

Baloxavir vs Oseltamivir: Reduced Utilization and Costs in Influenza

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Influenza is a contagious respiratory illness of varying severity, estimated to affect 3% to 11% of people in the United States each year¹ and resulting in a substantial burden to the health care system. The CDC estimated that influenza has resulted in 9.3 million to 45 million symptomatic illnesses, 4.3 million to 21 million medical visits, 140,000 to 810,000 hospitalizations, and 12,000 to 61,000 deaths annually since 2010, with preliminary estimates of 490,000 hospitalizations and 34,000 deaths for the 2018-2019 season.² In 2015, the estimated average annual economic burden of influenza to the health care system was \$11.2 billion, with \$3.2 billion and \$8.0 billion attributed to direct and indirect costs, respectively.³

Although most individuals with influenza recover within 2 weeks, the infection can trigger complications that range from moderate (sinus and ear infections) to serious (pneumonia, myocarditis, encephalitis, myositis, and multiorgan failure), and the infection can worsen chronic medical conditions such as asthma, chronic obstructive pulmonary disease (COPD), and heart disease.⁴ Airway inflammation triggered by the influenza virus can damage tissue and compromise pulmonary function, resulting in lower respiratory infections and other respiratory conditions.⁵ Populations at increased risk for serious influenza-related complications include adults 65 years or older, residents of long-term care facilities, persons with certain chronic medical conditions, and children younger than 2 years, among others.^{6,7}

Antiviral therapy is a useful adjunct to influenza immunization for managing symptoms and reducing the risk of secondary complications, including bacterial infections.⁸ Expert guidelines recommend initiation of antiviral therapy within 48 hours for patients with more severe illness or who are at higher risk for complications.^{9,10} Early treatment with neuraminidase inhibitors (eg, oseltamivir), the current standard of care, relieves influenza symptoms, reduces the risk of complications, lowers health care resource utilization (HCRU), and decreases mortality in hospitalized patients.¹¹⁻¹⁶

Baloxavir marboxil ("baloxavir") is an oral single-dose treatment for influenza that was FDA approved in October 2018; it has a mechanism of action distinct from that of neuraminidase inhibitors. Baloxavir

ABSTRACT

OBJECTIVES: To determine whether baloxavir use is associated with lower health care resource utilization (HCRU) and costs for secondary influenza complications post treatment compared with oseltamivir.

STUDY DESIGN: Retrospective cohort study.

METHODS: Patients filling a prescription for baloxavir or oseltamivir within 48 hours following an influenza-related outpatient visit were identified in the 2018-2019 influenza season from the US Truven MarketScan Research Databases and propensity matched 1:2 (baloxavir:oseltamivir). Outcomes were assessed 15 and 30 days after antiviral treatment and included all-cause, all respiratory-related, and select respiratory-related (influenza, asthma, chronic obstructive pulmonary disease, or infection) HCRU and costs.

RESULTS: The study included 5080 baloxavir-treated and 10,160 matched oseltamivir-treated patients. All-cause emergency department (ED) visits and inpatient hospitalizations were lower in baloxavir-treated patients, with a statistically significant difference in the percentage hospitalized at 30 days (0.3% vs 0.5%; $P = .04$). ED visits for all or select respiratory-related conditions were significantly reduced with baloxavir ($P < .01$ for all comparisons). Mean per-patient cost savings at day 30 for all-cause, all respiratory-related, and select respiratory-related conditions were \$79, \$50, and \$51, respectively, despite slightly higher prescription costs for baloxavir. In high-risk patients (baloxavir: $n = 1958$; oseltamivir: $n = 3949$), the incidence of ED visits was significantly lower for all respiratory-related and select respiratory-related conditions ($P < .01$); cost savings with baloxavir in the high-risk cohort were substantially greater than in the overall cohort.

CONCLUSIONS: Treatment of patients with influenza with single-dose baloxavir was generally associated with lower HCRU and costs post treatment compared with oseltamivir, particularly in high-risk patients.

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is a cap-dependent endonuclease inhibitor that interferes with viral RNA transcription and blocks viral replication.¹⁷ In a phase 3 clinical study in outpatients with influenza-like illness, baloxavir significantly shortened the time to alleviation of influenza symptoms compared with placebo (53.7 hours vs 80.2 hours; $P < .0001$) and was as effective as twice-daily oseltamivir given for 5 days.¹⁸ Similarly, in a second phase 3 study in outpatients at high risk for influenza complications (mainly patients with asthma, chronic lung disease, and endocrine disorders, including diabetes), baloxavir treatment was associated with a significantly shorter time to improvement of influenza symptoms compared with placebo (73.2 hours vs 102.3 hours; $P < .0001$) and a numerically shorter time compared with oseltamivir (81.0 hours; $P = .8347$).¹⁹ In high-risk patients, baloxavir treatment resulted in significantly fewer complications compared with placebo treatment (2.8% vs 10.4%; $P < .0001$), with reduction of sinusitis and bronchitis being the main drivers of the difference.¹⁹

Although clinical trials were not powered to adequately assess rates of influenza complications post baloxavir compared with post oseltamivir, larger data sets may be better suited to examine this understudied aspect of therapeutic effectiveness. In this study we leveraged the large population afforded by an aggregated insurance claims database to further elucidate the impact of baloxavir on influenza-related complications. We compared the effects of baloxavir and oseltamivir on HCRU and costs, including those related to respiratory conditions, in patients with influenza over the 2018–2019 season.

METHODS

Data Source

Data were extracted from the MarketScan Commercial Claims and Encounters Database and the MarketScan Medicare Supplemental and Coordination of Benefits Database (IBM Watson Health). The databases include information on health insurance claims of employees, dependents, and retirees insured by employer-sponsored commercial and Medicare insurance. The claims capture inpatient and outpatient care, use of facilities and services, prescription fills, and payment information from approximately 350 payers. The study used deidentified data and was exempt from institutional review board review. The research was compliant with the Health Insurance Portability and Accountability Act.

Study Design

This retrospective cohort study compared HCRU and cost outcomes in patients who filled a prescription for baloxavir or oseltamivir between November 2018 and May 2019 (eAppendix Figure [eAppendix available at ajmc.com]). Patients 12 years and older with a prescription for baloxavir or oseltamivir were identified and were required

TAKEAWAY POINTS

We used insurance claims data to compare health care resource utilization (HCRU) and costs between baloxavir- and oseltamivir-treated patients with influenza 15 and 30 days post outpatient treatment.

- ▶ After adjusting for differences in the treated groups, baloxavir, compared with oseltamivir, was associated with lower HCRU and costs from secondary complications in patients with influenza.
- ▶ The incidence of hospitalization, emergency department visits, and outpatient visits for any cause was generally lower following treatment with baloxavir compared with oseltamivir, particularly among the high-risk subgroup of patients with influenza.
- ▶ Per-patient health care costs in most categories were lower with baloxavir than with oseltamivir, particularly among high-risk patients.

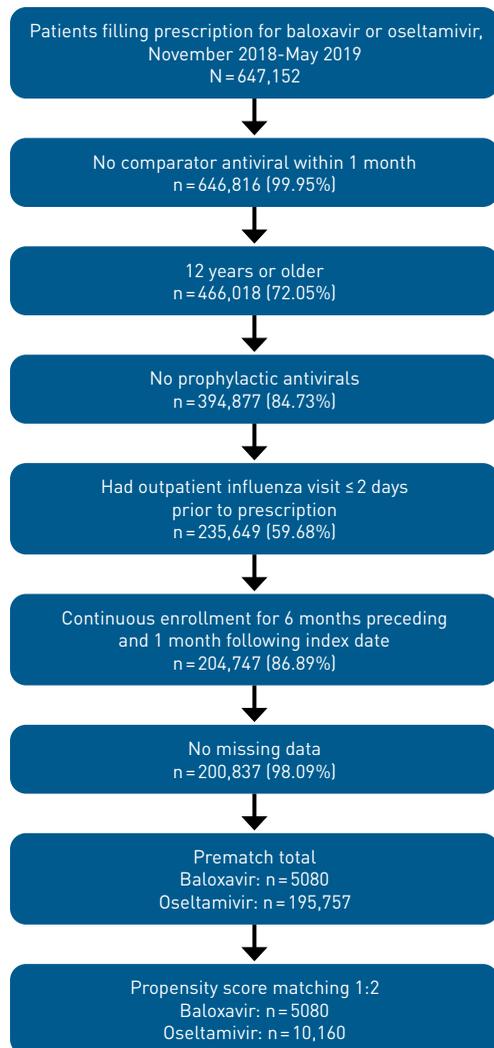
to have continuous enrollment data for at least 6 months preceding and 1 month following the index date of antiviral prescription fill. The prescription had to be filled within 2 days after an influenza-related outpatient visit. For any patient, only the first instance of an influenza-related outpatient visit followed by a relevant antiviral prescription within 2 days was included in the study. Additionally, patients could not have received the comparator antiviral within 1 month of the index prescription and could not have had any prophylactic fills (≥ 10 -day supply) for either antiviral agent.

To adjust for potential confounders, baloxavir-treated patients were propensity score matched at a 1:2 ratio to oseltamivir-treated patients using “nearest neighbor” matching (caliper = 0.1) for the following demographic and clinical variables: age, sex, geographic region, type of health plan, month of index event, preindex Charlson Comorbidity Index (CCI) score, preindex HCRU (emergency department [ED] visit or hospitalization), and days between outpatient visit and prescription fill.

A subgroup of patients at high risk of developing complications from influenza (high-risk subgroup) was defined based on age 65 years or older or presence of an inpatient or outpatient claim for any of the following conditions in the 6-month preindex period: obesity; pregnancy; neurological, chronic lung, cardiovascular, hematologic, endocrine, kidney, liver, or metabolic disease; or immune-related disease. Propensity score matching was not repeated for this specific subgroup.

Outcomes

Cumulative outcomes were assessed at 15 and 30 days after index prescription fill (excluding date of prescription). These included all-cause and respiratory-related HCRU and costs. The 2 types of respiratory-related HCRU were (1) HCRU for all respiratory-related conditions, which included a broad range of conditions (*International Classification of Diseases, Tenth Revision [ICD-10]* codes J00–J99) and (2) HCRU that focused on select respiratory-related conditions that included infection (J09–J16, J18, J20–21, J67), asthma (J45), and COPD (J40–J44) (eAppendix Table 1). HCRU and costs were assessed by health care setting (inpatient, outpatient, ED, pharmacy). All-cause pharmacy encounters were recorded as the total number of prescription fills and costs within the specified period. Costs

FIGURE 1. Flow Chart of Patients Who Filled a Prescription for Baloxavir or Oseltamivir Between November 2018 and May 2019

were based on actual 2018 and 2019 prices. A sensitivity analysis was performed to determine HCRU and costs starting from the day of the outpatient influenza diagnosis. This accounted for the cost of the antiviral as well as for the variable time frame of 0 to 48 hours after the outpatient visit during which any HCRU could have occurred.

Statistical Analysis

The propensity-matched cohorts were compared with the χ^2 test and Fisher's exact test (for frequency ≤ 5) for categorical measures and the Wilcoxon signed-rank test for counts and costs. Analyses were conducted using SAS version 9.4 software (SAS Institute Inc).

RESULTS

Study Population

Of 647,152 patients who filled a prescription for baloxavir or oseltamivir during the 2018-2019 influenza season, 200,837 patients (baloxavir: $n = 5080$; oseltamivir: $n = 195,757$) fulfilled the inclusion criteria (Figure 1). The 5080 baloxavir-treated patients were propensity matched with 10,160 oseltamivir-treated patients. Following matching, there were no statistically significant differences between cohort baseline characteristics (Table 1).

Most patients (56%) were aged between 18 and 49 years, 1% were 65 years or older, and 55% were female. Most patients lived in the southern United States (75%). Only 15% of patients had a comorbidity (CCI score ≥ 1), and 10% had been hospitalized or visited the ED in the preceding 6 months.

HCRU

In general, the cumulative incidence of all-cause ED visits and hospitalization was lower for baloxavir than for oseltamivir, despite slightly higher all-cause prescription fills in both the 15- and 30-day follow-up periods and outpatient visits in the 30-day follow-up period (Table 2). The cumulative incidence of all-cause, all respiratory-related, and select respiratory-related hospitalization in baloxavir-treated patients was lower than that in oseltamivir-treated patients over both periods. The cumulative incidence of all respiratory-related and select respiratory-related 15- and 30-day ED visits in the baloxavir-treated group was less than half that in the oseltamivir group ($P < .01$ for all comparisons). Although the incidence of all respiratory-related outpatient visits was similar in both groups, select respiratory-related outpatient visits were significantly lower over both the 15- and 30-day outcome periods ($P < .01$ for both comparisons).

Costs

Consistent with HCRU, costs were generally lower for baloxavir-treated patients. Overall mean all-cause per-patient costs were lower with baloxavir treatment than with oseltamivir treatment by \$74 (23% reduction) through day 15 and \$79 (13% reduction) through day 30, despite slightly higher all-cause prescription costs with baloxavir at day 30 (Figure 2). Mean 30-day all-cause hospitalization costs per patient were significantly lower for baloxavir-treated patients (\$47 vs \$119; $P = .03$). Mean per-patient cost savings (percent reduction) with baloxavir for all respiratory-related and select respiratory-related costs were \$42 (44%) and \$43 (64%), respectively, at day 15, and \$50 (41%) and \$51 (66%), respectively, at day 30. Costs for ED visits for all respiratory-related and select respiratory-related conditions and for select respiratory-related outpatient visits were significantly lower at both days 15 and 30 in the baloxavir cohort ($P < .01$ for all comparisons).

High-risk Subgroup Analysis

HCRU and costs were also analyzed for the subgroup of patients considered to be at high risk for influenza complications, which included 1958 patients (38%) in the baloxavir cohort and 3949

patients (39%) in the oseltamivir cohort (eAppendix Table 2). In this subgroup, the main ICD-10 code conditions reported in the baloxavir and oseltamivir cohorts were neurological disease (38% vs 35%; $P = .025$), amino acid-related metabolic diseases (35% vs 34%; $P = .379$), endocrine diseases (33% vs 31%; $P = .051$), and chronic lung disease (19% vs 19%; $P = .711$).

Propensity score matching was not repeated in the high-risk subgroup; however, no significant differences in baseline characteristics were observed between the 2 cohorts (eAppendix Table 3). Most patients were aged between 18 and 49 years (53%), 59% were female, and 3% were 65 years or older; 38% had a CCI score of at least 1 and 17% had been hospitalized or had visited the ED in the preceding 6 months.

In general, all-cause, all respiratory-related, and select respiratory-related HCRU in all categories was higher in the high-risk subgroup than in the entire cohort. The 15- and 30-day cumulative incidence of ED visits for baloxavir-treated patients was less than half that of oseltamivir-treated patients for all respiratory-related and select respiratory-related conditions ($P < .01$ for all comparisons) (eAppendix Table 4).

Treatment with baloxavir was associated with greater cost savings at both 15 and 30 days in the high-risk group than in the overall group. In the high-risk group, mean per-person cost savings (percent reduction) with baloxavir at days 15 and 30 were \$177 (29%) and \$204 (18%), \$65 (42%) and \$82 (39%), and \$67 (67%) and \$90 (73%) for all-cause, all respiratory-related, and select respiratory-related conditions, respectively (Figure 3). Cost savings with baloxavir treatment accrued in all utilization categories, except for 30-day prescription fill costs.

Sensitivity Analysis

The sensitivity analysis in which HCRU and costs were determined from the day of the outpatient influenza diagnosis (as opposed to the day following prescription antiviral fill) showed a lower 15- and 30-day cumulative incidence of all-cause, all respiratory-related, and select respiratory-related ED visits and hospitalizations. Results were statistically significant for all comparisons, with the exception of 15-day all-cause and all respiratory-related hospitalizations and 30-day all respiratory-related hospitalizations (eAppendix Table 5). At both 15 and 30 days, baloxavir treatment was associated with substantial per-patient cost savings for all conditions, despite higher prescription costs (eAppendix Table 6). Overall cost savings per patient with baloxavir were increased 2- to 3-fold in the sensitivity analysis compared with the base-case analysis.

DISCUSSION

We compared influenza-associated complications, HCRU, and costs in more than 15,000 commercially insured patients with acute influenza treated with baloxavir or oseltamivir. The wholesale acquisition cost for baloxavir marboxil is \$150, whereas that for a generic oseltamivir regimen ranges from \$19 to \$102 for 10 capsules. This study illustrates other important aspects of HCRU and health

TABLE 1. Baseline Demographic and Clinical Characteristics of Matched Cohorts

	Baloxavir (n = 5080) n (%)	Oseltamivir (n = 10,160) n (%)	P
Age group in years			.989
12-17	1090 (21)	2168 (21)	
18-49	2859 (56)	5724 (56)	
50-64	1074 (21)	2148 (21)	
≥ 65	57 (1)	120 (1)	
Sex			.936
Male	2816 (55)	5625 (55)	
Female	2264 (45)	4535 (45)	
Region			.995
North Central	483 (10)	978 (10)	
Northeast	527 (10)	1045 (10)	
South	3824 (75)	7674 (75)	
West	246 (5)	493 (5)	
Health plan type			.998
CDHP or HDHP	1031 (20)	2064 (20)	
HMO	316 (6)	622 (6)	
POS	1158 (23)	2318 (23)	
PPO	2485 (49)	4970 (49)	
Other	90 (2)	186 (2)	
Index month			>.999
November 2018	9 (<0.002)	18 (<0.002)	
December 2018	173 (3)	348 (3)	
January 2019	853 (17)	1704 (17)	
February 2019	2152 (42)	4293 (42)	
March 2019	1421 (28)	2857 (28)	
April 2019	381 (8)	752 (7)	
May 2019	91 (2)	188 (2)	
CCI score category			.974
0	4321 (85)	8669 (85)	
1	568 (11)	1118 (11)	
2	111 (2)	214 (2)	
≥3	80 (2)	159 (2)	
Preindex hospitalization/ED visit	487 (10)	976 (10)	.969
Days to prescription fill			.053
0	4744 (93)	9518 (94)	
1	308 (6)	612 (6)	
2	28 (0.006)	30 (0.003)	

CCI, Charlson Comorbidity Index; CDHP, consumer-driven health plan; ED, emergency department; HDHP, high-deductible health plan; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization.

care costs that should be considered, despite higher prescription costs, when managing influenza illness.

To ensure that the 2 cohorts in this study were comparable, we propensity score matched patients based on variables that could influence the outcomes. We did not specifically adjust for

TABLE 2. Health Care Resource Utilization in Baloxavir- and Oseltamivir-Treated Patients at Follow-up Days 15 and 30

	15-day follow-up			30-day follow-up		
	Baloxavir (n = 5080)	Oseltamivir (n = 10,160)	P	Baloxavir (n = 5080)	Oseltamivir (n = 10,160)	P
All cause						
Patients with outcome, n (%)						
ED visits	72 (1.4%)	174 (1.7%)	.173	111 (2.2%)	264 (2.6%)	.121
Hospitalizations	11 (0.22%)	35 (0.34%)	.175	15 (0.30%)	55 (0.54%)	.041
Outpatient visits	1411 (27.8%)	2925 (28.8%)	.191	2168 (42.7%)	4299 (42.3%)	.668
Prescription fills	1641 (32.3%)	3197 (31.5%)	.296	2447 (48.2%)	4742 (46.7%)	.081
Mean number [95% CI] per treated patient						
ED visits	0.017 (0.013-0.021)	0.020 (0.017-0.023)	.173	0.026 (0.021-0.031)	0.032 (0.028-0.036)	.119
Hospitalizations	0.002 (0.001-0.003)	0.004 (0.002-0.005)	.175	0.003 (0.002-0.005)	0.006 (0.004-0.007)	.034
Outpatient visits	0.41 (0.39-0.43)	0.42 (0.40-0.44)	.212	0.84 (0.80-0.88)	0.82 (0.80-0.85)	.592
Prescription fills	0.66 (0.63-0.70)	0.64 (0.62-0.67)	.278	1.25 (1.19-1.30)	1.18 (1.14-1.21)	.033
All respiratory related						
Patients with outcome, n (%)						
ED visits	26 (0.51%)	105 (1.0%)	.001	29 (0.57%)	124 (1.2%)	<.001
Hospitalizations	7 (0.14%)	22 (0.22%)	.293	9 (0.18%)	25 (0.25%)	.395
Outpatient visits	561 (11.0%)	1160 (11.4%)	.491	808 (15.9%)	1569 (15.4%)	.458
Mean number [95% CI] per treated patient						
ED visits	0.005 (0.003-0.007)	0.011 (0.009-0.013)	.001	0.006 (0.004-0.008)	0.013 (0.011-0.016)	<.001
Hospitalizations	0.001 (0.000-0.002)	0.002 (0.001-0.003)	.293	0.002 (0.001-0.003)	0.003 (0.002-0.004)	.395
Outpatient visits	0.13 (0.12-0.14)	0.13 (0.13-0.14)	.501	0.21 (0.19-0.22)	0.20 (0.19-0.21)	.493
Select respiratory related						
Patients with outcome, n (%)						
ED visits	13 (0.26%)	69 (0.68%)	<.001	13 (0.26%)	70 (0.69%)	<.001
Hospitalizations	4 (0.08%)	20 (0.20%)	.127	5 (0.10%)	21 (0.21%)	.148
Outpatient visits	176 (3.5%)	454 (4.5%)	.003	194 (3.8%)	508 (5.0%)	.001
Mean number [95% CI] per treated patient						
ED visits	0.003 (0.001-0.004)	0.007 (0.005-0.009)	<.001	0.003 (0.001-0.004)	0.007 (0.005-0.009)	<.001
Hospitalizations	0.001 (0.00-0.002)	0.002 (0.001-0.003)	.083	0.001 (0.00-0.002)	0.002 (0.001-0.003)	.127
Outpatient visits	0.04 (0.03-0.05)	0.05 (0.05-0.06)	.003	0.04 (0.04-0.05)	0.06 (0.05-0.06)	.001

ED, emergency department.

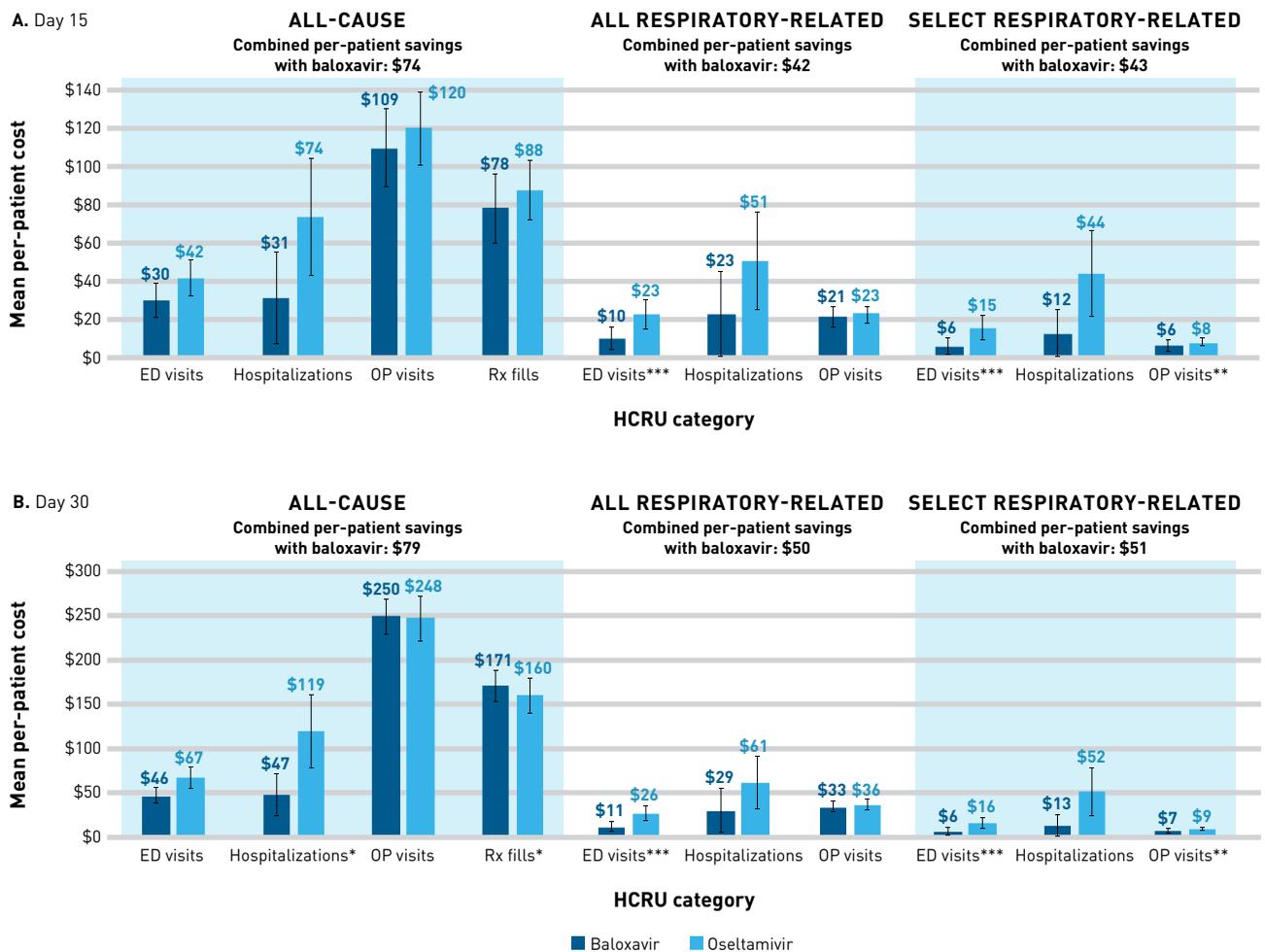
respiratory comorbidities in the propensity scoring model because they were already included in the CCI score, and we also did not want to overadjust, which would potentially bias results; however, post matching, there were no statistically significant differences between cohorts in regard to chronic lung disease. Outcomes were assessed following prescription fill to ensure that they could be influenced temporally only by the antiviral selected.

Results showed that, compared with oseltamivir-treated patients, those who received baloxavir had lower HCRU and costs over the first 15 days and up to 30 days after prescription fill for most HCRU categories. Differences in HCRU and costs between baloxavir and oseltamivir were amplified in the high-risk subgroup of patients with influenza. In our sensitivity analysis in which we determined outcomes from the day of the influenza-related outpatient diagnosis, we found similar results despite higher prescription costs.

Our analysis provides insight into overall real-world HCRU and costs for influenza patients following antiviral therapy. Our evaluation of more specific respiratory-related outcomes and the use of a shorter 15-day time horizon demonstrate the impact of antiviral selection on conditions that may more likely be related to the influenza episode. For example, hospitalizations for conditions such as asthma or COPD within 15 days may more confidently be associated with the influenza episode. Importantly, we observed lower HCRU and costs in baloxavir-treated patients regardless of time horizon or outcomes assessed.

This is the first real-world study that compared HCRU and costs associated with baloxavir and oseltamivir. Previous real-world studies in patients with influenza have compared HCRU and costs associated with oseltamivir vs no treatment. In a similar study using MarketScan claims data from the 2000 to 2005 influenza seasons

FIGURE 2. All-Cause, All Respiratory-Related, and Select Respiratory-Related Costs in Baloxavir- or Oseltamivir-Treated Patients*

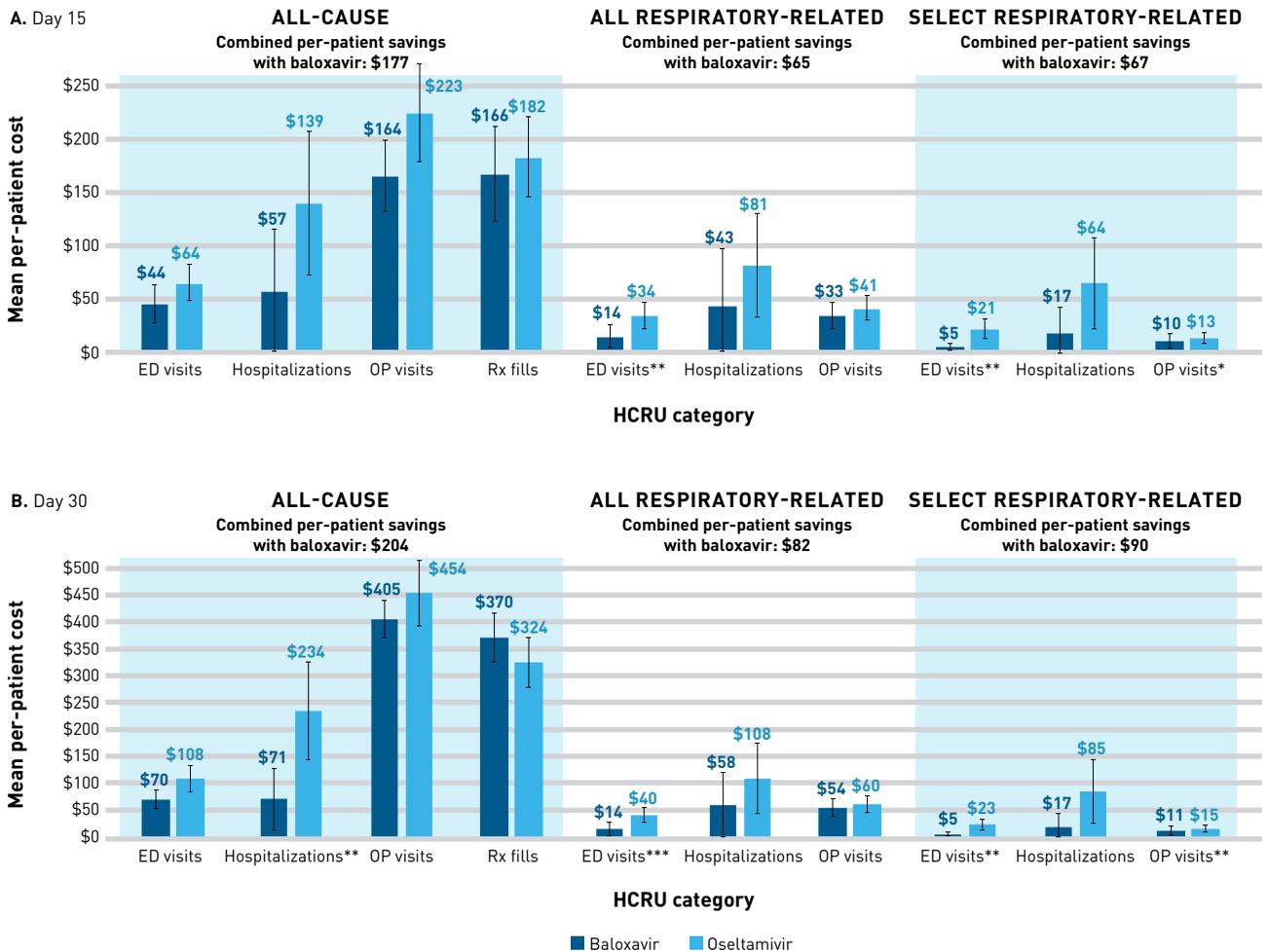


ED, emergency department; HCRU, health care resource utilization; OP, outpatient; Rx, prescription.
 * $P < .05$; ** $P < .01$; *** $P < .001$.
 *Costs on the figure are rounded to the nearest dollar but cost savings are based on nonrounded values.

for patients of any age, oseltamivir reduced the risk of 14-day all-cause hospitalization and respiratory-related hospitalization by 38% and 57%, respectively, compared with no treatment.²⁰ We found that baloxavir reduced 15-day all-cause and respiratory-related hospitalizations by 38% (calculated as $1 - [0.22 / 0.34\%]$) and 36% (calculated as $1 - [0.14\% / 0.22\%]$), respectively, compared with oseltamivir, although the differences were not significant. The all-cause 30-day per-patient cost of \$968 associated with oseltamivir treatment in our sensitivity analysis (calculated from the day of outpatient influenza visit) was similar to the 2019 US\$-adjusted²¹ \$820 cost reported in the previous study,²⁰ providing validity to our results. However, in that study, all-cause health care costs were similar among oseltamivir-treated and untreated patients, whereas we identified lower costs with baloxavir (mean costs, \$877 [9.4% reduction]). Another analysis using PharMetrics

data identified 30-day all-cause hospitalization rates of 0.9% in oseltamivir-treated adult patients with influenza compared with 1.2% in untreated patients.²² The 2019 US\$-adjusted costs for total health care and hospitalization were approximately \$740 and \$160 in oseltamivir-treated patients, respectively, and approximately \$760 and \$200 in untreated patients, respectively. We found a similar statistically significant reduction in the 30-day all-cause hospitalization rate in our analysis (baloxavir, 0.3%; oseltamivir, 0.5%) and a reduction in all-cause total and hospitalization-related costs with baloxavir (Figure 2). A more recent claims analysis of more than 1.5 million influenza cases between 2006 and 2010 found that antivirals (> 90% oseltamivir) reduced the risks of 30-day hospitalization and ED use by 29% and 24%, respectively, compared with no antiviral treatment.¹⁴ In our study, risk of 30-day hospitalization and ED use for baloxavir-treated patients was

FIGURE 3. All-Cause, All-Respiratory, and Select-Respiratory Costs in High-Risk Baloxavir- or Oseltamivir-Treated Patients*



ED, emergency department; HCRU, health care resource utilization; OP, outpatient; Rx, prescription.

* $P < .05$; ** $P < .01$; *** $P < .001$.

*Costs on the figure are rounded to the nearest dollar but cost savings are based on nonrounded values.

lower by 45% (1 – [0.30%/0.54%]) and 16% (1 – [2.19% / 2.60%]), respectively, compared with oseltamivir.

The need to reduce influenza-related complications is especially urgent in vulnerable populations at increased risk of deleterious outcomes. In the current study, all-cause, all respiratory-related, and select respiratory-related HCRU in all categories was greater in the high-risk group than in the overall group for both treatment cohorts. However, differences between baloxavir and oseltamivir in reduced HCRU and costs were more pronounced in high-risk patients. All-cause per-patient cost savings with baloxavir were greater in the high-risk group than in the overall population at both day 15 (\$177 vs \$74) and day 30 (\$204 vs \$79); for all respiratory-related and select respiratory-related conditions, per-patient cost savings with baloxavir ranged between \$65 and \$90 in the high-risk group and between \$42 and \$51 in the overall patient population.

In addition to the direct clinical and economic benefits to patients, providers, and payers from reductions in influenza complications, HCRU, and costs for individual patients, the overall health care system also reaps benefits. In periods of constrained health care resources, such as during the COVID-19 global pandemic, a reduction in influenza-related ED visits and hospitalizations would increase the ability to provide health care to other patients and could mitigate capacity-dependent deaths. Atkins et al calculated that 8000 to 13,000 hospitalizations, representing 4% to 5% of total pandemic-related hospitalizations, were averted during the 2009-2010 influenza pandemic because of oseltamivir and zanamivir treatment alone.²³

Limitations

This study has limitations. First, although propensity score matching was used to balance populations in this retrospective study, some

variables such as income, influenza vaccination status, and potential differences in provider prescribing practices for baloxavir vs oseltamivir could not be measured reliably. However, we have no reason to suspect substantial differences in income, vaccination status, or other possibly unmeasured predictors of HCRU or costs. Second, because patients were selected based on diagnosis codes in the claims database, the diagnosis of influenza was not necessarily laboratory confirmed. However, unlike some previously conducted analyses, we compared 2 active treatment arms. Therefore, we would expect fewer systematic differences such as differences in severity or “true” diagnoses between treated and untreated populations to bias our analysis. Third, the database represents individuals enrolled in commercial health plans and some supplemental Medicare plans and may therefore not be representative of the entire US population; the population was skewed to the southern United States. Also, only 3% of our study population were older than 65 years because our data source primarily covered commercially insured patients, most of whom were younger than 65 years. The results may therefore not be generalizable to the population older than 65 years, in whom the burden of influenza is substantially higher: 50% to 70% of influenza-related hospitalizations and 70% to 85% of influenza-related deaths occur in individuals older than 65 years.²⁴ Fourth, physicians’ prescribing preferences may present a confounder in assessing differences between the treatment groups, although this should be offset by matching of the cohorts based on age, region, and baseline comorbidities. Finally, because of the rarity of certain outcomes (eg, hospitalization), the sample size in this study confers low statistical power. Although most outcomes numerically favored baloxavir treatment, many of the comparisons were not statistically significant, particularly among the more general all-cause outcomes.

CONCLUSIONS

Claims data for the 2018–2019 influenza season showed that patients who filled a prescription for single-dose baloxavir following an outpatient visit for influenza had lower HCRU and costs than patients who filled a prescription for oseltamivir. In particular, ED visits and outpatient visits for all respiratory-related and select respiratory-related complications were significantly lower in the baloxavir cohort. Costs for baloxavir-treated patients were lower than for oseltamivir-treated patients across multiple health care settings, despite higher prescription fills and costs. The reduction in HCRU and cost advantage with baloxavir compared with oseltamivir was even greater in high-risk patients. These data suggest that baloxavir is associated with fewer secondary complications and reduced HCRU and costs compared with oseltamivir. ■

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eAppendix Table 1. ICD-10 Codes Used to Identify Complications

ICD-10 Code	Diagnosis
J00-J06	Acute upper respiratory infections
J09-J18	Influenza and pneumonia
J10	Influenza due to other identified influenza virus
J11	Influenza due to unidentified influenza virus
J12	Viral pneumonia, not elsewhere classified
J13	Pneumonia due to <i>Streptococcus pneumoniae</i>
J14	Pneumonia due to <i>Haemophilus influenzae</i>
J15	Bacterial pneumonia, not elsewhere classified
J16	Pneumonia due to other infectious organisms, not elsewhere classified
J18	Pneumonia, unspecified organism
J20-J22	Other acute lower respiratory infections
J20	Acute bronchitis
J21	Acute bronchiolitis
J22	Unspecified acute lower respiratory infection
J30-J39	Other diseases of upper respiratory tract
J40-J47	Chronic lower respiratory diseases
J41	Simple and mucopurulent chronic bronchitis
J42	Unspecified chronic bronchitis
J43	Emphysema
J44	Other chronic obstructive pulmonary disease
J45	Asthma
J47	Bronchiectasis
J60-J70	Lung diseases due to external agents
J67	Pneumonitis
J80-J84	Other respiratory diseases principally affecting the interstitium
J85-J86	Suppurative and necrotic conditions of the lower respiratory tract
J90-J94	Other diseases of the pleura
J95	Intraoperative and postprocedural complications and disorders of respiratory system, not elsewhere classified
J96-J99	Other diseases of the respiratory system

ICD-10, International Classification of Diseases, 10th Revision.

eAppendix Table 2. Patients with High-Risk Conditions in the Overall Population

Variable	Baloxavir (N = 1958) n (%)	Oseltamivir (N = 3949) n (%)	P value
Age 65+	57 (3)	120 (3)	.809
Obesity	288 (15)	658 (17)	.054
Pregnancy	38 (2)	170 (4)	<.001
Neurological disease	740 (38)	1375 (35)	.025
Chronic lung disease	365 (19)	752 (19)	.711
Cardiovascular disease	217 (11)	427 (11)	.754
Hematologic disease	207 (11)	427 (11)	.778
Endocrine disease	652 (33)	1216 (31)	.051
Kidney disease	62 (3)	141 (4)	.422
Liver disease	76 (4)	141 (4)	.550
Metabolic disease	688 (35)	1342 (34)	.379
Immune-related disease	213 (11)	411 (10)	.580

eAppendix Table 3. Baseline Demographic and Clinical Characteristics of the Baloxavir and Oseltamivir Cohorts in the High-Risk Subgroup

	Baloxavir (N = 1958) n (%)	Oseltamivir (N = 3949) n (%)	<i>P</i> value
Age group (y)			.639
12-17	208 (11)	386 (10)	
18-49	1016 (52)	2105 (53)	
50-64	677 (35)	1338 (34)	
65+	57 (3)	120 (3)	
Sex			.460
Female	1150 (59)	2359 (60)	
Male	808 (41)	1590 (40)	
Region			.727
North Central	187 (10)	384 (10)	
Northeast	241 (12)	499 (13)	
South	1449 (74)	2880 (73)	
West	81 (4)	186 (5)	
Plan Type			.420
CDHP or HDHP	378 (19)	722 (18)	
HMO	127 (6)	240 (6)	
Other	48 (2)	95 (2)	
POS	386 (20)	861 (22)	
PPO	1019 (52)	2031 (51)	
Index month			.819
November 2018	3 (0)	7 (0)	
December 2018	67 (3)	155 (4)	
January 2019	315 (16)	618 (16)	
February 2019	810 (41)	1645 (42)	
March 2019	554 (28)	1130 (29)	
April 2019	173 (9)	312 (8)	
May 2019	36 (2)	82 (2)	
CCI category			.870
0	1207 (62)	2478 (63)	
1	560 (29)	1098 (28)	
2	111 (6)	214 (5)	
3+	80 (4)	159 (4)	
Preindex hospitalization/ED	338 (17)	653 (17)	.482
Days to prescription fill			.169
0	1828 (93)	3686 (93)	
1	115 (6)	247 (6)	
2	15 (1)	16 (0)	

CCI, Charlson comorbidity index; CDHP, consumer-driven health plan; ED, emergency department; HDHP, high-deductible health plan; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization.

eAppendix Table 4. Health Care Resource Utilization in High-Risk Patients Treated with Baloxavir- or Oseltamivir-Treated at Follow-Up Days 15 and 30

	15-Day Follow-Up			30-Day Follow-Up		
	Baloxavir (N = 1958)	Oseltamivir (N = 3949)	<i>P</i> value	Baloxavir (N = 1958)	Oseltamivir (N = 3949)	<i>P</i> value
All-cause						
Proportion of patients with outcome						
Emergency department visits	41 (2.1%)	103 (2.6%)	.228	64 (3.3%)	158 (4.0%)	.164
Hospitalizations	6 (0.31%)	27 (0.68%)	.067	7 (0.36%)	44 (1.1%)	.003
Outpatient visits	766 (39.1%)	1659 (42.0%)	.034	1140 (58.2%)	2330 (59.0%)	.567
Prescription fills	936 (47.8%)	1823 (46.2%)	.234	1335 (68.2%)	2619 (66.3%)	.152
Mean number (95% CI) per treated patient						
Emergency department visits	0.025 (0.017 – 0.032)	0.031 (0.025 – 0.038)	.227	0.038 (0.028 – 0.048)	0.052 (0.043 – 0.060)	.158
Hospitalizations	0.003 (0.001 – 0.006)	0.007 (0.004 – 0.010)	.067	0.004 (0.001 – 0.006)	0.011 (0.008 -0.015)	.003
Outpatient visits	0.63 (0.58 – 0.67)	0.66 (0.63 – 0.700)	.061	1.31 (1.23 – 1.38)	1.32 (1.26 – 1.38)	.671
Prescription fills	1.09 (1.02 – 1.16)	1.05 (1.02 – 1.10)	.274	2.08 (1.97 – 2.19)	1.96 (1.89 – 2.03)	.061
All-respiratory						
Proportion of patients with outcome						
Emergency department visits	13 (0.66%)	60 (1.5%)	.005	14 (0.72%)	75 (1.9%)	<.001
Hospitalizations	4 (0.20%)	15 (0.38%)	.334	5 (0.26%)	18 (0.46%)	.277
Outpatient visits	303 (15.5%)	640 (16.2%)	.460	431 (22.0%)	850 (21.5%)	.669
Mean number (95% CI) per treated patient						
Emergency department visits	0.007 (0.003 – 0.010)	0.016 (0.012 – 0.021)	.005	0.007 (0.003 – 0.011)	0.02 (0.017- 0.027)	<.001

Hospitalizations (n)	0.002 (0.000 – 0.004)	0.004 (0.002 – 0.006)	.262	0.003 (0.000 – 0.005)	0.005 (0.003 – 0.007)	.244
Outpatient visits (n)	0.19 (0.17 – 0.21)	0.20 (0.18 – 0.21)	.481	0.30 (0.27 – 0.34)	0.30 (0.28 – 0.32)	.690
Select-respiratory						
Proportion of patients with outcome						
Emergency department visits	7 (0.36%)	42 (1.1%)	.005	7 (0.36%)	43 (1.1%)	.004
Hospitalizations	2 (0.10%)	13 (0.33%)	.167	2 (0.10%)	14 (0.35%)	.109
Outpatient visits	95 (4.9%)	254 (6.4%)	.015	103 (5.3%)	285 (7.2%)	.004
Mean number (95% CI) per treated patient						
Emergency department visits	0.004 (0.001 -0.006)	0.011 (0.008 – 0.014)	.005	0.004 (0.001 – 0.006)	0.012 (0.008 – 0.015)	.004
Hospitalizations	0.001 (0.00 – 0.002)	0.003 (0.002 – 0.005)	.103	0.001 (0.00 – 0.002)	0.004 (0.002 – 0.006)	.079
Outpatient visits	0.06 (0.04 – 0.07)	0.08 (0.07 – 0.09)	.008	0.06 (0.05 – 0.08)	0.09 (0.077 – 0.099)	.004

eAppendix Table 5. Sensitivity Analysis of Health Care Resource Utilization in Baloxavir- and Oseltamivir-Treated Patients at Follow-Up Days 15 and 30

	15-Day Follow-Up			30-Day Follow-Up		
	Baloxavir (N = 5080)	Oseltamivir (N = 10,160)	<i>P</i> value	Baloxavir (N = 5080)	Oseltamivir (N = 10,160)	<i>P</i> value
All-cause						
Proportion of patients with outcome						
Emergency department visits	155 (3.1%)	739 (7.3%)	<.001	192 (3.8%)	823 (8.1%)	<.001
Hospitalizations	11 (0.22%)	42 (0.41%)	.052	15 (0.30%)	62 (0.61%)	.010
Outpatient visits	5029 (99.0%)	9901 (97.5%)	<.001	5037 (99.2%)	9956 (98.0%)	<.001
Prescription fills	5080 (100%)	10,160 (100%)	--	5080 (100%)	10,160 (100%)	--
Mean number (95% CI) per treated patient						
Emergency department visits	0.034 (0.029 – 0.040)	0.085 (0.079 – 0.091)	<.001	0.044 (0.037 – 0.050)	0.097 (0.090 – 0.104)	<.001
Hospitalizations	0.002 (0.001 – 0.003)	0.004 (0.003 – 0.006)	.052	0.003 (0.002 – 0.005)	0.007 (0.005 – 0.008)	.010
Outpatient visits	1.40 (1.38 – 1.42)	1.39 (1.37 – 1.40)	.352	1.83 (1.79 – 1.87)	1.79 (1.76 – 1.82)	.049
Prescription fills	2.39 (2.35 – 2.44)	2.40 (2.37 – 2.43)	.392	2.97 (2.91 – 3.03)	2.92 (2.88 – 2.96)	.660
All-respiratory						
Proportion of patients with outcome						
Emergency department visits	108 (2.1%)	678 (6.7%)	<.001	111 (2.2%)	695 (6.8%)	<.001
Hospitalizations	7 (0.14%)	30 (0.30%)	.063	9 (0.18%)	33 (0.32%)	.101
Outpatient visits	5020 (98.8%)	9778 (96.2%)	<.001	5020 (98.8%)	9794 (96.4%)	<.001
Mean number (95% CI) per treated patient						
Emergency department visits	0.023 (0.018 – 0.027)	0.075 (0.069 – 0.081)	<.001	0.023 (0.019 – 0.028)	0.078 (0.072 – 0.083)	<.001

Hospitalizations (n)	0.001 (0.00 – 0.002)	0.003 (0.002 – 0.004)	.063	0.002 (0.001 – 0.003)	0.003 (0.002 – 0.005)	.101
Outpatient visits (n)	1.12 (1.11 – 1.13)	1.09 (1.08 – 1.10)	<.001	1.19 (1.18 – 1.21)	1.16 (1.15 – 1.17)	<.001
Select-respiratory						
Proportion of patients with outcome						
Emergency department visits	100 (2.0%)	644 (6.3%)	<.001	100 (2.0%)	645 (6.4%)	<.001
Hospitalizations	4 (0.08%)	28 (0.28%)	.013	5 (0.10%)	29 (0.29%)	.027
Outpatient visits	5014 (98.7%)	9725 (95.7%)	<.001	5014 (98.7%)	9727 (95.7%)	<.001
Mean number (95% CI) per treated patient						
Emergency department visits	0.020 (0.016 – 0.024)	0.070 (0.065 – 0.076)	<.001	0.020 (0.016 – 0.024)	0.070 (0.065 – 0.076)	<.001
Hospitalizations	0.001 (0.000 – 0.002)	0.003 (0.002 – 0.004)	.012	0.001 (0.000 – 0.002)	0.003 (0.002 – 0.004)	.021
Outpatient visits	1.03 (1.02 – 1.03)	1.01 (1.00 – 1.01)	<.001	1.03 (1.02 – 1.04)	1.01 (1.01 – 1.02)	<.001

eAppendix Table 6. Sensitivity Analysis of Costs in Baloxavir- and Oseltamivir-Treated Patients at Days 15 and 30 After Outpatient Visit

	15-Day Follow-Up			30-Day Follow-Up		
	Baloxavir (N = 5080)	Oseltamivir (N = 10,160)	<i>P</i> value	Baloxavir (N = 5080)	Oseltamivir (N = 10,160)	<i>P</i> value
All-cause costs (US\$) per treated patient, mean (95% CI)						
Emergency department visits	58 (44 -71)	154 (138 - 170)	<.001	74 (59 - 89)	179 (162 - 197)	<.001
Hospitalizations	31 (7 -55)	82 (50 - 114)	.051	47 (15 - 80)	128 (86 - 170)	<.010
Outpatient visits	271 (250 - 291)	281 (261 - 300)	.005	411 (375 - 447)	410 (384 - 436)	<.001
Prescription fills	252 (223 - 282)	179 (163 - 194)	<.001	345 (291 - 399)	251 (231 - 271)	<.001
Overall per-patient cost savings with baloxavir	83			90		
All-respiratory costs (US\$) per treated patient, mean (95% CI)						
Emergency department visits	36 (25 - 48)	129 (115 - 144)	<.001	37 (26 - 48)	133 (118 - 147)	<.001
Hospitalizations (n)	23 (0.4 - 45)	59 (33 - 85)	.062	29 (4 - 54)	69 (38 - 100)	.101
Outpatient visits (n)	174 (167 - 180)	172 (167 - 178)	<.001	186 (178 - 193)	185 (178 - 192)	<.001
Overall per-patient cost savings with baloxavir	128			135		
Select-respiratory costs (US\$) per treated patient, mean (95% CI)						
Emergency department visits	32 (22 - 42)	119 (105 - 133)	<.001	32 (22 - 42)	119 (105 - 133)	<.001
Hospitalizations	12 (0 - 25)	52 (28 - 77)	.012	13 (0.5 - 26)	60 (31 - 89)	.021
Outpatient visits	154 (151 -158)	154 (150 - 157)	<.001	155 (151 - 158)	155 (151 - 158)	<.001
Overall per-patient cost savings with baloxavir	127			135		

eAppendix Figure.

