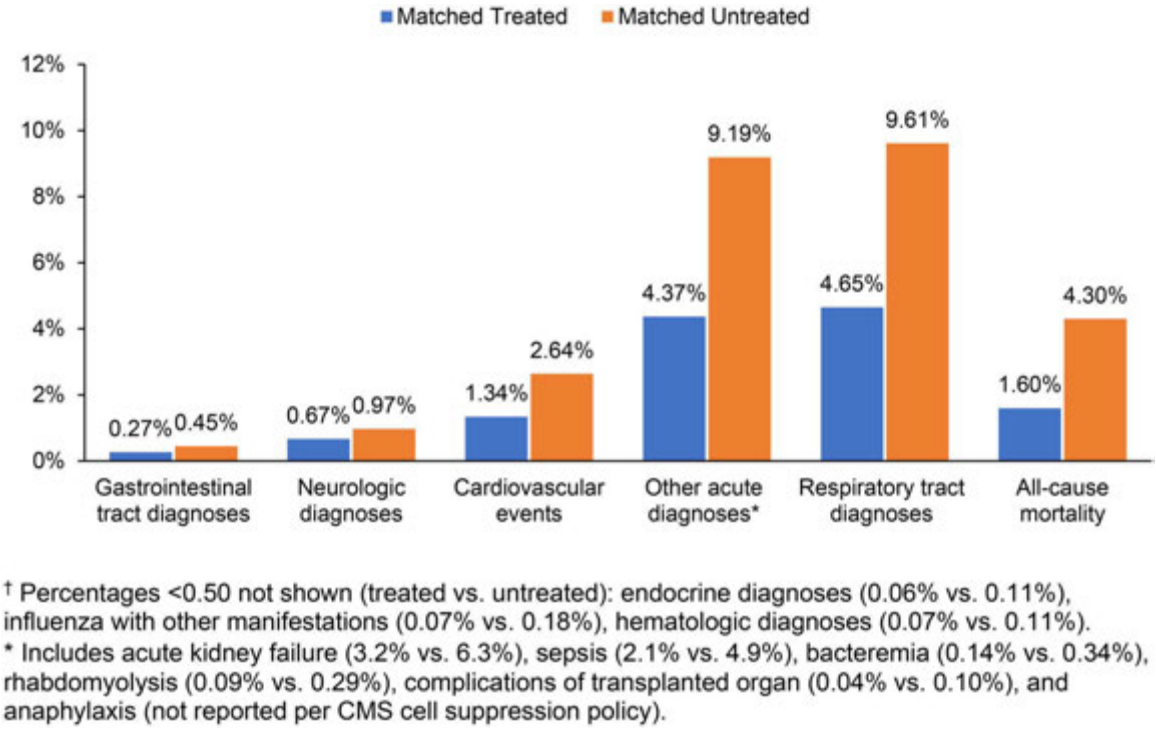

Figure 2. Acute complications† and mortality. Treated patients had lower rates of acute complications and mortality during the follow-up period (6 months after index date, defined as date of first claim with an influenza diagnosis).

mortality within 6 months from index diagnosis was as low as 1.6% among treated patients compared to 4.3% among untreated patients ($p < 0.001$).

Healthcare utilization and costs

Healthcare utilization was generally statistically significantly lower in treated patients than in untreated patients (Table 2). In particular, rates of all-cause inpatient hospitalizations during follow-up were 13.9% versus 22.7% for treated versus untreated patients ($p < 0.001$) while rates of respiratory-related hospitalizations were 4.2% vs. 9.0% for treated versus untreated patients ($p < 0.001$). Similar differences were observed for services at other service locations. Treated patients versus untreated patients had lower rates of all-cause ED visits compared to untreated (18.9% vs. 21.5%), as

Table 2. Healthcare utilization during the 6-month follow-up period.

	Matched Treated $N = 116,901$	Matched Untreated $N = 116,901$
All-cause mortality within 6 months[a]	1911 (1.6)	5,074 (4.3)
All-cause healthcare utilization[a]		
Any inpatient hospitalizations, n (%)	16,293 (13.9)	26,501 (22.7)
Hospital stay days among utilizers, mean (SD)	6.2 (8.4)	8.5 (11.2)
Hospital stay days among all patients, mean (SD)	0.9 (3.8)	1.9 (6.4)
Any ICU, n (%)	4,971 (4.3)	9,206 (7.9)
Any inpatient hospitalizations with ventilator use, n (%)	1,042 (0.9)	2,508 (2.1)
Any ED visits, n (%)	22,066 (18.9)	25,125 (21.5)
No. of office visits, mean (SD)	9.8 (8.1)	9.3 (8.1)
Any outpatient hospitalizations (excluding ED visits), n (%)	74,510 (63.7)	72,676 (62.2)
Skilled Nursing Facility (SNF) care, n (%)	2,890 (2.5)	8,519 (7.3)
Hospice care, n (%)	1,372 (1.2)	3,410 (2.9)
Home Health Agency (HHA) visit, n (%)	7,695 (6.6)	14,408 (12.3)
Durable Medical Equipment (DME) claim, n (%)	32,944 (28.2)	33,750 (28.9)
No. of prescription drug fills, mean (SD)	18.8 (15.1)	17.2 (15.2)
Respiratory-related [b] healthcare utilization[a]		
Any respiratory inpatient hospitalizations, n (%)	4,899 (4.2)	10,534 (9.0)
Respiratory hospital stay days among utilizers, mean (SD)	4.1 (4.9)	6.1 (7.4)
Respiratory hospital stay days among all patients, mean (SD)	0.2 (1.3)	0.5 (2.8)
Any respiratory ED visits, n (%)	3,813 (3.3)	4,699 (4.0)
No. of respiratory office visits, mean (SD)	1.4 (2.1)	1.2 (2.0)
Any respiratory outpatient hospitalizations (excluding ED visits), n (%)	8,469 (7.2)	9,421 (8.1)
Respiratory Skilled Nursing Facility (SNF) care, n (%)	662 (0.6)	3,193 (2.7)
Respiratory hospice care, n (%)	199 (0.2)	645 (0.6)
Respiratory Home Health Agency (HHA) visit, n (%)	1,615 (1.4)	3,696 (3.2)
Respiratory Durable Medical Equipment (DME) claim, n (%)	6,599 (5.6)	8,216 (7.0)

[a]All comparisons were $p < 0.001$.
[b]Respiratory-related defined as a claim with a primary diagnosis of respiratory disease: ICD-10-CM: J00.xx-J99.xx.

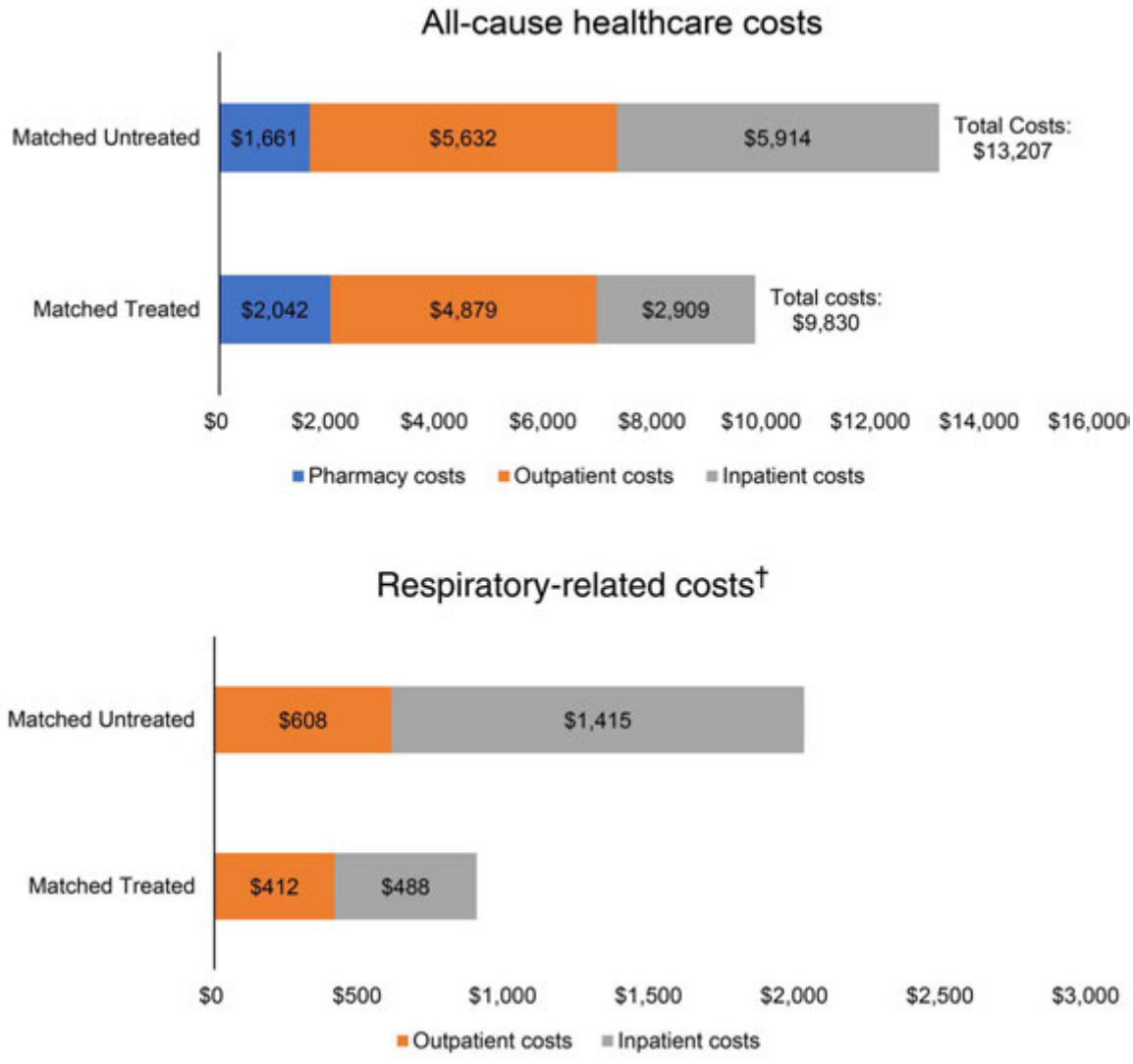

Figure 3. Healthcare costs (adjusted to 2019 US Dollars) during the 6-month follow-up period. Healthcare utilization and costs were generally statistically significantly lower in treated patients than in untreated patients.

well as lower rates of skilled nursing facility care (2.5% vs. 7.3%), home health agency visits (6.6% vs. 12.3%), and hospice care (1.2% vs. 2.9%). However, the rate of all-cause outpatient hospitalizations (excluding ED visits) was higher in treated compared to untreated patients (63.7% vs. 62.2%), as were mean number of office visits (9.8 visits vs. 9.3). All differences were statistically significant ($p < 0.001$). The results for respiratory-related utilization and costs showed a similar pattern, with treated patients having lower utilization, except for a slightly higher mean number of respiratory-related office visits, which was lower among untreated patients (1.4 vs. 1.2 visits) (Table 2). Healthcare costs were significantly lower in treated patients. Mean (SD) total all-cause and respiratory-related costs were $9,830 ($18,616.0) and $900 ($4,016.4) among the treated patients, respectively, compared to $13,207 ($24,405.1) and $2,024 ($7,623.7) among untreated patients, respectively ($p < 0.001$ for all cost outcomes) (Figure 3). Inpatient services accounted for 30% of total all-cause costs for treated patients compared to 45% for untreated patients. Outpatient services accounted for 50% of total all-cause costs for treated patients compared to 43% for untreated patients.

Discussion

Elderly adults (65 years and older) are at higher risk of influenza-related complications, morbidity, and increased healthcare costs[4–6]. Vaccination is a recommended intervention for prevention of influenza, nevertheless, more than half of the elderly and other persons at high risk do not receive the influenza vaccine[8,14]. Additionally, prompt antiviral treatment after symptom detection can further alleviate the burden of disease. This study quantifies the significant clinical and economic benefits of antiviral influenza treatment in a large cohort of Medicare beneficiaries from three influenza seasons between 2016 and 2019.

For elderly Medicare beneficiaries diagnosed with influenza, we found that treatment with antiviral medication was associated with lower mortality rates, lower rates of influenza-related complications, lower healthcare utilization, and lower healthcare costs, both all-cause and respiratory-related. Observed differences were statistically significant for nearly all outcome measures assessed in this study. For example, treated patients experienced overall complication rates that were nearly half of rates for untreated patients. This difference was most pronounced for respiratory-related complications, which were also the most common complication observed (4.7% vs. 9.6%). Antiviral treatment was also associated with better survival following an influenza diagnosis, as about 16 out of 1000 treated elderly patients died within 6 months after diagnosis versus about 43 out of 1000 untreated patients. In addition, the data showed that treated patients compared to untreated patients used healthcare resources much less intensively in the 6 months following an influenza diagnosis, particularly for all-cause and respiratory-related hospitalization, which were less than two-thirds (13.9% vs. 22.7%) and half (4.2% vs. 9.0%), respectively. Finally, the mean total all-cause healthcare costs were about 25% lower for treated patients compared to untreated patients ($9,830 vs. $13,207) while respiratory-related costs were less than half for treated versus untreated individuals with influenza ($900 vs. $2,024).

Prior research

Two earlier studies using large commercial claims data examined the association between antiviral treatment and patient outcomes. Spanguolo and colleagues (2016)[28] used regression analyses while Wallick and colleagues (2021)[29] created a propensity score matched cohort of treated and untreated patients with influenza for the 2006-2010 and 2014-2016 influenza seasons, respectively. Both studies found that antiviral use is associated with a decrease in influenza-related complications and healthcare utilization and costs. However, their data source captures primarily data from a working age population. Neuberger and colleagues (2022) also use a propensity score matched design but their focus is the subpopulation with rheumatoid arthritis[30]. Their results show that prompt antiviral treatment after influenza diagnosis may reduce healthcare utilization and costs among this particular group of high-risk patients[30]. All studies above confirm the results of the present analysis, however, their findings are not directly comparable with ours due to differences in patient cohort.

Results of this study highlight that prompt intervention with antiviral treatment could reduce clinical and economic burden associated with influenza among older adults. These findings underscore the need to increase use of antiviral medications in this population. As older adults are underrepresented in clinical trials and commercial claims data sources[38,39], this study takes steps towards filling a current research gap by characterizing the clinical and economic burden in this vulnerable population, as well as highlighting a potential avenue (increased use of antivirals) for decreasing this burden.

Limitations

This retrospective cohort study uses administrative claims data. Such data are primarily designed to support reimbursement and may inaccurately represent clinical information. For example, the presence of a diagnosis code on a medical claim does not guarantee the presence of a disease, as the diagnosis code may be miscoded or included as a rule-out criterion. However, Feemster and colleagues (2012) found that diagnosis codes (ICD-9-CM) for influenza detected 73% of laboratory-confirmed influenza cases, and that fewer than 1% of patients without a diagnosis code had laboratory-confirmed influenza[40]. Additionally, a claim for an antiviral treatment indicates a drug fill but does not ensure that the treatment was actually taken. The results of this analysis may be conservative if some of the patients who filled an antiviral prescription didn't actually take the antiviral. Another data-related limitation is that the size of the analyzed populations may have impacted the observed statistically significant differences in outcomes among the treated and untreated patients. Even small differences in the percent of patients experiencing a complication can translate into a large number of patients because influenza affects many older adults. For example, in this study, there were a small proportion of patients who experienced hematologic conditions (0.11 for untreated vs 0.07 for treated patients). However, based on the estimate of 581,594 seniors with flu during 2021–2022 mild influenza season[41], even this small difference of 0.04 translates to 233 fewer people experiencing the complication, which may be meaningful.

The benefits of real-world data, including the use of large data sets, continue to be uncovered[42,43]. Real world evidence is often available more quickly than trial data and can supplement trial data by capturing measures such as adherence, hospitalizations, causes of death, and treatment patterns; this is significant as noted earlier, the current study's population (older adults) is often underrepresented in clinical trials[38]. The trends of greater healthcare utilization and associated costs in untreated patients with influenza is consistent with previously published work[28–30], even if the patient cohorts (e.g. younger and commercially insured populations) are not directly comparable. Another limitation of this study is that additional factors, beyond treatment status, that could impact outcomes (e.g. income or education levels, or additional barriers to treatment access) were not examined. Lastly, as this study focused on Medicare beneficiaries 66 years of age or older and who were predominantly white (>90%), results may not be generalizable to uninsured individuals or those with other types of insurance or to individuals of a different age group or race.

Conclusion

Lack of antiviral treatment is associated with increased mortality, healthcare resource utilization, and economic burden

in elderly Medicare beneficiaries with seasonal influenza, a population already at risk for increased resource use and associated costs compared to their counterparts without influenza. Promoting antiviral treatment for patients at high risk of influenza like older adults, is warranted. Future research should investigate whether the choice of antivirals affects the clinical and economic burden of influenza.

Transparency

Declaration of funding

This research was funded by Genentech, Inc. The sponsor provided input on the design and methods (protocol) and review of the manuscript (PHAR authors prepared the manuscript). The sponsor did not have a role in subject recruitment, data collections, or analysis.

Declaration of financial/other relationships

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Author contributions

Concept and design (JB, SRR, EC, KB, AS); acquisition of subjects and/or data (SRR, EC, KB, MHT), data analysis (SRR, EC) and interpretation (JB, SRR, EC, KB, AS), and preparation of manuscript (SRR, JB, EC, KB, MHT, SC, AS).

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Appendix Tables

Appendix Table 1. Acute complications by categories and associated ICD-10 code.

Appendix Table 1.

DISEASE CONDITION	ICD-10
ACUTE RESPIRATORY TRACT DIAGNOSES	
Acute respiratory distress syndrome	J80
Acute upper respiratory infections	J00-J06
Mild intermittent asthma with acute exacerbation	J45.21
Mild intermittent asthma with status asthmaticus	J45.22
Mild persistent asthma with acute exacerbation	J45.31
Mild persistent asthma with status asthmaticus	J45.32
Moderate persistent asthma with acute exacerbation	J45.41
Moderate persistent asthma with status asthmaticus	J45.42
Severe persistent asthma with acute exacerbation	J45.51
Severe persistent asthma with status asthmaticus	J45.52
Unspecified asthma with acute exacerbation	J45.901
Unspecified asthma with status asthmaticus	J45.902
COPD with acute exacerbation	J44.1
Mediastinitis	J98.51
Acute bronchitis	J20
Acute bronchiolitis	J21
Unspecified acute lower respiratory infection	J22
COPD with acute lower respiratory infection	J44.0
Bronchiectasis with acute lower respiratory infection	J47.1
Bronchiectasis with acute exacerbation	J47.9
Gangrene and necrosis of lung	J85.0
Abscess of lung without pneumonia	J85.2
Abscess of mediastinum	J85.3
Pyothorax	J86
Pyothorax with fistula	J86.0
Pyothorax without fistula	J86.9
Viral pneumonia	J12
Streptococcus pneumoniae pneumonia	J13
Hemophilus influenzae pneumonia	J14
Other bacterial pneumonia	J15
Pneumonia due to other specified organism	J16
Pneumonia in infectious diseases classified elsewhere	J17
Pneumonia, unspecified organism	J18
Abscess of lung with pneumonia	J85.1
Influenza due to identified novel influenza A virus with pneumonia	J09.X1
Influenza due to other identified influenza virus with pneumonia	J10.0
Influenza due to unidentified influenza virus with pneumonia	J11.0
Pneumothorax and air leak	J93
Atelectasis	J98.11
Other pulmonary collapse	J98.19
Acute respiratory failure	J96.0
Acute and chronic respiratory failure	J96.2
Respiratory arrest	R09.2
Influenza due to identified novel influenza A virus with other respiratory manifestations	J09.X2
Influenza due to other identified influenza virus with other respiratory manifestations	J10.1
Influenza due to unidentified influenza virus with other respiratory manifestations	J11.1
INFLUENZA WITH OTHER MANIFESTATIONS	
Influenza due to identified novel influenza A virus with other manifestations	J09.X9
Influenza due to other identified influenza virus with otitis media	J10.83
Influenza due to other identified influenza virus with other manifestations	J10.89
Influenza due to unidentified influenza virus with otitis media	J11.83
Influenza due to unidentified influenza virus with other manifestations	J11.89
Influenza due to other identified influenza virus with encephalopathy	J10.81
Influenza due to unidentified influenza virus with encephalopathy	J11.81
ACUTE NEUROLOGIC DIAGNOSES	
Acute disseminated encephalitis and encephalomyelitis (ADEM)	G04.0
Cerebral Infarction	I63
Acute cerebrovascular insufficiency	I67.81
Cerebral ischemia	I67.82
Transient cerebral ischemic attacks and related syndromes	G45
Transient global amnesia	G45.4
Other acute disseminated demyelination	G36
Encephalitis, myelitis and encephalomyelitis	G04
Encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere	G05

(*continued*)

Appendix Table 1. Continued.

DISEASE CONDITION	ICD-10
Guillain-Barre syndrome	G61.0
Nontraumatic subarachnoid hemorrhage	I60
Nontraumatic intracerebral hemorrhage	I61
Other and unspecified nontraumatic intracranial hemorrhage	I62
Bacterial meningitis, not elsewhere classified	G00
Meningitis in bacterial diseases classified elsewhere	G01
Meningitis in other infectious and parasitic diseases classified elsewhere	G02
Meningitis due to other and unspecified causes	G03
ACUTE CARDIOVASCULAR EVENTS	
Acute myocarditis	I40
Influenza due to other identified influenza virus with myocarditis	J10.82
Influenza due to unidentified influenza virus with myocarditis	J11.82
Acute pericarditis	I30
Cardiac tamponade	I31.4
Cardiogenic shock	R57.0
Acute systolic heart failure	I50.21
Acute on chronic systolic heart failure	I50.23
Acute diastolic heart failure	I50.31
Acute on chronic diastolic heart failure	I50.33
Acute combined systolic and diastolic heart failure	I50.41
Acute on chronic combined systolic and diastolic heart failure	I50.43
Acute right heart failure	I50.811
Acute on chronic right heart failure	I50.813
Hypertensive Crisis	I16
Hypertensive urgency	I16.0
Hypertensive emergency	I16.1
Hypertensive crisis, unspecified	I16.9
Unstable angina	I20.0
Acute myocardial infarction	I21
ST elevation myocardial infarction of anterior wall	I21.0
ST elevation myocardial infarction of inferior wall	I21.1
ST elevation myocardial infarction of other sites	I21.2
ST elevation myocardial infarction of unspecified site	I21.3
Non-ST elevation myocardial infarction	I21.4
Acute myocardial infarction, unspecified	I21.9
Subsequent ST elevation and non-ST elevation myocardial infarction	I22
Subsequent ST elevation myocardial infarction of anterior wall	I22.0
Subsequent ST elevation myocardial infarction of inferior wall	I22.1
Subsequent non-ST elevation myocardial infarction	I22.2
Subsequent ST elevation myocardial infarction of other sites	I22.8
Subsequent ST elevation myocardial infarction of unspecified site	I22.9
Other acute and subacute forms of ischemic heart disease	I24
ACUTE ENDOCRINE DIAGNOSES	
Diabetes mellitus due to underlying condition with ketoacidosis	E08.1
… without coma	E08.10
… with coma	E08.11
Drug or chemical induced diabetes mellitus with ketoacidosis	E09.1
… without coma	E09.10
… with coma	E09.11
Type 1 diabetes mellitus with ketoacidosis	E10.1
… without coma	E10.10
… with coma	E10.11
Type 2 diabetes mellitus with ketoacidosis	E11.1
… without coma	E11.10
… with coma	E11.11
Other specified diabetes mellitus with ketoacidosis	E13.1
… without coma	E13.10
… with coma	E13.11
Diabetes mellitus due to underlying condition with hyperosmolarity	E08.0
… without nonketotic hyperglycemic-hyperosmolar coma	E08.00
… with coma	E08.01
Drug or chemical induced diabetes mellitus with hyperosmolarity	E09.0
… without nonketotic hyperglycemic-hyperosmolar coma	E09.00
… with coma	E09.01
Type 2 diabetes mellitus with hyperosmolarity	E11.0
… without nonketotic hyperglycemic-hyperosmolar coma	E11.00
… with coma	E11.01
Other specified diabetes mellitus with hyperosmolarity	E13.0
… without nonketotic hyperglycemic-hyperosmolar coma	E13.00
… with coma	E13.01
Thyrotoxicosis	E05
ACUTE GASTROINTESTINAL TRACT DIAGNOSES	
Acute and subacute hepatic failure	K72.0
Acute hepatitis A	B15

(*continued*)

Appendix Table 1. Continued.

DISEASE CONDITION	ICD-10
Acute hepatitis B	B16
Other acute viral hepatitis	B17
Unspecified viral hepatitis with hepatic coma	B19.0
Unspecified viral hepatitis B with hepatic coma	B19.11
Unspecified viral hepatitis C with hepatic coma	B19.21
Acute pancreatitis	K85
Influenza due to identified novel influenza A virus with gastrointestinal manifestations	J09.X3
Influenza due to other identified influenza virus with gastrointestinal manifestations	J10.2
Influenza due to unidentified influenza virus with gastrointestinal manifestations	J11.2
ACUTE HEMATOLOGIC DIAGNOSES	
Disseminated intravascular coagulation	D65
Acute embolism and thrombosis of superior vena cava	I82.210
Acute embolism and thrombosis of other thoracic veins	I82.290
Acute embolism and thrombosis of inferior vena cava	I82.220
Acute embolism and thrombosis of unspecified deep veins of lower extremity	I82.4
Acute embolism and thrombosis of veins of upper extremity	I82.6
Acute embolism and thrombosis of axillary vein	I82.A1
Acute embolism and thrombosis of subclavian vein	I82.B1
Acute embolism and thrombosis of internal jugular vein	I82.C1
Hemophagocytic lymphohistiocytosis	D76.1
Hemophagocytic syndrome, infection-associated	D76.2
Immune thrombocytopenic purpura	D69.3
Pulmonary embolism	I26
Hb-SS disease with crisis	D57.0
Hb-SS with acute chest syndrome	D57.01
Hb-SS disease with splenic sequestration	D57.02
Sickle-cell/Hb-C disease with crisis	D57.21
Sickle-cell/Hb-C disease with acute chest syndrome	D57.211
Sickle-cell/Hb-C disease with splenic sequestration	D57.212
Sickle-cell thalassemia with crisis	D57.41
Sickle-cell thalassemia with acute chest syndrome	D57.411
Sickle-cell thalassemia with splenic sequestration	D57.412
Other sickle-cell disorders with crisis	D57.81
Other sickle-cell disorders with acute chest syndrome	D57.811
Other sickle-cell disorders with splenic sequestration	D57.812
OTHER ACUTE DIAGNOSES	
Acute kidney failure	N17
Anaphylactic shock, unspecified, initial encounter	T782XXA
Bacteraemia	R78.81
Rhabdomyolysis	M62.82
Streptococcal sepsis	A40
Other sepsis	A41
Symptoms and signs specifically associated with systemic inflammation and infection	R65
Complications of transplanted organ	T86

Appendix Table 2. ICD-9 and 10 codes for CDC-defined high-risk conditions for influenza[a].

Condition	ICD-9 Code(s)	ICD-10 Code(s)
Asthma	493	J45
Chronic lung disease	416.8, 416.9, 490-496, 500, 501, 502, 503, 504, 505, 506.4, 508.1, 508.8, 508.9, 491, 492, 494, 495, 496, 506.4, 508.1, 508.8, 416, 277.0, 516.31, 515, 518.83, 515, 516.9	E84, I27, J07.8, J07.9, J40, J41, J42, J43, J44, J45, J46, J47, J60, J61, J62, J63, J64, J65, J66, J67, J68.4, J70.1, J70.3, J84, J96.1
Heart disease	093.0, 398.91, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93, 412, 414, 425.4, 425.5, 425.6, 425.7, 425.8, 425.9, 428.0, 428.1, 428.20, 428.22, 428.30, 428.32, 428.40, 428.42, 428.9, 429.7, 437.3, 440, 441, 443.1, 443.2, 443.3, 443.4, 443.5, 443.6, 443.7, 443.8, 443.9, 447.1, 557.1, 557.9, 745, 746, 747, V43.4	A52.01, I09.9, I23.0, I25.2, I25.5, I25, I42.0, I42.5, I42.6, I42.7, I42.8, I42.9, I43, I50.1, I50.20, I50.22, I50.30, I50.32, I50.40, I50.42, I50.8, I50.9, I50, I51.0, I70, I70, I71, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, P29.0, Q20, Q21, Q22, Q23, Q24, Q25, Q26, Q27, Q28, Z95.8, Z95.9
Blood disorders	280-289	D50-D59, D60-D69, D70, D71, D72, D73, D74, D75, D76, D77
Endocrine disorders[b]	240, 241, 242.00, 242.10, 242.20, 242.30, 242.40, 242.80, 242.90, 243, 244, 245, 246, 247, 248, 249.0, 249.4, 249.5, 249.6, 249.7, 249.8, 249.9, 250.0, 250.4, 250.5, 250.6, 250.7, 250.8, 250.9, 251.1, 251.2, 251.3, 251.4, 251.5, 251.8, 251.9, 252, 253, 254, 255, 256, 257, 258, 259	E00, E01, E02, E03, E04, E05.00, E05.10, E05.20, E05.30, E05.40, E05.80, E05.90, E06, E07, E08.2, E08.3, E08.4, E08.5, E08.6, E08.7, E08.8, E08.9, E09, E10, E11.2, E11.3, E11.4, E11.5, E11.6, E11.7, E11.8, E11.9, E12, E13, E14, E15, E16, E17, E18, E19, E20, E21, E22, E23, E24, E25, E26, E27, E28, E29, E30, E31, E32, E33, E34, E35
Kidney disorders	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 581, 582, 583, 583.0, 583.1, 583.2, 583.3, 583.4, 583.5, 583.6, 583.7, 585, 586, 587, 588, 794.4, V42.0, V45.1, V45.11, V56	I12.0, I13.1, N03, N04, N05, N18, N18, N19, N19, N25, N25.0, N26.9, R94.4, Z49.0, Z49.1, Z49.2, Z94.0, Z99.2
Liver disorders	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 456.0, 456.1, 456.2, 571, 572.3, 572.4, 572.5, 572.6, 572.7, 572.8, 573.3, 573.8, 573.9, V42.7	B18, I85.0, I85.9, I86.4, I98.2, K70.0, K70.1, K70.2, K70.3, K70.4, K70.9, K71.1, K71.3, K71.4, K71.5, K71.7, K72.1, K73, K74, K76.0, K76.4, K76.5, K76.6, K76.7, K76.8, K76.9, Z94.4
Metabolic disorders[c]	270, 271, 272, 273, 274, 275, 276, 277.1-277.9, 278, 330.0, 330.1, 330.2	E70-E79, E80, E81, E82, E83, E85, E86, E87, E88
Extreme obesity	V85.4	Z68.4
COPD	491.0, 491.1, 491.2x, 491.8, 491.9, 492.0, 492.8, 493.2x, 496	J41.x, J42.x, J43.x, J44.x
Immunosuppressive conditions (MS, HIV, RA)	HIV/AIDS: 042.x–044.x MS: 340.x RA: 714.0x	HIV/AIDS: B20.x–B22.x, B24.x MS: G35.x RA: M05.7x, M05.8x, M06.0x, M06.9x

[a]List of conditions adapted from the CDC's list of people at higher risk of influenza complications, available at: https://www.cdc.gov/flu/highrisk/index.htm.
[b]Includes diabetes without mention of complication; and diabetes with renal, ophthalmic, neurological, peripheral circulatory, or other specified manifestations; and diabetes with unspecified complication. [c] Excludes code 277.0 and E84, cystic fibrosis, which are listed under chronic lung disease.