

Demographic, Geographic, and Clinical Characteristics Associated with Receipt of
Influenza Outpatient Oral Antiviral Treatment in Commercially Insured US Patients: An
Exploration of Potential Health Disparities

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Abstract

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Background: Marginalized groups have been shown to experience a greater portion of the annual morbidity of influenza in the US. Identifying characteristics associated with receipt of outpatient oral antiviral treatment (OOAT) is important to determine if similar disparities exist with prescribing of these treatments.

Objective: To identify demographic, geographic, and clinical characteristics associated with OOAT in commercially insured US beneficiaries with influenza.

Methods: We conducted a retrospective cohort study using IBM MarketScan® commercial claims to identify unique influenza cases between May 1, 2016 and April 30, 2019. For each annual cohort, odds of OOAT were determined for association with age, sex, level of rurality, region, health plan type, employment classification (hourly/salary), Charlson Comorbidity Index (CCI) score, influenza vaccination, and presence of a respiratory condition. Annual cohorts were analyzed separately for adults and children/adolescents.

Results: Across all annual cohorts and ages, females, those whose primary beneficiary was paid hourly, and those who were not vaccinated against influenza all had lower odds of receiving OOAT. Adult beneficiaries living in more rural areas also had lower

odds of OOAT in all annual cohorts, whereas no such association was seen in beneficiaries <18 years of age. Across all ages, at least 25% decreased odds of OOAT were observed for those enrolled in high deductible health plans (HDHP) as compared to those enrolled in any other type of health plan in the total study population, except for adults enrolled in HDHPs compared to adults enrolled in basic medical coverage plans.

Conclusion: Generally, lower odds of receiving an antiviral were seen in beneficiaries who were female, with a primary beneficiary paid hourly, and enrolled in a high deductible health plan. Adult beneficiaries living in more rural areas had lower odds of OOAT suggesting that disparities may exist in this context. Future research capturing characteristics that better represent marginalization is needed to more definitely determine if disparities exist in oral influenza antiviral treatment.

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Introduction

Influenza is a substantial burden both clinically and economically to patients and the US healthcare system. Using a 2013 population, it was estimated that annual influenza results in over 600,000 hospitalizations and over 27,000 deaths. (1). Annual influenza was estimated to cost patients and the healthcare system \$11.2 billion (2). Research has shown that influenza has a greater burden in African Americans, those living in rural areas, and Medicaid beneficiaries (3, 4, 5). These disparities in influenza remain in areas where higher proportions of adults live below the poverty line (6). Rural and racial disparities also exist in influenza vaccination (7, 8).

In addition to annual vaccination, outpatient oral antiviral treatment (OOAT) of influenza is recommended by the Infectious Disease Society of America (IDSA) for patients who are at high risk of complications from influenza, including those with chronic medical conditions and immunocompromised patients, regardless of age or vaccination status. These high-risk conditions include chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematologic, metabolic (including type 2 diabetes), immunologic, and neurologic conditions (strong recommendation based on multiple well-designed clinical trials). Additionally, outpatient oral antiviral treatment should be considered for all patients, regardless of vaccination status, if onset of illness is within two days of diagnosis (weak recommendation) (9).

Outpatient oral antiviral treatment has been shown to not only decrease influenza-related complications, but also the costs and healthcare resource utilization associated with these complications (10, 11). A better understanding of factors associated with antiviral use is needed to facilitate use of these medications in the guideline-recommended populations and investigate if the disparities seen in influenza morbidity and vaccination persist when applied to oral antiviral treatment. Factors associated with OOAT could then be targeted in future health disparity research. Determinants of oral

influenza antiviral use have been studied in a commercially insured US population (12). However, due to previous research being conducted on influenza seasons before oseltamivir generic medications were available in 2016 and examining a small number of characteristics, we aimed to address these gaps.

Objective

The primary objective of this study was to identify demographic, geographic, and clinical characteristics associated with receipt of OOAT in beneficiaries less than 65 years of age with influenza when generic oseltamivir was available. A secondary objective was to identify these same characteristics associated with receipt of OOAT within 2 days of influenza diagnosis.

Methods

Study Design and Data Source

This study was a retrospective cohort analysis using medical and pharmacy claims from the IBM MarketScan® Commercial Claims and Encounters database (13). The IBM MarketScan® Commercial Claims and Encounters database contains de-identified health data on patient's utilization of inpatient, outpatient, and prescription services. The database represents over 215 million individuals, encompassing employees, their spouses, and dependents who are covered by employer-sponsored private health insurance in the US.

Eligibility Criteria

Any patient with one or more outpatient claims for an influenza diagnosis in the primary position from May 1, 2016 to April 30, 2019 were eligible for study inclusion, and the date of the claim served as the patient's index date (Figure 1). To ensure the claim represented incident influenza, patients were required to have no inpatient or outpatient claim with an influenza diagnosis in any position ≥ 90 days prior to their index date. Influenza diagnosis was assessed using International Classification of Diseases (ICD)

10 codes J09.xx, J10.xx, and J11.xx. Patients were required to have continuous medical enrollment for at least one year prior to their index date to assess comorbidities and influenza vaccination status. Patients were required have continuous prescription enrollment for at least 30 days after their index date to assess receipt of OOAT.

Three annual cohorts were constructed from the study period based on influenza activity observed by the Centers for Disease Control and Prevention (CDC) (Figure 2) (14). Annual separation dates represented periods at which low influenza activity was recorded. Beneficiaries with claims missing age or sex and where age was ≥ 65 were excluded from this analysis (Figure 3). Differences in annual cohort sizes were verified against CDC laboratory confirmed influenza case counts (15).

Characteristics of Interest

Characteristics analyzed for potential association with outpatient oral antiviral treatment were age, sex, level of rurality, geographic region, health plan type, employment classification of the primary beneficiary, Charlson Comorbidity Index (CCI) score, receipt of an influenza vaccine, and presence of a respiratory condition.

Demographic Characteristics

Age was analyzed as a continuous variable. Sex was analyzed according to MarketScan® defined categories. Health plan types were grouped according to similar payment structures and features offered to beneficiaries. Specifically, plan types were grouped on a combination of whether primary care physicians are assigned, out of network services are covered, and if referrals to specialists are required. Employment classification of the primary beneficiary was dichotomized as either salary or hourly.

Geographic Characteristics

Region was analyzed according to Marketscan® defined categories. Level of rurality was assigned using metropolitan statistical area (MSA) as captured by Marketscan®. MSAs are a collection of counties around a densely populated area defined by the US Office of Management and Budget (16). MSAs were then mapped to counties with Federal Information Processing Series (FIPS) codes using the National Bureau of Economic Research's (NBER) MSA to County Crosswalk (17). County rurality was classified into 1 of 6 categories according to the National Center for Health Statistics' (NCHS) Urban-Rural Classification Scheme for Counties (Appendix 1) (18).

If counties within MSAs encompassed multiple rurality categories, the most commonly occurring rurality category was chosen to represent that MSA. Because a portion of US counties are not part of an MSA, an additional classification of "rural" was assigned to all claims coded as "non-MSA". Because NCHS's "noncore" classification required counties to not exist within an MSA, no MSAs qualified as noncore. MSAs not listed in the NBER crosswalk were excluded from level of rurality analysis. The level of rurality was ordered from lowest to highest population concentration as follows: rural, micropolitan, small metro, medium metro, large fringe metro, and large central metro.

Clinical Characteristics

CCI score was analyzed as a continuous variable and calculated according to previous literature (19). Receipt of an influenza vaccine was verified using National Drug Codes (NDC) and Common Procedural Terminology (CPT) codes (Appendix 2). Presence of a respiratory condition was evaluated using ICD-9 and 10 codes (Appendix 3). CCI score, influenza vaccination, and respiratory conditions were collected in the year prior to the index date.

Outcomes

The outcome for the primary objective of this study is receipt of an oral outpatient antiviral within 30 days of influenza diagnosis. The secondary objective outcome is

receipt of an antiviral within 2 days of influenza diagnosis. Outcomes were captured using pharmacy claims containing NDC codes for oseltamivir and baloxavir marboxil within the follow up period (Appendix 4). Oseltamivir and baloxavir marboxil were chosen according to current CDC recommendations for oral outpatient influenza treatment options (20).

Statistical Analysis

An adjusted multivariable logistic regression was performed to detect any differences in the odds of outpatient oral antiviral treatment by demographic, geographic, and clinical characteristics, for each annual cohort and the study sample overall. Missingness of each variable was assessed (Appendix 5). Hosmer-Lemeshow goodness-of-fit tests were used to assess model fit for each cohort. For all statistical analyses, an alpha level of 0.05 was set and 95% confidence intervals (CI) were obtained.

Software

SAS version 9.4 (SAS Institute Inc., Cary, NC) was used for obtaining the dataset for each cohort. R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses.

Results

Baseline characteristics of each annual cohort and the overall study sample are presented in Table 1. Based on the age distribution of the data, characteristics were analyzed separately for adults (≥ 18 years of age) and children/adolescents (< 18 years of age).

Adults

Demographic Characteristics

OOAT were associated with older age, although effect size was minimal (Table 2). Adult females had lower odds of OOAT across all annual cohorts. Apart from basic major

medical insurance coverage, adults enrolled in a high deductible health plan (HDHP), or similarly structured plan, had lower odds of OOAT when compared with adults enrolled in any other type of health plan. At least 25% greater odds of receiving an oral antiviral was observed when comparing each of these health plans with those adults enrolled in HDHPs in the total study sample. Across all annual cohorts, at least 15% greater odds of OOAT were seen when salaried primary beneficiaries were compared with primary beneficiaries who were paid hourly.

Geographic Characteristics

In 2 of 3 annual cohorts, increased odds of OOAT were observed for adults living in more urban areas, with at least 20% greater odds when those in large metro areas were compared with adults living in rural areas (Table 2). Lower odds of OOAT were associated with adults living in the North Central region compared with the Northeast region across all cohorts. Adults residing in the South region had at least a 25% greater chance of receiving an oral antiviral versus adults living in the Northeast region across all annual cohorts.

Clinical Characteristics

Adults who were vaccinated for influenza had at least 10% greater odds of receiving an outpatient oral antiviral than those who were unvaccinated across all annual cohorts (Table 2). Higher CCI scores and presence of a respiratory condition was not associated with odds of OOAT in adults in any of the annual cohorts.

Children/Adolescents

Demographic Characteristics

Slightly higher odds of outpatient oral antiviral treatment were associated with older age of children/adolescents (Table 3). Across all annual cohorts, female children/adolescents had lower odds of OOAT than males. Those children/adolescents enrolled in a HDHP had lower odds of OOAT when compared with any other type of health plan. When each of these types of health plans was compared to HDHPs,

children/adolescents had at least 30% greater odds of receiving an antiviral than children/adolescents enrolled in a HDHP in the total study population.

Children/adolescents of primary beneficiaries who were salaried had higher odds of OOAT than children/adolescents of beneficiaries who were paid hourly across all cohorts.

Geographic Characteristics

Generally, level of rurality was not associated with odds of OOAT when children/adolescents living in rural areas were compared with those living in more urban areas (Table 3). Children/adolescents living in the Northeast region had lower odds of OOAT when compared with those living in any other region across all cohorts. Within the entire study population, children/adolescents living in the South had 50% greater odds of receiving an influenza antiviral than those living in the Northeast region.

Clinical Characteristics

Children/adolescents with a higher CCI score were more likely to receive an antiviral than those with lower CCI scores (Table 3). Vaccination against influenza increased the odds of OOAT by at least 20% when compared with children/adolescents who were not vaccinated. Higher odds of OOAT were seen in children/adolescents with a respiratory condition compared to those with no such conditions.

Secondary Analysis- OOAT within 2 days of influenza diagnosis

No significant differences in characteristics were seen when each cohort was examined for outpatient oral antiviral treatment within 2 days of influenza diagnosis in both adults and children/adolescents (Appendix 6, Appendix 7). Only 0.5% of the sample size was lost from the study population when filtering for OOAT within 2 days of influenza diagnosis.

Goodness-of-Fit

The model fit the data well in 2 of 3 cohorts and 1 of 3 cohorts when applied to adults and children/adolescents, respectively (Table 2, Table 3).

Discussion

We examined the association of demographic, geographic, and clinical characteristics with oral outpatient antiviral treatment across three annual cohorts in a retrospective cohort study of US commercially insured beneficiaries <65 years of age diagnosed with influenza. Female beneficiaries were found to have lower odds of OOAT than male patients across all ages and annual cohorts. Generally, adult beneficiaries living in rural areas had lower odds of receiving an antiviral when compared with adults in more urban areas. A consistently large difference between odds of OOAT was seen when residents living in the South were compared to those living in the Northeast region across all ages and cohorts. Beneficiaries enrolled in high deductible health plans, or similarly structured plans, experienced lower odds of OOAT when compared with any other type of health plan across all ages and annual cohorts. Beneficiaries whose primary beneficiary was salaried had a greater chance of receiving an antiviral than those whose primary beneficiary was paid hourly across all ages and annual cohorts. Influenza vaccination increased the likelihood of receiving OOAT across all ages and cohorts.

Results of this study suggest that disparities may exist in influenza OOAT regarding those living in rural areas. Further research is needed that assess better proxies of socioeconomic status for OOAT than the ones used in this study (hourly versus salary pay of the primary beneficiary and enrollment in a high deductible health plan). The decreased likelihood of females to receive OOAT should also be further investigated for potential explanations. Finally, the large association of living in the South region with OOAT should be further studied using smaller geographic units to better understand the differences within a given region.

Generally, our results conflict with previously published literature on odds of receiving influenza antivirals (12, 21). Franklin et. al found that those living in urban areas were less likely to receive OOAT, whereas Leon et. al found no difference by rural vs. urban living in a disabled Medicaid population. However, both studies dichotomized the characteristic as urban or rural compared to NCHS's classification scheme that our study used. Additionally, no difference in OOAT was found between males and females in either study. Notably, females only had a slightly decreased odds (<10%) of OOAT in our study. Franklin et. al found the same increased odds of OOAT in those living in the South. Both studies did not assess health plan type or any of the clinical characteristics evaluated in our analysis. High deductible health plans have been shown to be associated with a reduction of healthcare utilization in general (22). Franklin et. al found that those living in zip codes with higher median incomes were more likely to receive OOAT than those in lower income zip codes. Leon et. al reported that beneficiaries that identified as Black had lower odds of receiving an antiviral than all other race categories. These findings, along with our findings, strengthen the argument for further investigation into disparities within influenza antiviral treatment.

A major limitation of this study stems from the nature of the Marketscan® database, which did not allow for smaller geographic units other than MSA to be assessed. This lack of granularity was partially addressed with the rurality classification allowing individual counties to be represented in the rurality calculation for each MSA. Another limitation inherent to Marketscan® is that it is known to oversample the Southern region. In addition, there were some variables with a moderate degree of missingness. Notably, employment classification likely has a lower degree of missingness than reported due to our dataset coding "union," "non-union," and "other" as missing. This variable was tested in and out of our adjusted model, and goodness of fit did not substantively change.

Conclusions

We analyzed demographic, geographic, and clinical characteristics associated with influenza oral antiviral treatment in a US commercially insured population. Generally, lower odds of receiving an antiviral were seen in beneficiaries who were female, lived in more rural areas, with a primary beneficiary paid hourly, and enrolled in a high deductible health plan. Higher odds of receiving an antiviral were seen in those living in the South. Taken together, these results suggest that influenza oral antiviral treatment should be further studied as another potential source of health disparities within influenza prevention and treatment.

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Figures and Tables

Figure 1: Overall Study Design.

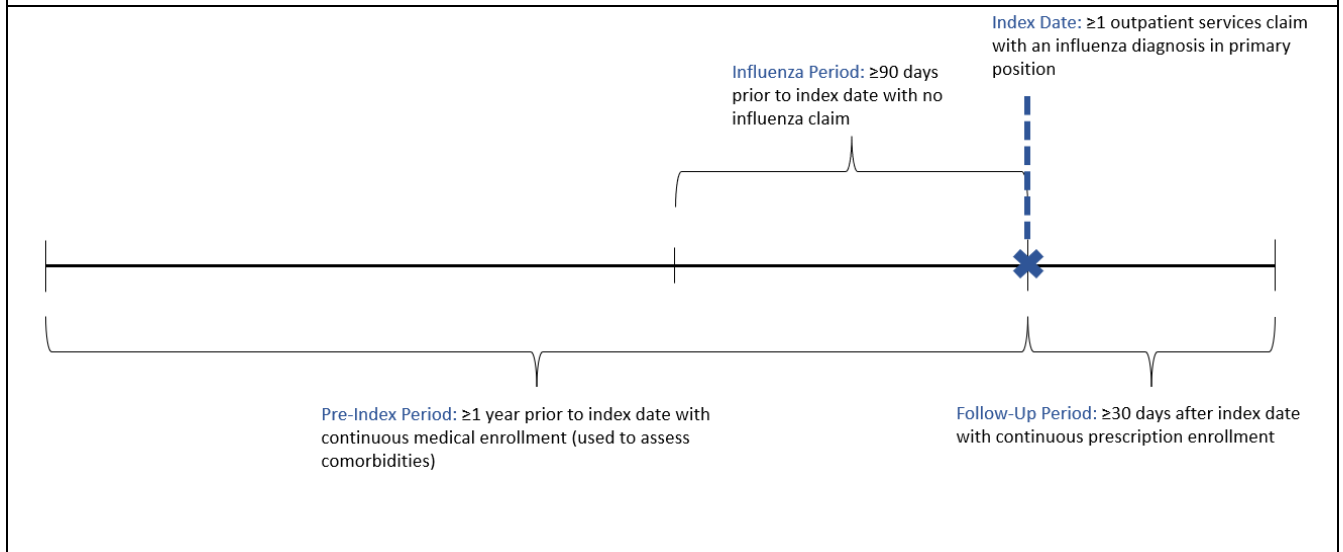


Figure 2: Annual Cohort Construction.

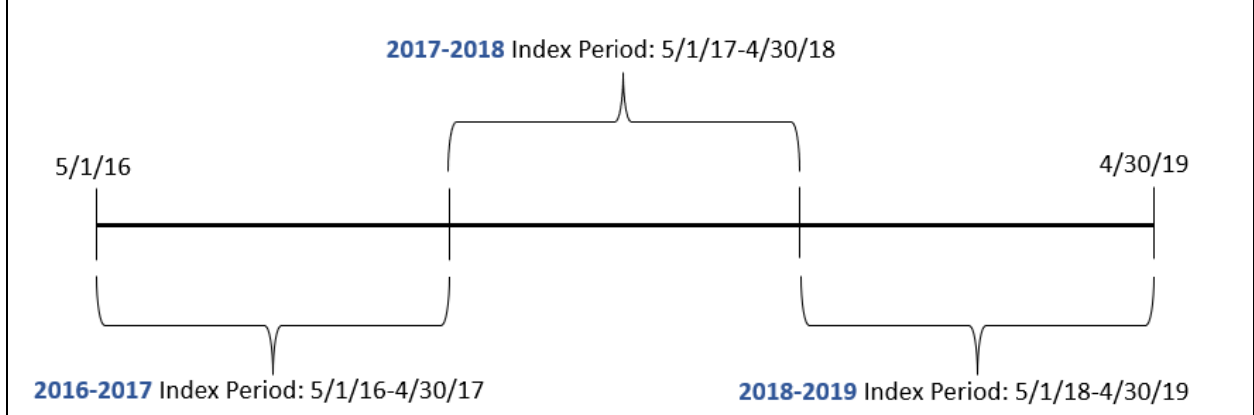


Figure 3: Sample Attrition Diagram.

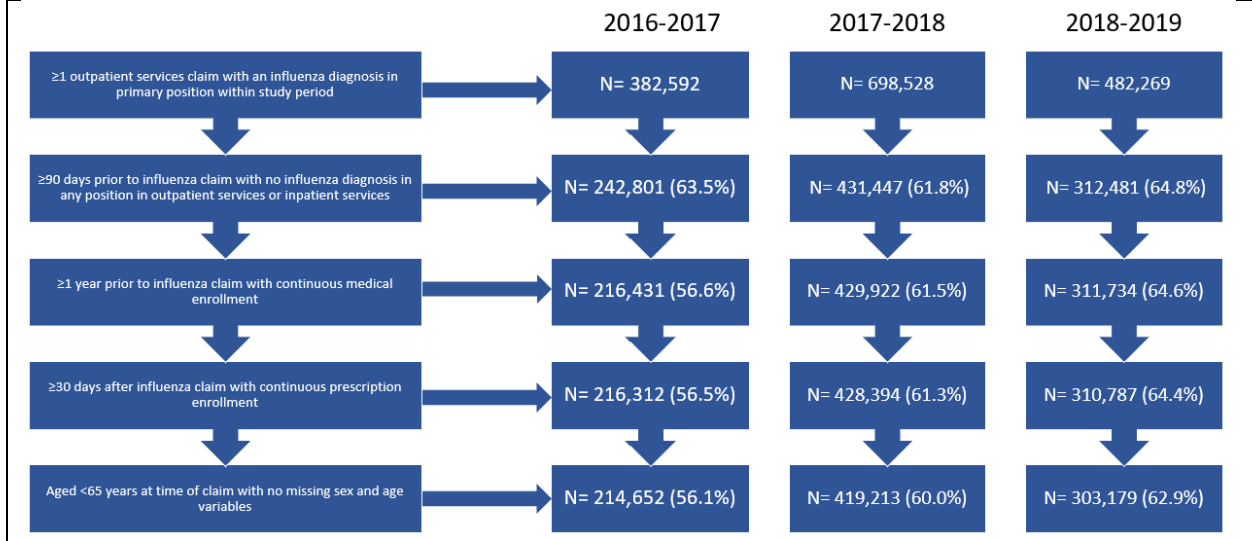


Table 1: Baseline Characteristics of Annual Cohorts.

	2016-2017	2017-2018	2018-2019	Total
	N=214,652	N=419,213	N=303,179	N=937,044
Age (Mean (SD))	28.3 (20)	29.8 (20)	25.7 (19)	28.1 (20)
Sex (# male) (n (%))	92,310 (43)	176,341 (42)	129,770 (43)	398,421 (43)
Level of Rurality (n (%))				
Rural	31,692 (15)	56,447 (14)	39,262 (13)	127,401 (14)
Micropolitan	30,816 (14)	56,432 (14)	37,695 (12)	124,943 (13)
Small Metro	13,425 (6)	22,326 (5)	15,315 (5)	51,066 (5)
Medium Metro	33,416 (16)	64,943 (16)	46,637 (15)	144,996 (16)
Large Fringe Metro	83,904 (39)	175,308 (42)	126,344 (42)	385,556 (41)
Large Central Metro	5,156 (2)	12,249 (3)	9,902 (3)	27,307 (3)
Geographic Region (n (%))				
Northeast	32,634 (15)	57,930 (14)	54,993 (18)	145,557 (16)
North Central	30,108 (14)	66,959 (16)	43,628 (14)	140,695 (15)
South	136,326 (64)	257,652 (62)	175,147 (58)	569,125 (61)
West	14,635 (7)	35,190 (8)	28,093 (9)	77,918 (8)
Health Plan Type (n (%))				
CDHP/HDHP	46,357 (22)	96,465 (23)	71,667 (24)	214,489 (23)
EPO/PPO	125,426 (58)	223,323 (53)	162,711 (54)	511,460 (55)
B/MM/COMP	4,788 (2)	8,404 (2)	3,979 (1)	17,171 (2)
HMO	18,224 (9)	40,155 (10)	29,600 (10)	87,979 (9)
Non-Cap POS	15,460 (7)	36,850 (9)	26,566 (9)	78,876 (8)
Cap/Part Cap POS	1,346 (1)	3,161 (1)	2,838 (1)	7,345 (1)
Employment Classification (# salary) (n (%))	55,426 (26)	114,155 (27)	81,339 (27)	250,920 (27)
CCI Score (Mean (SD))	0.46 (1.02)	0.45 (1.04)	0.41 (0.98)	0.44 (1.02)
Influenza Vaccination Status (# vaccinated) (n (%))	52,229 (24)	111,499 (27)	103,763 (34)	267,491 (29)
Respiratory Condition Diagnosis (n (%))	28,670 (13)	52,403 (13)	39,380 (13)	120,453 (13)

Abbreviations: CDHP/HDHP = consumer-driven health plan/high deductible health plan, EPO/PPO = exclusive provider organization/preferred provider organization, B/MM/COMP = basic/major medical/comprehensive, HMO = health maintenance organization, Non-Cap POS = non-capitated point of service, Cap/Part Cap POS = capitated or partially capitated point of service, CCI = Charlson Comorbidity Index

Table 2: Adjusted Odds Ratios (95% CI) of OOAT- Adults (≥18 years of age).

	2016-2017	2017-2018	2018-2019	Total
Age	1.002 (1.001-1.003) ^c	1.004 (1.003-1.005) ^c	1.004 (1.003-1.004) ^c	1.004 (1.003-1.004) ^c
Sex				
Male	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Female	0.93 (0.91-0.96) ^c	0.93 (0.92-0.95) ^c	0.94 (0.92-0.96) ^c	0.93 (0.92-0.94) ^c
Level of Rurality				
Rural	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Micropolitan	1.22 (1.17-1.28) ^c	1.11 (1.07-1.14) ^c	1.20 (1.15-1.25) ^c	1.16 (1.14-1.19) ^c
Small Metro	0.95 (0.90-1.01)	1.03 (0.99-1.07)	1.14 (1.08-1.20) ^c	1.04 (1.01-1.07) ^b
Medium Metro	0.97 (0.93-1.01)	1.12 (1.08-1.15) ^c	1.23 (1.19-1.28) ^c	1.12 (1.09-1.14) ^c
Large Fringe Metro	1.09 (1.05-1.13) ^c	1.23 (1.19-1.26) ^c	1.33 (1.29-1.38) ^c	1.22 (1.20-1.24) ^c
Large Central Metro	1.03 (0.95-1.13)	1.28 (1.21-1.35) ^c	1.56 (1.46-1.67) ^c	1.29 (1.24-1.35) ^c
Geographic Region				
Northeast	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
North Central	0.87 (0.83-0.91) ^c	0.87 (0.85-0.90) ^c	0.94 (0.90-0.98) ^b	0.90 (0.88-0.92) ^c
South	1.48 (1.43-1.54) ^c	1.42 (1.38-1.45) ^c	1.25 (1.21-1.29) ^c	1.39 (1.36-1.41) ^c
West	0.84 (0.80-0.88) ^c	0.85 (0.82-0.88) ^c	0.98 (0.94-1.03)	0.89 (0.87-0.91) ^c
Health Plan Type				
CDHP/HDHP	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
EPO/PPO	1.21 (1.17-1.24) ^c	1.29 (1.26-1.32) ^c	1.28 (1.25-1.32) ^c	1.27 (1.25-1.29) ^c
B/MM/COMP	0.95 (0.88-1.03)	1.15 (1.09-1.22) ^c	1.04 (0.96-1.14)	1.07 (1.03-1.11) ^b
HMO	1.25 (1.19-1.31) ^c	1.29 (1.25-1.33) ^c	1.31 (1.26-1.37) ^c	1.29 (1.26-1.32) ^c
Non-Cap POS	1.17 (1.11-1.23) ^c	1.24 (1.20-1.28) ^c	1.34 (1.28-1.40) ^c	1.27 (1.24-1.30) ^c
Cap or Part Cap POS	1.89 (1.61-2.23) ^c	1.61 (1.45-1.79) ^c	0.89 (0.80-0.996) ^a	1.32 (1.23-1.41) ^c
Employment Classification*				
Hourly	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Salary	1.21 (1.17-1.25) ^c	1.20 (1.17-1.23) ^c	1.16 (1.13-1.19) ^c	1.19 (1.17-1.21) ^c
CCI Score	0.99 (0.98-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.01)	1.00 (0.99-1.00)
Influenza Vaccine				
Unvaccinated	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Vaccinated	1.13 (1.10-1.16) ^c	1.22 (1.19-1.24) ^c	1.13 (1.10-1.16) ^c	1.16 (1.15-1.18) ^c
Respiratory Condition				
No Respiratory Condition	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Respiratory Condition	0.96 (0.93-1.00)	0.98 (0.95-1.00)	0.99 (0.95-1.02)	0.98 (0.96-0.99) ^b
Hosmer Lemeshow Goodness of Fit p-value	0.34	0.22	0.001	0.01

^ap<0.05; ^bp<0.01; ^cp<0.001; *employment classification of the primary beneficiary; Abbreviations: OOAT = outpatient oral antiviral treatment, CDHP/HDHP = consumer-driven health plan/high deductible health plan, EPO/PPO = exclusive provider organization/preferred provider organization, B/MM/COMP = basic/major medical/comprehensive, HMO = health maintenance organization, Non-Cap POS = non-capitated point of service, Cap/Part Cap POS = capitated or partially capitated point of service, CCI = Charlson Comorbidity Index

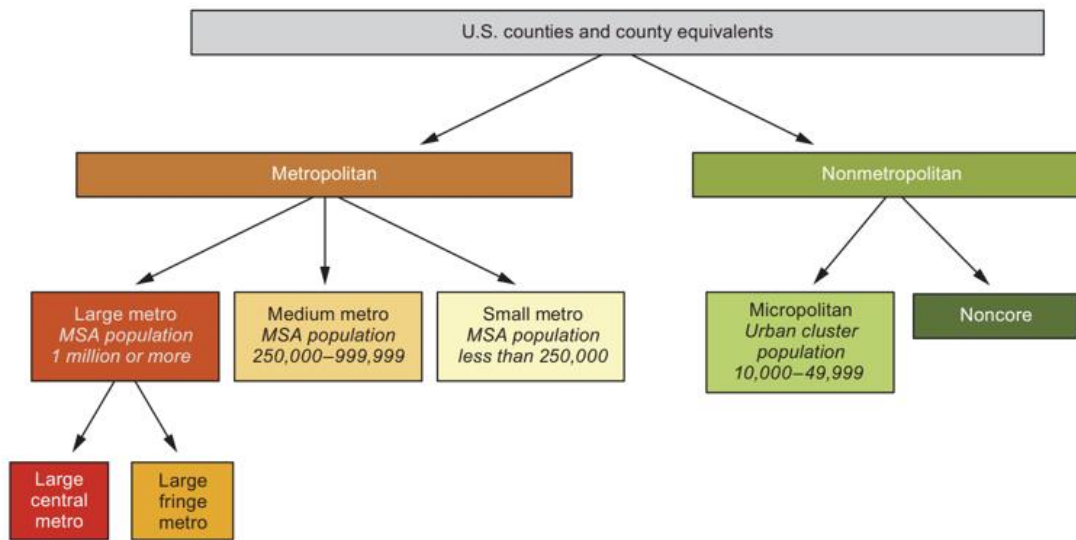
Table 3: Adjusted Odds Ratios (95% CI) of OOAT- Children/Adolescents (<18 years of age).

	2016-2017	2017-2018	2018-2019	Total
Age	1.04 (1.04-1.04) ^c	1.03 (1.03-1.03) ^c	1.02 (1.02-1.03) ^c	1.03 (1.03-1.03) ^c
Sex				
Male	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Female	0.96 (0.93-0.98) ^b	0.94 (0.92-0.96) ^c	0.95 (0.93-0.98) ^c	0.95 (0.94-0.96) ^c
Level of Rurality				
Rural	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Micropolitan	0.95 (0.90-1.00)	0.85 (0.82-0.89) ^c	0.93 (0.89-0.98) ^b	0.91 (0.89-0.94) ^c
Small Metro	0.86 (0.81-0.92) ^c	0.92 (0.87-0.97) ^b	1.06 (1.00-1.12)	0.95 (0.92-0.99) ^c
Medium Metro	0.90 (0.86-0.95) ^c	0.97 (0.93-1.01)	1.08 (1.04-1.11) ^b	0.99 (0.97-1.02)
Large Fringe Metro	0.87 (0.84-0.91) ^c	0.99 (0.96-1.02)	1.07 (1.03-1.11) ^c	0.99 (0.97-1.01)
Large Central Metro	0.80 (0.72-0.89) ^c	0.96 (0.89-1.03)	1.10 (1.03-1.18) ^b	0.98 (0.93-1.02)
Geographic Region				
Northeast	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
North Central	1.06 (1.01-1.12) ^a	1.11 (1.06-1.15) ^c	1.08 (1.04-1.13) ^b	1.10 (1.07-1.12) ^c
South	1.58 (1.52-1.65) ^c	1.56 (1.51-1.62) ^c	1.38 (1.33-1.43) ^c	1.50 (1.47-1.53) ^c
West	1.16 (1.08-1.25) ^c	1.29 (1.22-1.35) ^c	1.45 (1.38-1.52) ^c	1.34 (1.30-1.38) ^c
Health Plan Type				
CDHP/HDHP	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
EPO/PPO	1.31 (1.26-1.35) ^c	1.36 (1.32-1.40) ^c	1.48 (1.44-1.52) ^c	1.40 (1.37-1.42) ^c
B/MM/COMP	1.34 (1.21-1.48) ^c	1.32 (1.21-1.43) ^c	1.49 (1.35-1.66) ^c	1.38 (1.30-1.45) ^c
HMO	1.20 (1.14-1.27) ^c	1.26 (1.21-1.32) ^c	1.52 (1.45-1.58) ^c	1.34 (1.31-1.37) ^c
Non-Cap POS	1.34 (1.26-1.43) ^c	1.46 (1.40-1.53) ^c	1.55 (1.48-1.62) ^c	1.49 (1.45-1.53) ^c
Cap or Part Cap POS	1.85 (1.50-2.27) ^c	1.64 (1.43-1.88) ^c	1.20 (1.06-1.35) ^b	1.43 (1.31-1.55) ^c
Employment Classification*				
Hourly	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Salary	1.09 (1.05-1.14) ^c	1.10 (1.06-1.13) ^c	1.17 (1.14-1.21) ^c	1.13 (1.11-1.15) ^c
CCI Score	1.07 (1.03-1.12) ^c	1.10 (1.07-1.14) ^c	1.13 (1.09-1.17) ^c	1.10 (1.08-1.13) ^c
Influenza Vaccine				
Unvaccinated	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Vaccinated	1.21 (1.17-1.24) ^c	1.25 (1.22-1.27) ^c	1.20 (1.17-1.23) ^c	1.21 (1.20-1.23) ^c
Respiratory Condition				
No Respiratory Condition	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Respiratory Condition	1.14 (1.08-1.20) ^c	1.13 (1.08-1.18) ^c	1.10 (1.05-1.15) ^c	1.12 (1.09-1.15) ^c
Hosmer Lemeshow	0.21	0.01	0.0003	0.00001
Goodness of Fit p-value				

^ap<0.05; ^bp<0.01; ^cp<0.001; *employment classification of the primary beneficiary; Abbreviations: OOAT = outpatient oral antiviral treatment, CDHP/HDHP = consumer-driven health plan/high deductible health plan, EPO/PPO = exclusive provider organization/preferred provider organization, B/MM/COMP = basic/major medical/comprehensive, HMO = health maintenance organization, Non-Cap POS = non-capitated point of service, Cap/Part Cap POS = capitated or partially capitated point of service, CCI = Charlson Comorbidity Index

Appendix

Appendix 1: NCHS's Urban-Rural Classification Scheme for Counties



Abbreviations: NCHS = National Center for Health Statistics, MSA = Metropolitan Statistical Area

Appendix 2: Influenza Vaccination NDC and CPT codes.

Influenza Vaccine NDC codes

00003132510, 00003132610, 00003132810, 00003132901,
00003132910, 00003133010, 00003133210, 00003133301,
00003133315, 00003133410, 00003133501, 00003133515,
00003133710, 00003133801, 00003133815, 00003133910,
00003134015, 00003134031, 00003134110, 00003134215,
00003134231, 00008064701, 00008064702, 00008068501,
00008068502, 00008069901, 00008069902, 00008073001,
00008073002, 00008076001, 00008076002, 00008079501,
00008079502, 00008080801, 00008080802, 00071400608,
00071408508, 00071408608, 00071408640, 00071408708,
00071408740, 00071408808, 00071408840, 00071408908,
00071408940, 00071409008, 00071409040, 00071409108,
00071409140, 19515081641, 19515081652, 19515089101,
19515089111, 19515089302, 19515089307, 19515089441,
19515089452, 19515089601, 19515089611, 19515089701,
19515089711, 19515089801, 19515089811, 19515090001,
19515090011, 19515090301, 19515090311, 19515090641,
19515090652, 19515090841, 19515090852, 19515090941,
19515090952, 19515091241, 19515091252, 19650010001,
19650010010, 33332001301, 33332001302, 33332001401,
33332001402, 33332001501, 33332001502, 33332001601,
33332001602, 33332001701, 33332001702, 33332001801,
33332001802, 33332011110, 33332011310, 33332011311,
33332011410, 33332011411, 33332011510, 33332011511,
33332011610, 33332011611, 33332011710, 33332011711,
33332011810, 33332011811, 33332021920, 33332021921,
33332022020, 33332022021, 33332031601, 33332031602,
33332031701, 33332031702, 33332031801, 33332031802,
33332031901, 33332031902, 33332032001, 33332032002,
33332041710, 33332041711, 33332041810, 33332041811,
33332041910, 33332041911, 33332042010, 33332042011,
33335001301, 42874001401, 42874001410, 42874001501,
42874001510, 42874001601, 42874001610, 42874001701,
42874001710, 42874011701, 42874011710, 49281001450,
49281001488, 49281012065, 49281012088, 49281039415,
49281039478, 49281039565, 49281039588, 49281039615,
49281039678, 49281039765, 49281039788, 49281039965,
49281039988, 49281040165, 49281040188, 49281040365,
49281040388, 49281040565, 49281040588, 49281041410,
49281041450, 49281041458, 49281041488, 49281041510,
49281041550, 49281041558, 49281041588, 49281041610,
49281041650, 49281041658, 49281041688, 49281041710,
49281041750, 49281041758, 49281041788, 49281041810,
49281041850, 49281041858, 49281041888, 49281041910,
49281041950, 49281041958, 49281041988, 49281042010,
49281042050, 49281042058, 49281042088, 49281051400,
49281051425, 49281051500, 49281051525, 49281051600,
49281051625, 49281051700, 49281051725, 49281051800,
49281051825, 49281051900, 49281051925, 49281062115,
49281062178, 49281062315, 49281062378, 49281062515,
49281062578, 49281062715, 49281062778, 49281062915,
49281062978, 49281063115, 49281063178, 49281063315,
49281063378, 49281064015, 49281065010, 49281065025,
49281065050, 49281065070, 49281065090, 49281070840,
49281070848, 49281070948, 49281070955, 49281071040,
49281071048, 49281071240, 49281071248, 49281071810,
49281071888, 49281071910, 49281071988, 49281072010,
49281072088, 53014010001, 53014010010, 54569597100,
54868594100, 58160087952, 58160088141, 58160088152,
58160088541, 58160088552, 58160089641, 58160089652,
58160089841, 58160089852, 58160090141, 58160090152,
58160090341, 58160090352, 58160090541, 58160090552,
58160090741, 58160090752, 62577061301, 62577061311,
62577061401, 62577061411, 63851061101, 63851061201,

	64029409801, 64029409802, 66019030101, 66019030110, 66019030201, 66019030210, 66019030301, 66019030310, 66019030401, 66019030410, 66019030501, 66019030510, 66019030601, 66019030610, 66019030701, 66019030710, 66521000001, 66521000011, 66521011502, 66521011510, 66521011602, 66521011610, 66521011611, 66521011612, 66521011702, 66521011710, 66521011711, 66521011712, 66521011802, 66521011810, 66521011811, 66521011812, 70461000101, 70461000111, 70461000201, 70461000211, 70461001803, 70461001804, 70461001903, 70461001904, 70461002003, 70461002004, 70461011902, 70461011910, 70461011911, 70461011912, 70461012002, 70461012003, 70461012004, 70461012010, 70461012011, 70461012012, 70461020001, 70461020011, 70461020101, 70461020111, 70461030110, 70461030112, 70461031803, 70461031804, 70461031903, 70461031904, 70461032003, 70461032004, 70461041810, 70461041811, 70461041910, 70461041911, 70461042010, 70461042011, 76420049101, 76420049301, 76420049501, 76420051001, 76420051101, 76420051501, 76420051701, 76420052101
Influenza Vaccine CPT codes	90630, 90653, 90654, 90655, 90656, 90657, 90658, 90660, 90662, 90672, 90673, 90674, 90682, 90685, 90686, 90687, 90688, 90689, 90694, 90756, Q2034, Q2035, Q2036, Q2037, Q2038, Q2039, G0008
Abbreviations: NDC = National Drug Code, CPT = Common Procedural Terminology	

[Appendix 3: Respiratory Condition ICD codes.](#)

Asthma ICD-9,-10 codes	493.xx, J45.xx
COPD ICD-9,-10 codes	492.xx, 496.xx, J43.xx, J44.xx
Chronic Bronchitis ICD-9,-10 codes	491.xx, J40.xx, J41.xx, J42.xx
Bronchiectasis ICD-9,-10 codes	494.xx, J47.xx
Interstitial Lung Disease ICD-9,-10 codes	515.xx, 516.3, J84.xx
Abbreviations: ICD = International Classification of Diseases	

Appendix 4: Oral Influenza Antiviral NDC codes.

Oseltamivir NDC codes	00004080085, 00004080185, 00004080285, 00004082205, 00093818064, 16714081701, 16714081801, 16714081901, 27241013909, 31722063031, 31722063131, 31722063231, 33261058601, 33342025666, 33342025766, 33342025866, 38779310203, 38779310204, 38779310205, 38779310208, 42291056760, 42291066410, 42291066610, 47781038426, 47781046813, 47781046913, 47781047013, 50090124400, 50090272600, 50090334500, 52959080110, 52959083200, 53217028001, 54569488800, 54569626400, 54569671000, 54569677300, 54868447600, 54868608300, 54868631500, 55700079310, 55700079860, 62332041310, 62332041410, 62332041510, 63739003807, 63739004407, 63739005007, 63874009810, 64380079701, 64380079801, 64380079901, 68180067511, 68180067611, 68180067711, 68180067801, 68788728501, 68788729601, 68788760006, 69238126401, 69238126501, 69238126601, 69238127306, 70710100802, 70710100902, 70710101002, 70710116506, 71205010710, 71205020610, 71205035910, 71205036010, 71205039710, 71205041710, 72205004211, 72205004311, 72205004411
Baloxavir Marboxil NDC codes	50242082802, 50242082886, 50242086002, 50242086087
Abbreviations: NDC = National Drug Code	

Appendix 5: Missing Variable Proportions (N (%)).

	2016-2017	2017-2018	2018-2019	Total
Geographic Region	949 (0.4)	1,482 (0.4)	1,318 (0.4)	3,749 (0.4)
Health Plan Type	3,051 (1.4)	10,855 (2.6)	5,818 (1.9)	19,724 (2.1)
Employment Classification*	106,131 (49.4)	201,025 (48.0)	149,846 (49.4)	457,002 (48.8)
Level of Rurality	16,243 (7.6)	31,508 (7.5)	28,024 (9.2)	75,775 (8.1)

*Includes any employment classification of the primary beneficiary that did not specify hourly or salary

Appendix 6: Secondary Analysis of Adjusted Odds Ratios (95% CI) of Receipt of Antiviral within 2 Days of Influenza Diagnosis- Adults (≥18 years of age).

	2016-2017	2017-2018	2018-2019	Total
Age	1.002 (1.001-1.003) ^c	1.004 (1.003-1.004) ^c	1.004 (1.003-1.004) ^c	1.004 (1.003-1.004) ^c
Sex				
Male	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Female	0.93 (0.91-0.95) ^c	0.93 (0.92-0.95) ^c	0.94 (0.92-0.96) ^c	0.93 (0.92-0.94) ^c
Level of Rurality				
Rural	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Micropolitan	1.23 (1.17-1.28) ^c	1.11 (1.07-1.14) ^c	1.20 (1.15-1.25) ^c	1.16 (1.14-1.19) ^c
Small Metro	0.95 (0.90-1.01)	1.03 (0.99-1.07)	1.14 (1.08-1.20) ^c	1.04 (1.02-1.07) ^b
Medium Metro	0.97 (0.93-1.02)	1.12 (1.08-1.15) ^c	1.24 (1.19-1.28) ^c	1.12 (1.09-1.14) ^c
Large Fringe Metro	1.09 (1.05-1.13) ^c	1.23 (1.20-1.26) ^c	1.33 (1.29-1.38) ^c	1.22 (1.20-1.24) ^c
Large Central Metro	1.03 (0.94-1.12)	1.27 (1.20-1.35) ^c	1.56 (1.45-1.67) ^c	1.29 (1.24-1.34) ^c
Geographic Region				
Northeast	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
North Central	0.87 (0.83-0.91) ^c	0.87 (0.85-0.90) ^c	0.94 (0.90-0.98) ^b	0.90 (0.88-0.92) ^c
South	1.48 (1.43-1.54) ^c	1.42 (1.38-1.45) ^c	1.25 (1.22-1.29) ^c	1.39 (1.36-1.41) ^c
West	0.84 (0.79-0.88) ^c	0.84 (0.81-0.88) ^c	0.98 (0.94-1.03)	0.89 (0.87-0.91) ^c
Health Plan Type				
CDHP/HDHP	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
EPO/PPO	1.21 (1.17-1.25) ^c	1.29 (1.26-1.31) ^c	1.28 (1.25-1.32) ^c	1.27 (1.25-1.29) ^c
B/MM/COMP	0.95 (0.88-1.02)	1.15 (1.09-1.22) ^c	1.04 (0.96-1.14)	1.07 (1.03-1.11) ^b
HMO	1.25 (1.19-1.31) ^c	1.29 (1.25-1.33) ^c	1.31 (1.26-1.37) ^c	1.29 (1.26-1.31) ^c
Non-Cap POS	1.17 (1.11-1.23) ^c	1.24 (1.20-1.28) ^c	1.34 (1.28-1.40) ^c	1.27 (1.24-1.30) ^c
Cap or Part Cap POS	1.88 (1.60-2.22) ^c	1.61 (1.45-1.79) ^c	0.89 (0.80-0.99) ^a	1.31 (1.23-1.41) ^c
Employment Classification*				
Hourly	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Salary	1.21 (1.17-1.25) ^c	1.20 (1.17-1.23) ^c	1.16 (1.13-1.20) ^c	1.20 (1.18-1.21) ^c
CCI Score	0.99 (0.98-0.99) ^b	1.00 (0.99-1.00)	1.00 (0.99-1.01)	0.99 (0.99-0.99) ^b
Influenza Vaccine				
Unvaccinated	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Vaccinated	1.13 (1.10-1.16) ^c	1.22 (1.19-1.24) ^c	1.13 (1.10-1.16) ^c	1.16 (1.15-1.18) ^c
Respiratory Condition				
No Respiratory Condition	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Respiratory Condition	0.96 (0.93-0.99) ^a	0.97 (0.95-1.00)	0.98 (0.95-1.02)	0.97 (0.96-0.99) ^b
Hosmer Lemeshow Goodness of Fit p-value	0.28	0.24	0.0005	0.02

^ap<0.05; ^bp<0.01; ^cp<0.001; *employment classification of the primary beneficiary; Abbreviations: OOAT = outpatient oral antiviral treatment, CDHP/HDHP = consumer-driven health plan/high deductible health plan, EPO/PPO = exclusive provider organization/preferred provider organization, B/MM/COMP = basic/major medical/comprehensive, HMO = health maintenance organization, Non-Cap POS = non-capitated point of service, Cap/Part Cap POS = capitated or partially capitated point of service, CCI = Charlson Comorbidity Index

Appendix 7: Secondary Analysis of Adjusted Odds Ratios (95% CI) of Receipt of Antiviral within 2 Days of Influenza Diagnosis- Children/Adolescents (<18 years of age).

	2016-2017	2017-2018	2018-2019	Total
Age	1.04 (1.04-1.04) ^c	1.03 (1.03-1.03) ^c	1.03 (1.02-1.03) ^c	1.03 (1.03-1.03) ^c
Sex				
Male	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Female	0.96 (0.93-0.98) ^b	0.94 (0.92-0.96) ^c	0.95 (0.93-0.98) ^c	0.95 (0.94-0.96) ^c
Level of Rurality				
Rural	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Micropolitan	0.95 (0.91-1.01)	0.85 (0.82-0.89) ^c	0.93 (0.89-0.98) ^b	0.91 (0.89-0.94) ^c
Small Metro	0.86 (0.81-0.92) ^c	0.92 (0.87-0.97) ^b	1.06 (1.00-1.12)	0.95 (0.92-0.99) ^b
Medium Metro	0.90 (0.86-0.95) ^c	0.97 (0.93-1.01)	1.08 (1.04-1.12) ^c	0.99 (0.97-1.02)
Large Fringe Metro	0.87 (0.84-0.91) ^c	0.99 (0.96-1.02)	1.08 (1.04-1.11) ^c	0.99 (0.97-1.01)
Large Central Metro	0.80 (0.72-0.89) ^c	0.96 (0.89-1.03)	1.11 (1.03-1.19) ^b	0.98 (0.93-1.02)
Geographic Region				
Northeast	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
North Central	1.06 (1.01-1.12) ^a	1.11 (1.06-1.15) ^c	1.08 (1.04-1.13) ^c	1.09 (1.07-1.12) ^c
South	1.58 (1.51-1.65) ^c	1.56 (1.51-1.62) ^c	1.38 (1.33-1.43) ^c	1.50 (1.47-1.53) ^c
West	1.16 (1.08-1.25) ^c	1.29 (1.23-1.35) ^c	1.44 (1.38-1.52) ^c	1.34 (1.30-1.38) ^c
Health Plan Type				
CDHP/HDHP	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
EPO/PPO	1.31 (1.26-1.35) ^c	1.36 (1.33-1.40) ^c	1.48 (1.44-1.52) ^c	1.40 (1.37-1.42) ^c
B/MM/COMP	1.34 (1.21-1.48) ^c	1.31 (1.21-1.43) ^c	1.49 (1.34-1.65) ^c	1.38 (1.30-1.45) ^c
HMO	1.21 (1.14-1.28) ^c	1.27 (1.22-1.32) ^c	1.51 (1.45-1.58) ^c	1.34 (1.31-1.38) ^c
Non-Cap POS	1.35 (1.27-1.43) ^c	1.47 (1.41-1.53) ^c	1.55 (1.48-1.62) ^c	1.49 (1.45-1.53) ^c
Cap or Part Cap POS	1.86 (1.51-2.28) ^c	1.65 (1.44-1.89) ^c	1.20 (1.06-1.35) ^b	1.43 (1.32-1.56) ^c
Employment Classification*				
Hourly	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Salary	1.10 (1.05-1.14) ^c	1.10 (1.07-1.13) ^c	1.17 (1.14-1.21) ^c	1.13 (1.11-1.15) ^c
CCI Score	1.08 (1.03-1.12) ^c	1.10 (1.07-1.14) ^c	1.13 (1.09-1.17) ^c	1.10 (1.08-1.12) ^c
Influenza Vaccine				
Unvaccinated	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Vaccinated	1.21 (1.17-1.25) ^c	1.25 (1.22-1.28) ^c	1.20 (1.18-1.23) ^c	1.22 (1.20-1.24) ^c
Respiratory Condition				
No Respiratory Condition	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Respiratory Condition	1.14 (1.08-1.20) ^c	1.13 (1.08-1.18) ^c	1.10 (1.05-1.15) ^c	1.12 (1.09-1.15) ^c
Hosmer Lemeshow Goodness of Fit p-value	0.36	0.01	0.0002	5.0e ⁻⁶

^ap<0.05; ^bp<0.01; ^cp<0.001; *employment classification of the primary beneficiary; Abbreviations: OOAT = outpatient oral antiviral treatment, CDHP/HDHP = consumer-driven health plan/high deductible health plan, EPO/PPO = exclusive provider organization/preferred provider organization, B/MM/COMP = basic/major medical/comprehensive, HMO = health maintenance organization, Non-Cap POS = non-capitated point of service, Cap/Part Cap POS = capitated or partially capitated point of service, CCI = Charlson Comorbidity Index