

Supplemental Online Content

Tran PT, Antonelli PJ, Hincapie-Castillo JM, Winterstein AJ. Association of US Food and Drug Administration removal of indications for use of oral quinolones with prescribing trends. *JAMA Intern Med*. Published online April 19, 2021. doi:10.1001/jamainternmed.2021.1154

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This supplemental material has been provided by the authors to give readers additional information about their work.

40 **eMethod 1. Model specification for interrupted time series analysis**

41 The ITS regression was modeled as

42 $Y_t = \beta_0 + \beta_1 * T_t + \beta_2 * X_t + \beta_3 * (T_t - T_0) * X_t + \beta_m * \text{month} + \varepsilon$ where,

43 β_0 (baseline level): prevalence of oral quinolone use at the beginning of the study
44 period;

45 β_1 (pre-label change trend): average monthly change of oral quinolone prevalence
46 between January 2013 and April 2016;

47 β_2 (level change): Immediate change in quinolone prevalence between April to May
48 2016;

49 β_3 (slope change): average monthly change in trend of oral quinolone use after the label
50 change;

51 T_t : time since January 2013;

52 T_0 : time of the label change in May 2016;

53 X_t : dummy variable for pre and post label change;

54 β_m : a series of indicators for calendar months; ε : the random error term.

55 We assumed the level and the trend of oral quinolones after May 2016 would have
56 remained the same as before if no label changes of quinolones were introduced (i.e.,
57 counterfactual).

58 We provided monthly aggregated data of our main analyses for replication in **eTable 8**.

59 For falsification analysis we applied the same model to a series of hypothetical change
60 points surrounding the tested FDA label change. We fit models using the same 24
61 months period before and after each hypothesized change point and, to improve model
62 fit across data points with actual interruptions, an alternative set of models that used
63 only 12 months before and after. All other model specifications were identical.

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66 **eMethod 2: Specifications for the sensitivity analysis testing spill-over effects on**
67 **treatment of community-acquired pneumonia and examination of a negative**
68 **control cohort of with skin infections.**

69 For community-acquired pneumonia, similar to the other cohorts, patients ≥ 19
70 years of age entered the cohort at a new outpatient encounter with principal diagnosis
71 for pneumonia (**eTable 1**) (index day). We required patients to have continuous health
72 plan enrollment and prescription coverage 90 days before and 5 days after the index
73 day. This time window was used to exclude patients with other infections except upper
74 respiratory tract infections (**eTable 2**) and hospitalizations (to focus on community-
75 acquired pneumonia). We applied the same algorithm to measure antibiotics use as for
76 the three main study cohorts.

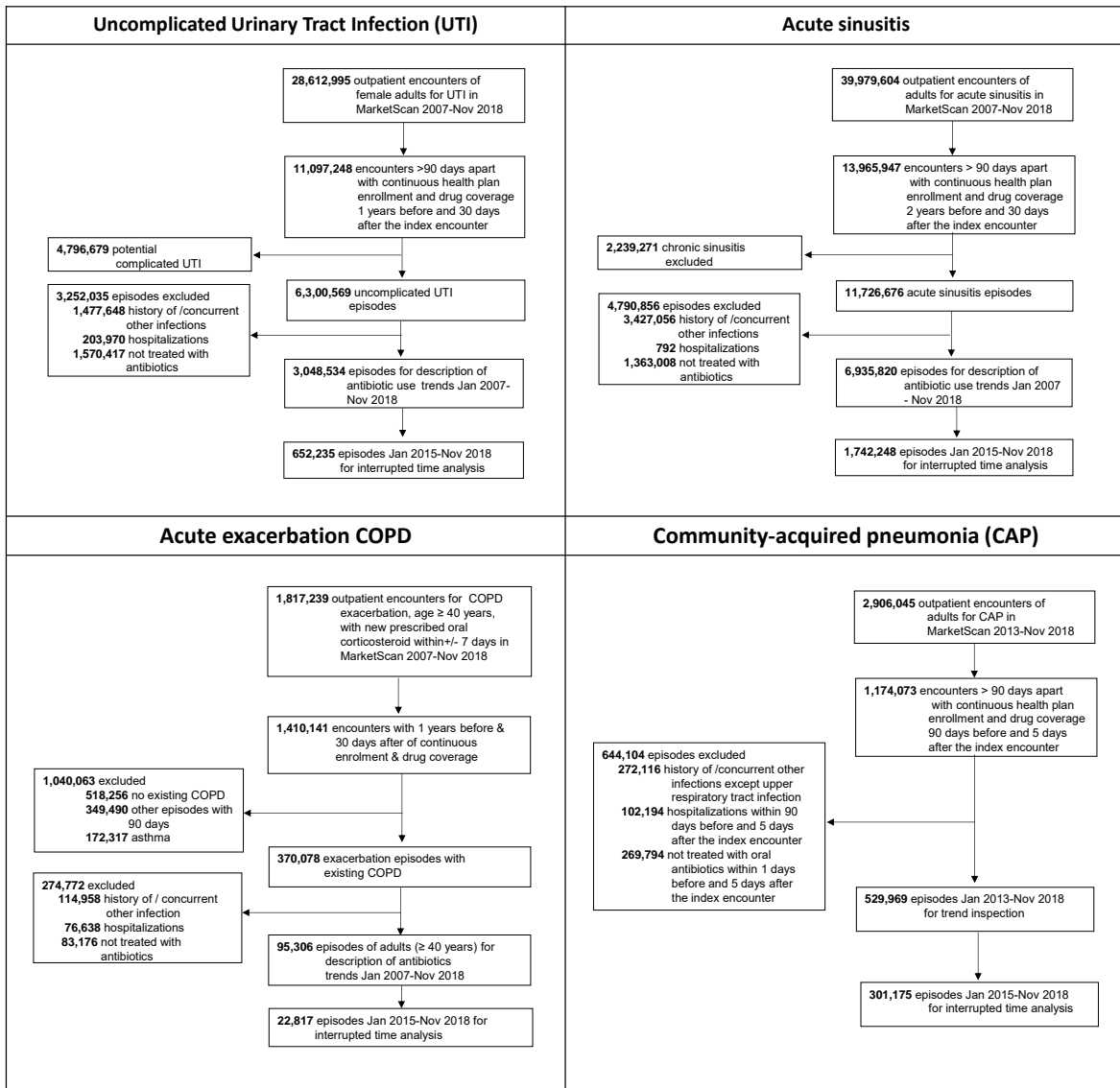
77 For examination of skin and soft tissue infections, adult patients (≥ 19 years of
78 age) entered for evaluation when they had a primary or secondary diagnosis for skin or
79 subcutaneous tissue infections in the outpatient setting (**eTable 1**). We required patients
80 to have continuous health plan enrollment and prescription coverage 365 days before
81 and 5 days after the index day to exclude history of diabetes and external injury which
82 may require quinolone use (**eTable 3**). We also excluded patients with previous
83 infections within 90 days and captured all dispensed non-quinolone antibiotics within ± 5
84 days of the index day similar to our main study cohorts. While quinolones are typically
85 not recommended for treatment of soft tissue infections, delafloxacin (a quinolone) was
86 approved specifically for skin infection in June 2017. Thus, we shortened the post label
87 change period (May 2016 to April 2017) to avoid any impact of this approval decision on
88 the interrupted time-series analysis. Of note, while the denominators of other analyses
89 were antibiotic-treated episodes, the denominator of this cohort included both episodes
90 of skin and soft tissue infections treated and non-treated with antibiotics.

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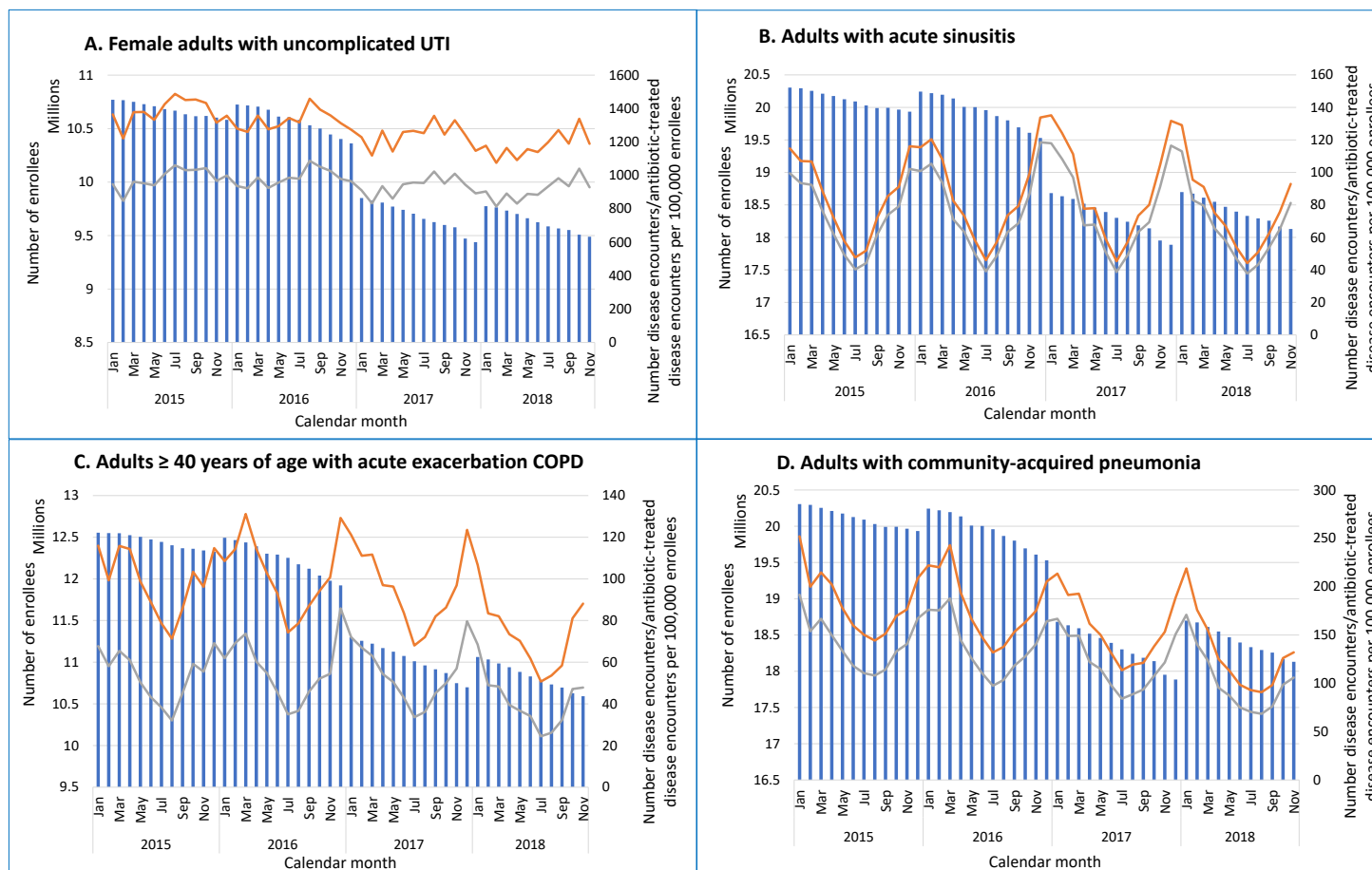
92 **eMethod 3: Joinpoint regression specifications**

93 Joinpoint regression has been developed by the National Cancer Institute
94 (<https://surveillance.cancer.gov/joinpoint/> accessed Dec 19, 2020). In brief, the software
95 detects natural breakpoints without any pre-specification using a Monte Carlo
96 permutation method. We specified a maximum of 3 break points, 10,000 permutations
97 and calculated 95% CI by empirical quantile (method 1) with 15,000 resamples. We
98 chose the option to fit autocorrelated errors model based on the data.

99 Joinpoint regression (i.e., change point or break point regression) assumes that data
100 can be divided into linear segments. In our case, we chose maximum of 3 break points
101 (i.e., 4 segments). The model will first fit with one point and identify the most significant
102 point in the time trend. The process is repeated with 2 break points, and 3 break points.
103 Finally, it will compare the fitted models and choose the best model. Joinpoint provides
104 significant break points with confidence intervals and an intercept and slope for each
105 segment. Our falsification test aimed to check whether our chosen point of the label
106 change is valid and thus, we reported only the significant break points, but the
107 intercepts and slopes can be found in the figure legends. **eFigure 1. Flow diagram for
108 inclusion and exclusion of enrollees to assemble study cohorts**



110 **eFigure 2. Trends of disease and antibiotic utilization rates for the four study conditions**

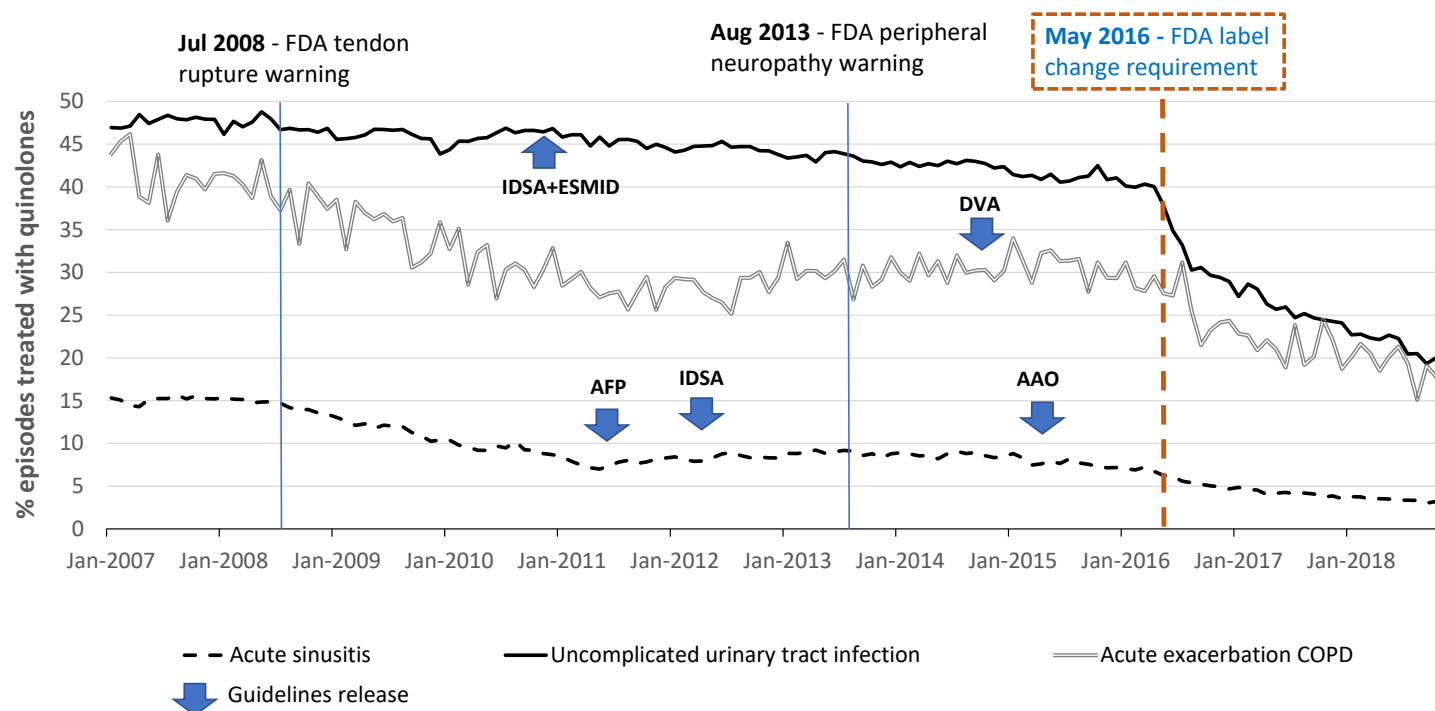


111 ■ Enrollee — Disease rate — Antibiotic-treated rate

112 Disease rates were calculated as the proportion of medical encounters with index diagnosis per 100,000 enrollee-months (denominator). Populations of the denominators were female
 113 adults for uncomplicated UTI, adults for acute sinusitis and community-acquired pneumonia, and adults ≥ 40 years of age for acute exacerbation COPD. These analyses were
 114 conducted before applying any exclusion criteria.

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116 **eFigure 3. Time trends of Oral Quinolone prevalence across all treated episodes by medical condition**



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118 **IDSA + ESMID** – A 2010 update guideline for the treatment of acute uncomplicated cystitis and pyelonephritis in women by the Infectious Diseases Society of America and the
 119 European Society for Microbiology and Infectious Diseases. A summary was published in March 2011.

120 **IDSA** – A clinical practice guideline for acute bacterial rhinosinusitis in children and adults published in April 2012.

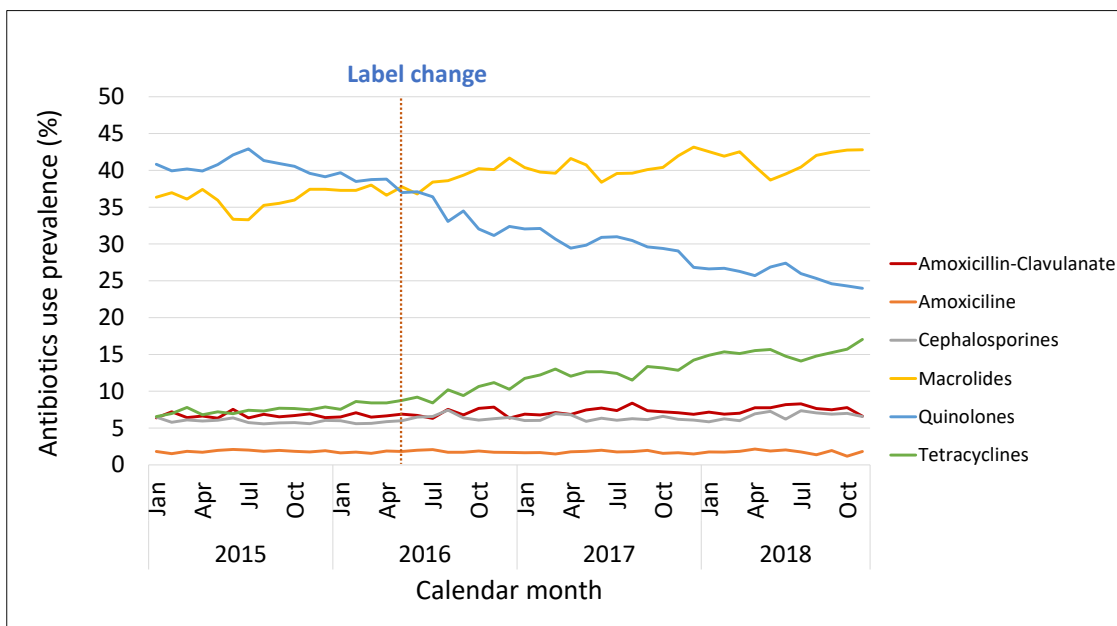
121 **AFP** – A clinical practice guideline for acute rhinosinusitis in adults published by American Family Physician in May 2011

122 **AAO** – An update of a clinical practice guideline for adult sinusitis by American Academy of Otolaryngology-Head and Neck Surgery Foundation in April 2015

123 **DVA** – A clinical practice guideline for the management of chronic obstructive pulmonary disease published by US Department of Veterans Affairs in December 2014.

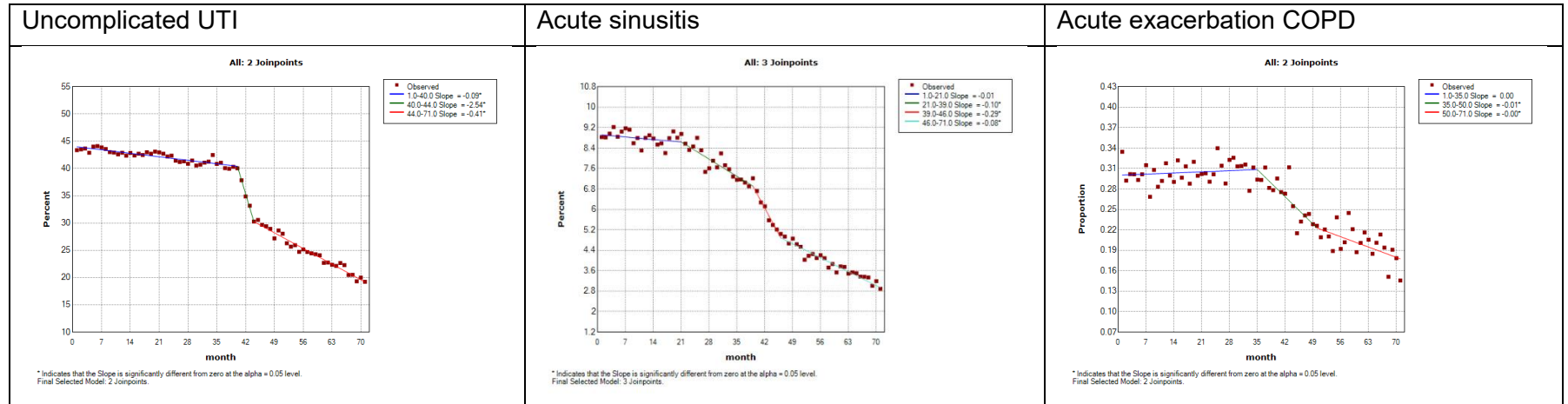
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125 **eFigure 4. Trends in oral antibiotic use prevalence among adults with community-**
126 **acquired pneumonia.**



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130 eFigure 5. Breakpoints and trend lines fitted by Joinpoint regression

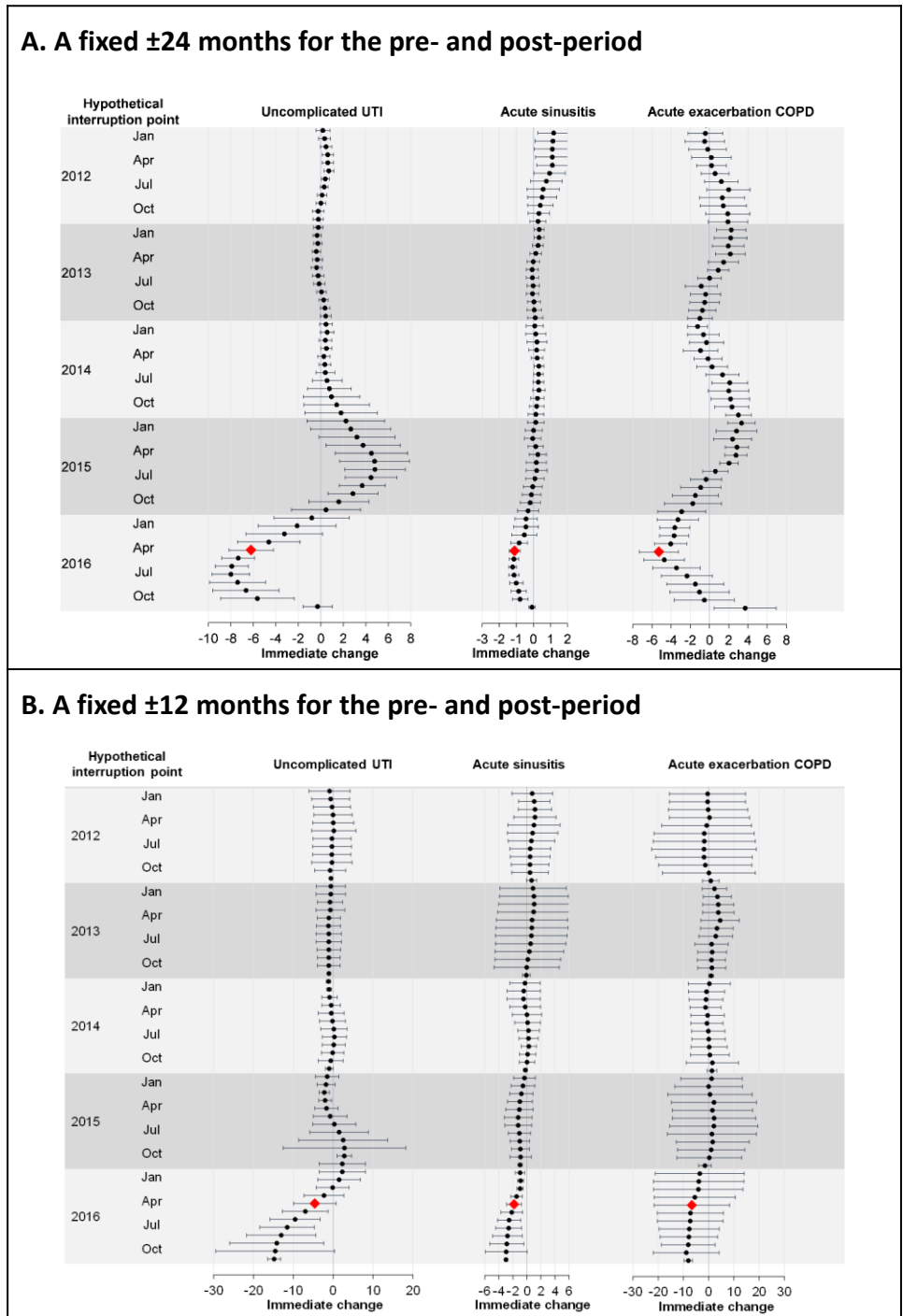


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134 **eFigure 6. Distribution of hypothetical change points surrounding the tested label**
 135 **change**



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137 The red diamond indicates our tested change point (May 2016).

138 These falsification tests include a consecutive series of hypothetical change points from Jan 2012 to Dec 2016. We used a fixed ± 24
 139 months (figure A) or ± 12 months (figure B) for the pre- and post-period for each hypothetical interruption point. Model specifications
 140 were similar to our main analyses.

141 **eTable 1. ICD-9-CM and ICD-10-CM* codes used to define study cohorts and**
 142 **excluded conditions**

Studied population/ excluded conditions	ICD-9-CM diagnosis codes (any position, unless specified)	ICD-10-CM diagnosis codes (any position, unless specified)
Uncomplicated urinary tract infection	595.0*, 595.9*, 599.0*	N30.0*, N30.9*, N39.0*
Acute sinusitis	461.**	J01.**
Acute exacerbation COPD	491.** -except 491.20 coded for obstructive chronic bronchitis without exacerbation, 492.**, or 496.** as primary diagnosis code or presence of a secondary diagnosis with a primary diagnosis of respiratory failure 518.81, 518.82, or 518.84	J41.**, J42.**, J43.**, or J44.** -except J44.9 coded for COPD, unspecified as primary diagnosis code or presence of a secondary diagnosis with a primary diagnosis of respiratory failure J96.00, J96.01, J96.02, J96.90, J96.91, J96.92, J80.**, R06.03, J96.20, J96.21, J96.22
Chronic sinusitis	471.*, 473.*	J32.*, J33.*
Asthma	493.*	J45.*
Pneumonia	480.0-487.0	J12.0, J12.1, J12.2, J12.81, J12.3, J12.89, J12.9, J13, J181, J150, J151, J14, J15.4, J15.3, J15.20, J15.211, J15.212, J15.29, J15.8, J15.5, J15.6, A48.1, J15.9, J15.7, J16.0, J16.8, B25.0, A37.01, A37.11, A37.81, A37.91, A22.1, B440, J17, B77.81, J18.0, J18.8, J18.9, J10.00, J1001, J10.08, J11.00, J11.08, J12.9
Skin and subcutaneous infections	020.1, 021.0, 022.0, 031.1, 032.85, 035, 039.0, 680.0, 680.1, 680.2, 680.3, 680.4, 680.5, 680.6, 680.7, 680.8, 680.9, 681.00, 681.01, 681.02, 681.10, 681.11, 681.9, 682.0, 682.1, 682.2, 682.3, 682.4, 682.5, 682.6, 682.7, 682.8, 689, 684, 685.0, 685.1, 686.0, 686.00, 686.01, 686.09, 686.1, 686.8, 686.9	A20.1, A21.0, A22.0, A31.1, A36.3, A43.1, A46, B78.1, E83.2, K12.2, L01.00, L01.01, L01.02, L01.03, L01.09, L01.1, L02.01, L02.02, L02.03, L02.11, L02.12, L02.13, L02.211, L02.212, L02.213, L02.216, L02.219, L02.221, L02.222, L02.223, L02.224, L02.225, L02.226, L02.229, L02.231, L02.232, L02.233, L02.234, L02.235, L02.236, L02.239, L02.31, L0232, L02.33, L02.411, L02.412, L02.413, L02.414, L02.415, L02.416, L02.419, L02.421, L02.422, L02.423, L02.424, L02.425, L02.426, L02.429, L02.431, L02.432, L02433, L02.434, L02.435, L02.436, L02439, L02.511, L02.512, L02.519, L02521, L02.522, L02.529, L02.531, L02532, L02.539, L02.611, L02.612, L02619, L02.621, L02.622, L02.629, L02631, L02.632, L02.639, L02811, L02.818, L02.821, L02.828, L02.831, L02.838, L02.91, L02.92, L02.93, L03.011, L03.012, L03.019, L03.021, L03.022, L03.029, L03.031, L03.032, L03.039, L03.041, L03.042, L03.049, L03.111, L03.112, L03.113,

		L03.114, L03.115, L03.116, L03.119, L03.121, L03.122, L03.123, L03.124, L03.125, L03.126, L03.129, L03.211, L03.212, L03.213, L03.221, L03.222, L03.311, L03.312, L03.313, L03.314, L03.315, L03.316, L03.317, L03.319, L03.321, L03.322, L03.323, L03.324, L03.325, L03.326, L03.327, L03.329, L03.811, L03.818, L03.891, L03.898, L03.90, L03.91, L05.01, L05.02, L05.91, L05.92, L08.0, L08.1, L08.81, L08.82, L08.89, L08.9, L88, L92.8, L98.0, L98.3
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(*) We cross-walked the original ICD-9-CM-based definitions of the target indications to the ICD-10-CM coding system using SuperCoder (TCI Supercoder, Durham, NC), which uses Medicare's General Equivalency Mapping (GEM) plus approximation codes and clinical judgment. We then inspected plots of the monthly prevalence of each indication grouping to ensure consistent study populations throughout the ICD transition period.

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149 **eTable 2. Infection categories based on Clinical Classification Software (CCS) for**
 150 **ICD-9-CM and Clinical Classification Software Refined (DXCCSR) for ICD-10-CM**

CCS for ICD-9-CM	DXCCSR for ICD-10-CM
Intestinal infection; Urinary tract infections; Skin and subcutaneous tissue infections; Infective arthritis and osteomyelitis; Bacterial infection (unspecified site) HIV infection; Viral infection; Other infections; including parasitic Sexually transmitted; Other CNS infection and poliomyelitis; Other upper respiratory infections; Septicemia	Intestinal infection; Urinary tract infections; Skin and subcutaneous tissue infection; Infective arthritis, Spondylopathies/ spondyloarthropathy (including infection); Bacterial infections; Maternal intrauterine infection; Perinatal infections; Sequela of specified infectious diseases condition HIV infection; Viral infection; Fungal infections, Parasitic, other infection Sexually transmitted infections; Other specified CNS infection and poliomyelitis; Other specified upper respiratory infections; Septicemia

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eTable 3. ICD-9-CM and ICD-10-CM* codes used for exclusion of patients with potentially complicated urinary tract infections

Conditions	ICD-9-CM diagnosis codes	ICD-10-CM diagnosis codes
Urologic abnormalities (not include malignancy)	594.*, 599.6, 599.9, 592.*, 619.0, 753.5, 753.9, V13.0, V44.6, V45.74	N21.*, N13.9, N36.9, N39.9, N20.*, N22, N82.0, N82.1, Q64.1, Q64.8, Q64.9, Z87.448, Z93.6, Z90.6
Spinal injury	344.*, 805.*, 806.*, 952.*	G82.20, G83, S32, S37
Malignancy	140.*-209.*, 230.*-239.*, 258.*, V10.*	C**, D0*, D1*, D2*, D4*, D37, D38, D39, E31, Z85
Chronic ulcer of skin	707.*	L97.*, L98.*
Multiple sclerosis	340	G35
Regional enteritis, ulcerative enterocolitis	555.*, 556.*	K50.*, K51
Organ transplant	996.8, V42.*	T86.*, Z94.*
HIV/AIDS	042.*	B20.*
Stroke	434.*, 435.*	I66.*, G45.*, I67.848
Chemotherapy or radiation	V58.0, V58.1, V66.1, V66.2, V67.1, V67.2, V15.3	Z51.0, Z51.1, Z51.89, Z08.*, Z09.*, Z92.3
Interstitial cystitis, other urologic problems, and other urologic infections	595.1, 595.2, 595.3, 595.4, 595.81, 595.82, 595.89, 596.0, 596.1, 596.2, 596.3, 596.4, 596.5, 596.51, 596.52, 596.53, 596.54, 596.55, 596.59, 596.6, 596.7596.8, 596.9, 788.31, 016.30, 098.0, 112.2, 131.00, 136.9, 760.1	N30.10, N30.11, N30.20, N30.21, N30.30, N30.31, N30.40, N30.41, N30.80, N30.81, N31, N32, N36.44, N39.41, A18.13, A54.0, A54.1, A56.01, A59.00, B37.41, B37.42, B37.49, B89, B64, B99.9, P00.1
Pyelonephritis	590.0, 590.1, 590.8	N11.0, N11.1, N11.8, N10.*, N12.*, N11.9, N13.6, N16.*
Renal failure	403.*, 404.*, 585.*, 586.*, V45.1, V56.*	I12.*, I13.*, N18.*, N19.*, Z91.15, Z99.2
Rheumatologic conditions	710.*, 714.*, 720.0,	M05.*, M06.*, M45, M08.1, M48.8X
Sarcoidosis	135.*	D86.*
Cystic fibrosis	277.0	E84.*
Parkinson's	332.*	G20.*, G21.*
Diabetes	249.*, 250.*	E891, O24, O998, E10, E11, E13
External injuries	E000-E999	S00-T88

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(* We cross-walked the original ICD-9-CM-based definitions of the target indications to the ICD-10-CM coding system using SuperCoder (TCI Supercoder, Durham, NC), which uses Medicare's General Equivalency Mapping (GEM) plus approximation codes and clinical judgment. We then inspected plots of the monthly prevalence of each indication grouping to ensure consistent study populations throughout the ICD transition period.

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eTable 4. Demographic characteristics of the three study cohorts

Uncomplicate UTI (female only)*				
Year	2015 (N=235777)	2016 (N=161474)	2017 (N=135729)	2018 (N=119250)
Age	43.0	42.0	42.0	41.0
Median (IQR)	(29.0–55.0)	(29.0–55.0)	(28.0–54.0)	(28.0–53.0)
Region N (%)				
Northeast	37653 (16.0)	22571 (14.0)	19851 (14.6)	18100 (15.2)
North Central	46891 (19.9)	32422 (20.1)	25289 (18.6)	24559 (20.6)
South	111625 (47.3)	80141 (49.6)	70378 (51.9)	58042 (48.7)
West	39186 (16.6)	26210 (16.2)	20018 (14.7)	18382 (15.4)
Unknown	422 (0.2)	128 (0.1)	193 (0.1)	167 (0.1)
Acute sinusitis				
Year	2015 (N=544186)	2016 (N=463401)	2017 (N=425974)	2018 (N=308631)
Age	48.0	48.0	48.0	48.0
Median (IQR)	(37.0–57.0)	(37.0–57.0)	(37.0–57.0)	(37.0–57.0)
Sex (Female) N (%)	338474 (62.2)	283784 (61.2)	259968 (61.0)	189203 (61.3)
Region N (%)				
Northeast	88423 (16.2)	66121 (14.3)	62236 (14.6)	50158 (16.3)
North Central	117616 (21.6)	97930 (21.1)	86424 (20.3)	60069 (19.5)
South	279585 (51.4)	252709 (54.5)	237460 (55.7)	167096 (54.1)
West	57778 (10.6)	46455 (10.0)	39547 (9.3)	30989 (10.0)
Unknown	784 (0.1)	186 (0.0)	307 (0.1)	319 (0.1)
Acute exacerbation COPD				
Year	2015 (N=8039)	2016 (N=6087)	2017 (N=5134)	2018 (N=3557)
Age	65.0	65.0	64.0	62.0
Median (IQR)	(60.0–75.0)	(60.0–75.0)	(60.0–74.0)	(58.0–70.0)
Sex (Female) N (%)	4169 (51.9)	3149 (51.7)	2687 (52.3)	1919 (53.9)
Region N (%)				
Northeast	1662 (20.7)	1165 (19.1)	992 (19.3)	796 (22.4)
North Central	2706 (33.7)	2127 (34.9)	1785 (34.8)	1047 (29.4)
South	3005 (37.4)	2327 (38.2)	1959 (38.2)	1342 (37.7)
West	660 (8.2)	460 (7.6)	394 (7.7)	368 (10.3)
Unknown	6 (0.1)	8 (0.1)	4 (0.1)	4 (0.1)

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(*) For uncomplicated urinary tract infection, we included female patients only because all urinary tract infections in men are considered complicated. The sample size decreased overtime in MarketScan due to changes in health plans participating in the database. The database includes more South region in recent years.

171 **eTable 5. Impact of Label Changes on Antibiotic Use by Medical Condition– Interrupted Time-series Analyses**

	Risk difference (95% CI)			
	Prevalence in Jan'2015	Average monthly change before May 2016	Immediate change after May 2016	Change in trend after May 2016
Uncomplicated UTI				
Nitrofurantoin (1 st line)	26.6 (26.0;27.2)	0.17 (0.15;0.19)	2.99 (2.40;3.58)	0.29 (0.24;0.34)
Trimethoprim-sulfamethoxazole (1 st line)	22.4 (21.7;23.2)	-0.06 (-0.09;-0.03)	3.48 (2.92;4.04)	-0.03 (-0.07;0.01) ^(a)
Quinolones (2 nd line)	41.6 (40.6;42.5)	-0.06 (-0.11;-0.01)	-7.21 (-8.62;-5.80)	-0.41 (-0.51;-0.31)
β-lactams (2 nd line, exclude amoxicillin, ampicillin)	6.3 (6.0;6.6)	0(-0.02;0.02) ^(a)	0.61 (0.37;0.86)	0.12 (0.1;0.14)
Acute sinusitis				
Amoxicillin-Clavulanate (1 st line)	30.2 (29.8;30.6)	0.17 (0.13;0.21)	-0.41 (-0.89;0.07) ^(a)	0.04 (0;0.08) ^(a)
Amoxicillin (1 st line)	13.1 (12.9;13.4)	0.03 (0.02;0.04)	0.66 (0.52;0.8)	-0.03 (-0.05;-0.01)
Cephalosporins (2 nd line)	12.1 (11.8;12.4)	-0.04 (-0.06;-0.02)	0.44 (0.19;0.69)	0 (-0.02;0.02) ^(a)
Tetracyclines (2 nd line)	4.1 (3.8;4.3)	0.08 (0.07;0.09)	0.22 (0.05;0.39)	0.04 (0.03;0.05)
Quinolones (2 nd line)	8.3 (7.9;8.6)	-0.09 (-0.12;-0.06)	-1.23 (-1.52;-0.94)	0 (-0.04;0.04) ^(a)
Macrolides (not recommended)	31.7 (31.2;32.2)	-0.15 (-0.19;-0.11)	0.28 (-0.03;0.59) ^(a)	-0.04 (-0.08;0) ^(a)
Acute exacerbation COPD				
Macrolides (1 st line)	36.4 (3.16;38.6)	0.17 (0.09;0.25)	0.80 (-0.27;1.87) ^(a)	-0.15 (-0.24;-0.06)
Cephalosporines (1 st line)	8.2 (6.5;9.9)	0.06 (-0.04;0.16) ^(a)	-0.24 (-1.22;0.74) ^(a)	-0.01 (-0.11;0.09) ^(a)
Quinolones (2 nd line)	31.9 (30.3;33.4)	-0.21 (-0.31;-0.11)	-2.58 (-4.05;-1.11)	-0.09 (-0.21;0.03) ^(a)
Amoxicillin-Clavulanate (2 nd line)	6.7 (5.4;8.0)	-0.01 (-0.07;0.05) ^(a)	1.05 (0.31;1.79)	0.02 (-0.04;0.08) ^(a)
Tetracyclines (not recommended)	11.2 (8.6;13.4)	0.03 (-0.07;0.13) ^(a)	1.14 (-0.08;2.36) ^(a)	0.20 (0.07;0.33)

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173 ^(a) p>0.05; Notes: Antibiotic classes with <5% of total antibiotics use are omitted, UTI: urinary tract infection, COPD: chronic obstructive pulmonary disease.

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175 **eTable 6. Sensitivity analyses for interrupted time series models when excluding the phase-in period surrounding**
 176 **the labeling change (Nov 2015 to Jul 2016), lag effect (May to Jul 2016), falsification test in non-quinolone**
 177 **antibiotic use for skin infection and testing for spillovers effects in quinolone use for community acquired**
 178 **pneumonia.**

		Prevalence at the beginning of the study period	Average monthly change before label change	Immediate change after label change	Change in trend after label change
Main design	Uncomplicated UTI	41.6 (40.6;42.5)	-0.06 (-0.11;-0.01)	-7.21 (-8.62;-5.80)	-0.41 (-0.51;-0.31)
	Acute sinusitis	8.3 (7.9;8.6)	-0.09 (-0.12;-0.06)	-1.23 (-1.52;-0.94)	0 (-0.04;0.04)
	Acute exacerbation COPD	31.9 (30.3;33.4)	-0.21 (-0.31;-0.11)	-2.58 (-4.05;-1.11)	-0.09 (-0.21;0.03)
Excluding phase-in period (Nov 15 – Jul 16)	Uncomplicated UTI	41.6 (40.8;42.3)	0.03 (-0.08;0.14)	-10.79 (-11.45;-10.13)	-0.43 (-0.55;-0.31)
	Acute sinusitis	8.4 (8.0;8.8)	-0.10 (-0.15;-0.05)	-2.19 (-2.4;-1.98)	0.02 (-0.02;0.06)
	Acute exacerbation COPD	33.6 (31.0;36.3)	-0.25 (-0.56;0.06)	-5.58 (-7.7;-3.46)	0 (-0.31;0.31)
Excluding phase-in period (May 16 – Jul 18)	Uncomplicated UTI	41.8 (41.5;42.3)	-0.09 (-0.12;-0.06)	-9.7 (-10.2;-9.2)	-0.32 (-0.36;-0.28)
	Acute sinusitis	8.3 (8.0;8.7)	-0.09 (-0.12;-0.06)	-1.67 (-1.91;-1.43)	0.01 (-0.02;0.04)
	Acute exacerbation COPD	32.1 (30.3;33.8)	-0.23 (-0.33;-0.13)	-4.32 (-5.67;-2.97)	-0.02 (-0.15;0.11)
Negative control indication *	Skin and subcutaneous infection	57.1 (56.1;58.0)	0.15 (0.13;0.17)	0.63 (-0.14;1.4)	-0.1 (-0.2;0)
Spill-over effects	Community-acquired pneumonia	41.0 (40.5;41.4)	-0.11 (-0.14;-0.08)	-4.05 (-4.5;-3.6)	-0.27 (-0.3;-0.24)

179 * Quinolones encompassed less than 5% of antibiotics used for these indications in both the pre- and post-label change periods. UTI: urinary tract infection, COPD: chronic obstructive
 180 pulmonary disease.

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182 **eTable 7. Joinpoint regression results**

	Best models		
	Joinpoint	Point estimate (95%CI)	Equivalent months (95%CI)
Uncomplicated UTI	1	40 (39-41)	Apr 2016 (Mar 2016 – May 2016)
	2	44 (43-45)	Aug 2016 (Jul 2016 – Sep 2016)
Acute sinusitis	1	21 (10-29)	Sep 2014 (Oct 2013 – May 2015)
	2	39 (35-43)	Mar 2016 (Nov 2015 – Jul 2016)
	3	45 (43-51)	Sep 2016 (Jul 2016 – Mar 2017)
Acute exacerbation COPD	1	35 (21-41)	Nov 2015 (Sep 2014 – May 2016)
	2	50 (32-64)	Feb 2017 (Aug 2015 – Apr 2018)

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185 **eTable 8: Monthly aggregated input data for the interrupted time series analysis of the three study cohorts**

Time	Uncomplicated UTI			Acute sinusitis			Acute exacerbation COPD		
	Total abx	Quinolone	%	Total abx	Quinolone	%	Total abx	Quinolone	%
Jan-15	20411	8456	41.43	69229	6093	8.80	874	297	33.98
Feb-15	17960	7398	41.19	63123	5247	8.31	796	250	31.41
Mar-15	20153	8329	41.33	63518	4746	7.47	868	250	28.80
Apr-15	20243	8272	40.86	52607	4001	7.61	877	283	32.27
May-15	20231	8390	41.47	41841	3307	7.90	743	242	32.57
Jun-15	22568	9152	40.55	32784	2507	7.65	642	201	31.31
Jul-15	24516	9974	40.68	26459	2168	8.19	577	181	31.37
Aug-15	23829	9789	41.08	29258	2262	7.73	472	149	31.57
Sep-15	21421	8836	41.25	38337	2902	7.57	606	168	27.72
Oct-15	16935	7193	42.47	40509	2950	7.28	565	176	31.15
Nov-15	14660	5987	40.84	40568	2903	7.16	487	143	29.36
Dec-15	12850	5275	41.05	45953	3296	7.17	532	156	29.32
Jan-16	13705	5493	40.08	53334	3760	7.05	549	171	31.15
Feb-16	13494	5391	39.95	57853	3993	6.90	643	181	28.15
Mar-16	14526	5855	40.31	52485	3788	7.22	701	195	27.82
Apr-16	13244	5301	40.03	38761	2606	6.72	606	179	29.54
May-16	13678	5176	37.84	34545	2166	6.27	570	157	27.54
Jun-16	14699	5126	34.87	26839	1642	6.12	491	134	27.29
Jul-16	14817	4916	33.18	20695	1154	5.58	369	115	31.17
Aug-16	15893	4812	30.28	25632	1382	5.39	377	96	25.46
Sep-16	13921	4254	30.56	31854	1661	5.21	414	89	21.50
Oct-16	12640	3749	29.66	32699	1648	5.04	422	98	23.22
Nov-16	11570	3403	29.41	40694	2008	4.93	456	110	24.12
Dec-16	9285	2686	28.93	48010	2241	4.67	489	119	24.34
Jan-17	10797	2934	27.17	55804	2712	4.86	556	127	22.84
Feb-17	10295	2948	28.64	52542	2435	4.63	531	120	22.60
Mar-17	11469	3216	28.04	47080	2135	4.53	526	110	20.91
Apr-17	10547	2773	26.29	32337	1302	4.03	467	103	22.06
May-17	11910	3058	25.68	33310	1393	4.18	471	99	21.02
Jun-17	12678	3289	25.94	24922	1061	4.26	450	85	18.89
Jul-17	13152	3250	24.71	18547	760	4.10	319	76	23.82
Aug-17	13703	3449	25.17	23283	979	4.20	349	67	19.20
Sep-17	11622	2868	24.68	29542	1209	4.09	372	75	20.16
Oct-17	11474	2805	24.45	29857	1112	3.72	380	93	24.47

Time	Uncomplicated UTI			Acute sinusitis			Acute exacerbation COPD		
	Total abx	Quinolone	%	Total abx	Quinolone	%	Total abx	Quinolone	%
Nov-17	10223	2482	24.28	38960	1506	3.87	430	95	22.09
Dec-17	7859	1893	24.09	39790	1406	3.53	283	53	18.73
Jan-18	10152	2304	22.70	47917	1807	3.77	478	96	20.08
Feb-18	9460	2153	22.76	35097	1316	3.75	370	80	21.62
Mar-18	10318	2304	22.33	34674	1209	3.49	370	76	20.54
Apr-18	10169	2251	22.14	29070	1028	3.54	357	66	18.49
May-18	11251	2550	22.66	26488	928	3.50	358	72	20.11
Jun-18	11575	2578	22.27	21142	712	3.37	305	65	21.31
Jul-18	12346	2525	20.45	16754	563	3.36	227	44	19.38
Aug-18	12682	2600	20.50	19114	638	3.34	245	37	15.10
Sep-18	11031	2131	19.32	22457	675	3.01	241	46	19.09
Oct-18	10800	2160	20.00	24930	795	3.19	297	53	17.85
Nov-18	9466	1818	19.21	30988	896	2.89	309	45	14.56

186 Abx: Antibiotics

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