

Supplemental Online Content

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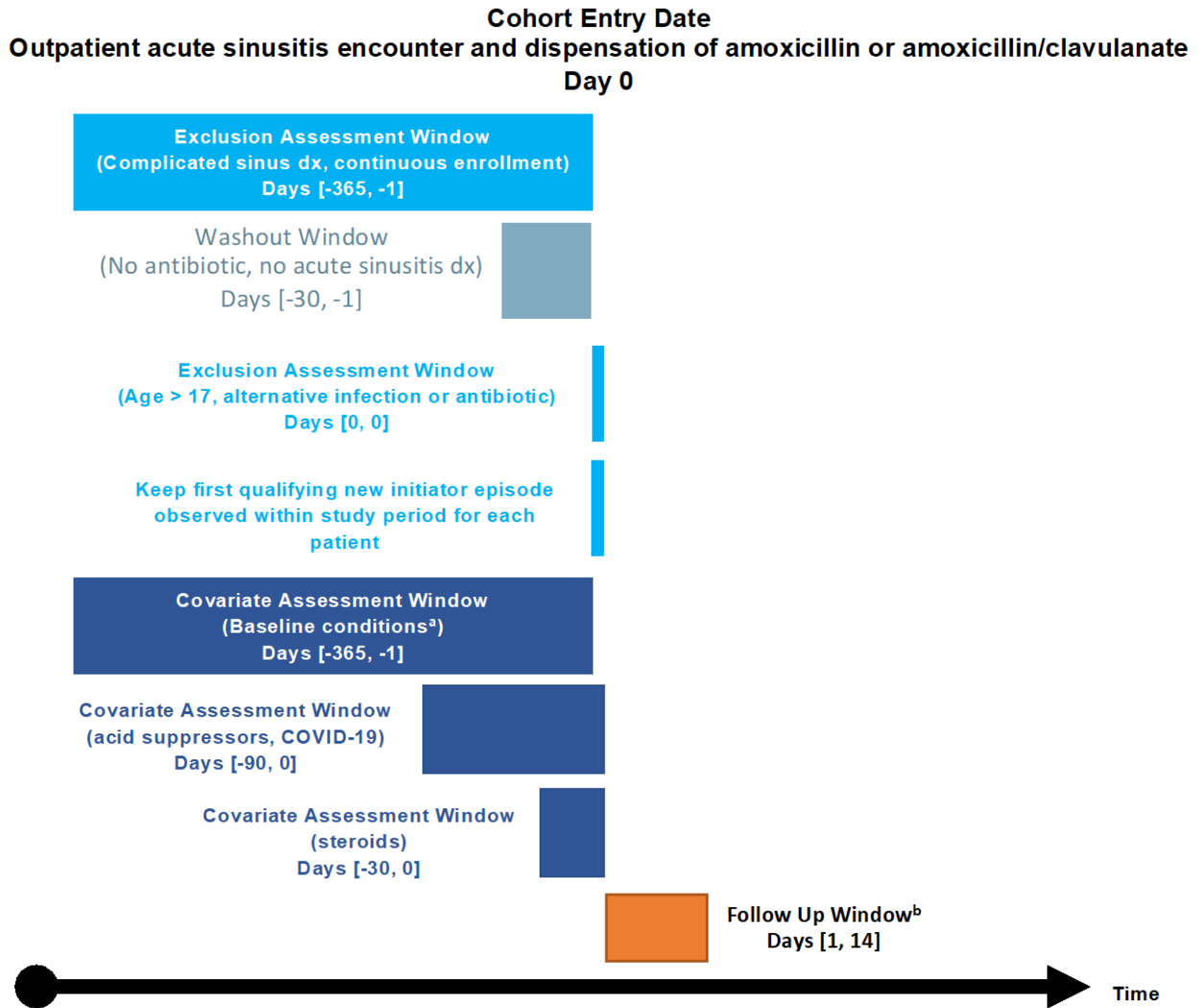
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This supplemental material has been provided by the authors to give readers additional information about their work.

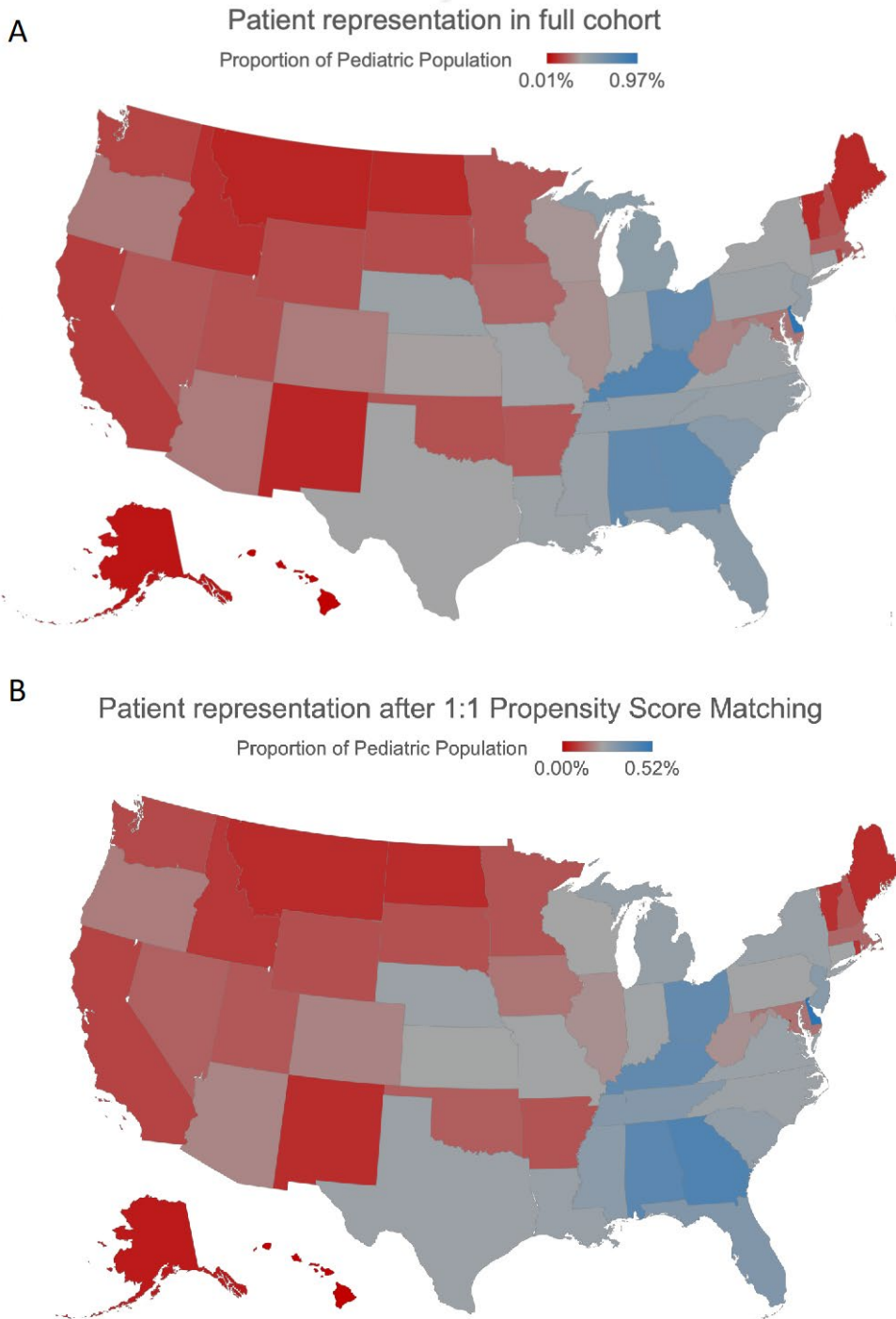
eFigure 1. Graphical Depiction of Study Design



^aBaseline conditions included: census region, metropolitan statistical area, pediatric comorbidity index, asthma, diabetes, immunocompromise, rhinitis, healthcare utilization, previous infectious disease diagnoses, and previous antibiotic use.

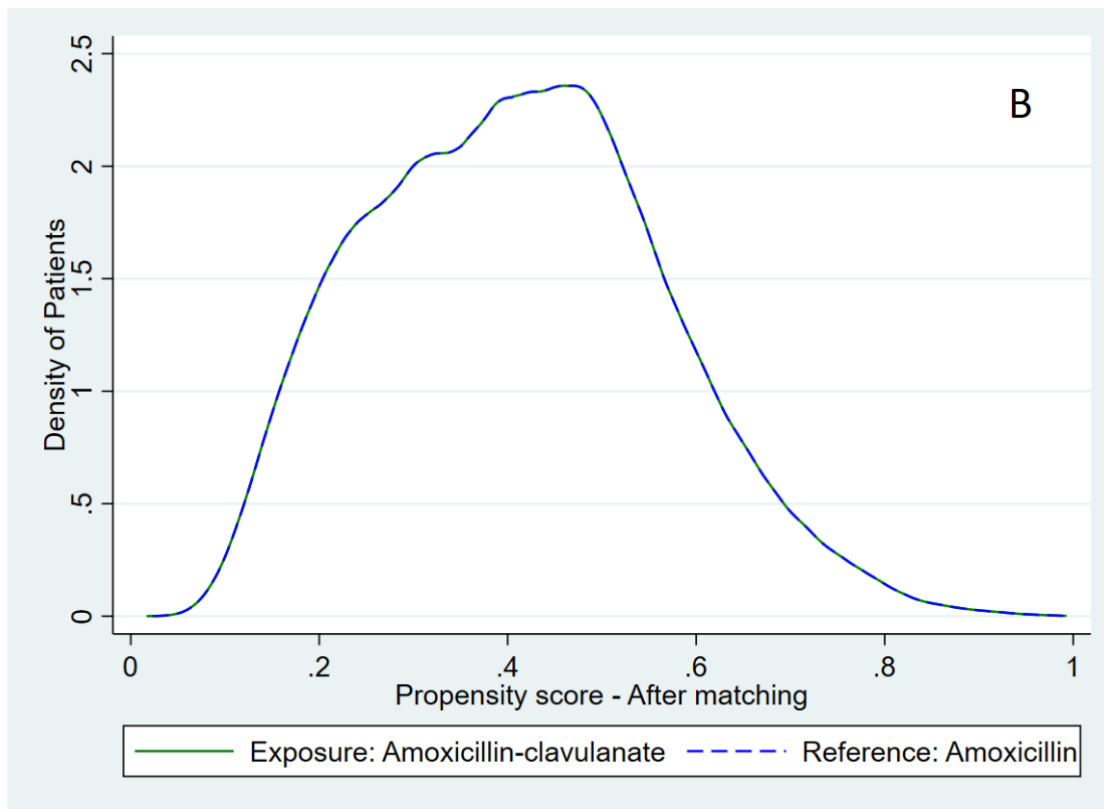
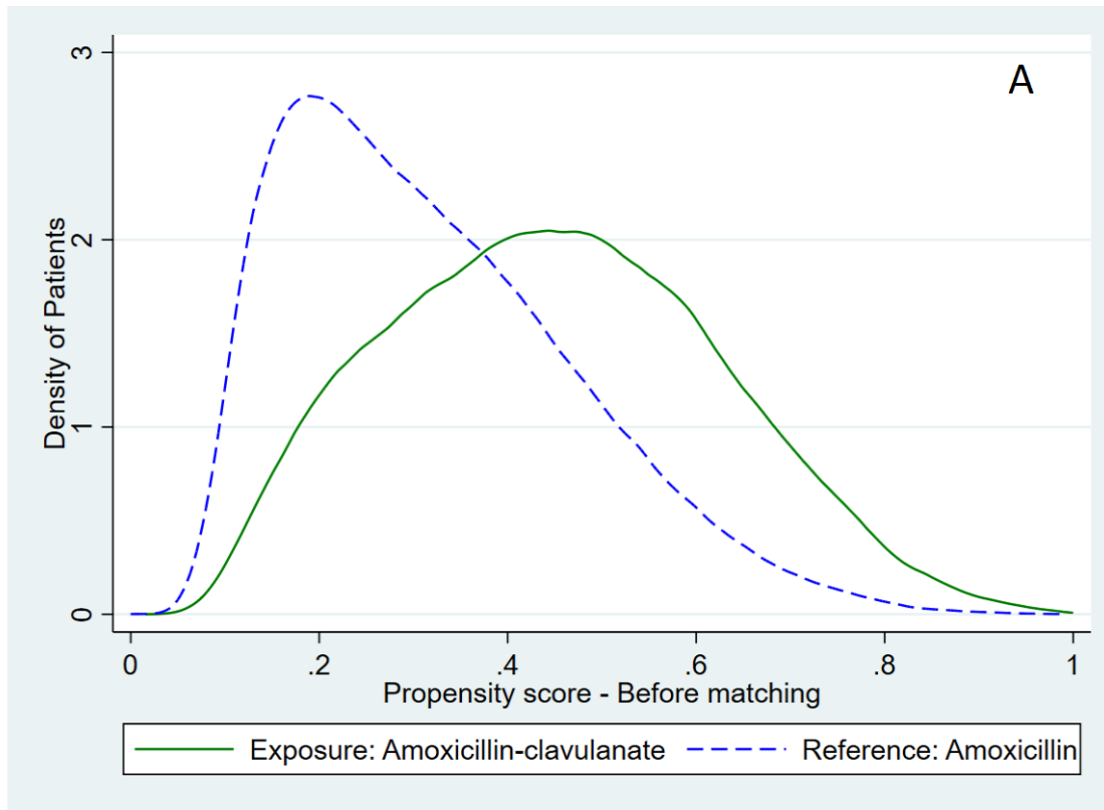
^bEarliest occurrence of: outcome of interest (treatment failure), death, disenrollment, end of data, end of the study period.

eFigure 2. Geographic Distribution of Patients



The total number of patients in the cohort, before (panel A) and after (panel B) 1:1 PS matching were compared against the total number of people younger than 19 years old in each state during the study period. Overall, the cohort comprised 0.422% of the US pediatric population during the study period, 0.26% after 1:1 PS matching. Blue shading indicates that a state contributed more patients to the cohort than the national average, while red shading indicates that a state contributed fewer patients to the cohort than the national average. 12.2% (39,050/320,141) patients had unknown state. The number of people less than 19 years old was identified via the American Community Survey, with annual totals across the study period (2017-2021) averaged to obtain a mean population size of 75,869,620.

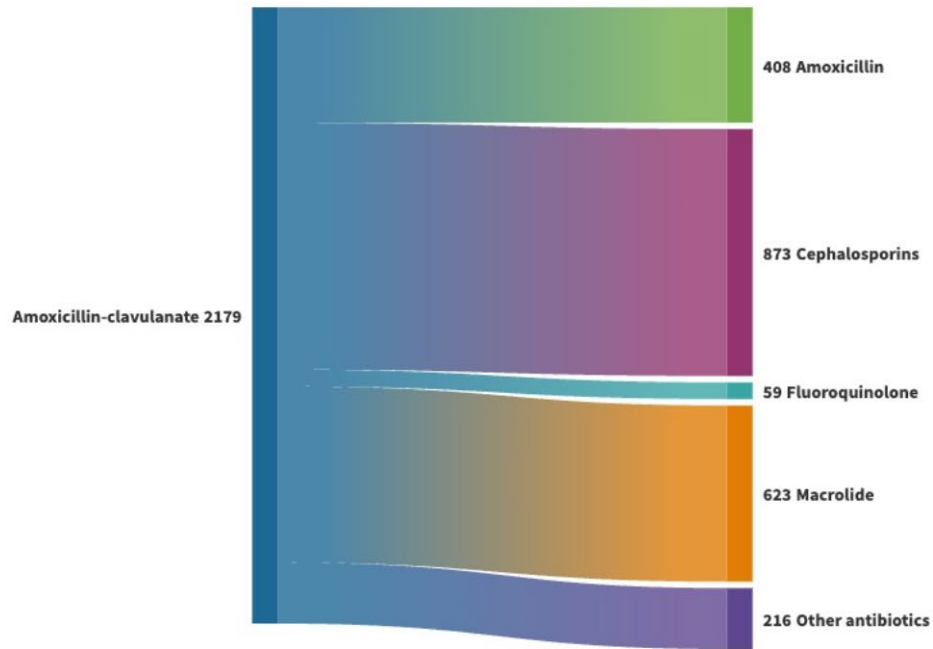
eFigure 3. Propensity Score Distribution and Overlap



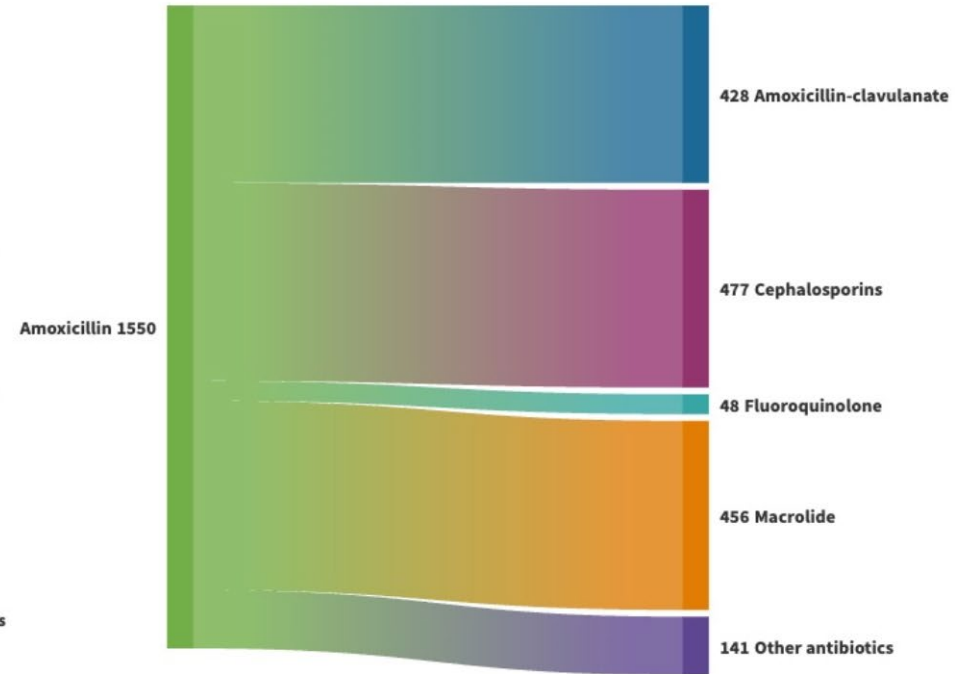
Propensity score distribution and density of the unadjusted cohort (Panel A) and after 1:1 PS matching (Panel B), by exposure. Pre-matching c-statistic was 0.714, post-matching c-statistic was 0.514.

eFigure 4. Antibiotic Switches – No Outpatient Encounter

A

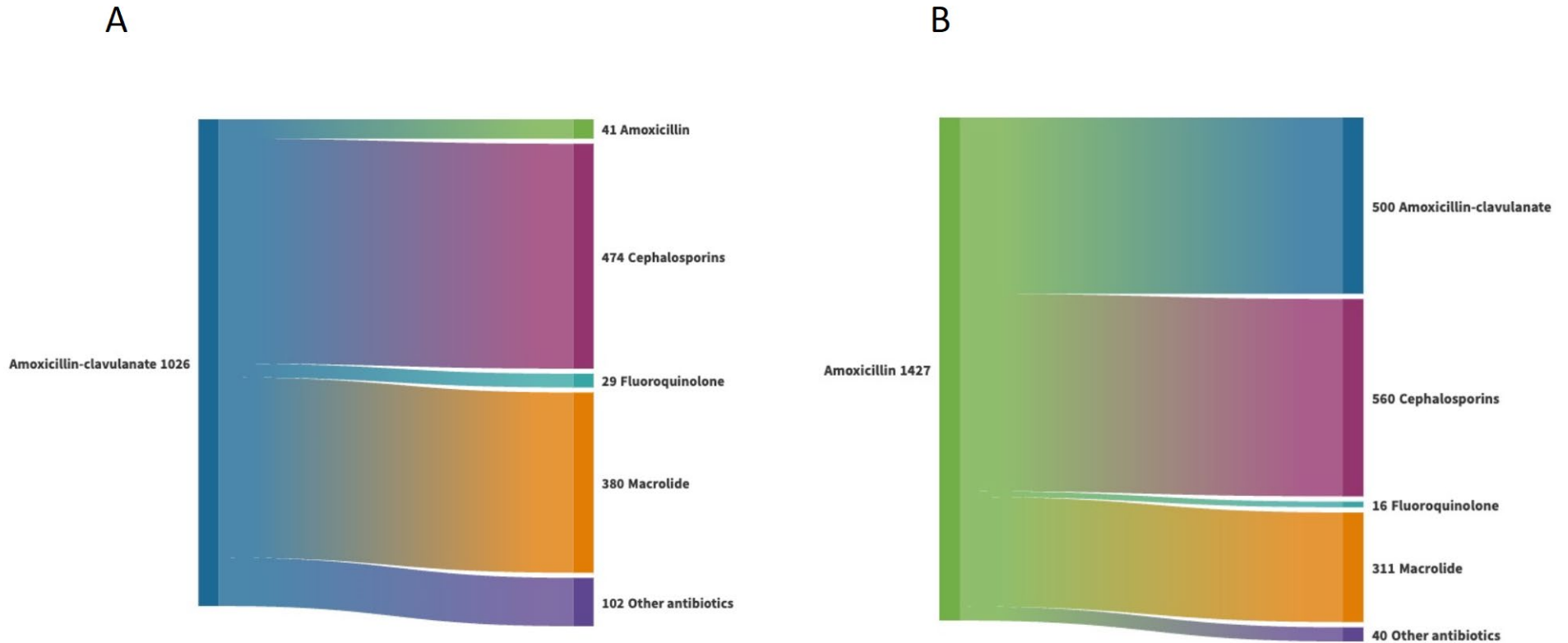


B



In the 1:1 propensity score matched cohort, individual antibiotic dispensations were captured and plotted on Sankey Diagrams. Antibiotic dispensations in the absence of an outpatient encounter following index exposure to amoxicillin-clavulanate (Panel A) and amoxicillin (Panel B) were identified in the 14 days after cohort entry. As antibiotics were assessed individually, a patient could potentially contribute more than one outcome if they had different antibiotics dispensed in the absence of outpatient encounters during the follow up window.

eFigure 5. Antibiotic Switches – Acute Sinusitis Outpatient Encounter



In the 1:1 propensity score matched cohort, individual antibiotic dispensations were captured and plotted on Sankey Diagrams. Antibiotic dispensations with a same-day outpatient encounter for acute sinusitis following index exposure to amoxicillin-clavulanate (Panel A) and amoxicillin (Panel B) were identified in the 14 days after cohort entry. As antibiotics were assessed individually, a patient could potentially contribute more than one outcome if they had more than the qualifying encounter in the follow up window, each with a different antibiotic.

eTable 1. Exclusion Criteria

Variable	Definition^a	Assessment period (relative to CED)
Acute sinusitis	J01.x0	Required on CED Excluded day -30 to -1
Chronic sinusitis	J32.x	Excluded day -365 to -1
Recurrent sinusitis	J01.x1	Excluded day -365 to -1
Cystic fibrosis	E84.0, E84.11, E84.19, E84.8, E84.9	Excluded day -365 to -1
Situs inversus	Q89.3	Excluded day -365 to -1
Choanal atresia	Q30.0, 30540 (CPT code), 30545 (CPT code)	Excluded day -365 to -1
Acute otitis media	H66.00x, H66.01x, H66.4x, H66.9x	Excluded on CED
Cellulitis/abscess	G06.x, H00.034, J39.0, J85.1, K12.2, M65.052, K65.1, K68.x, K75.0, L02.x	Excluded on CED
Community acquired pneumonia	A48.1, J13, J14, J15.x, J16.x, J17, J18.x	Excluded on CED
Group A Streptococcal pharyngitis	J02.x, J03.0x	Excluded on CED
Urinary tract infection	N03.2, N10, N11.x, N13.6, N30.x, N39.0	Excluded on CED
Oral antibiotics ^b	Azithromycin, cefaclor, cefadroxil, cefdinir, cefditoren, cefixime, cefpodoxime, cefprozil, cefuroxime, ceftibuten, cephalexin, ciprofloxacin, clarithromycin, clindamycin, delafloxacin, dicloxacillin, doxycycline, erythromycin, levofloxacin, linezolid, moxifloxacin, penicillin V, telithromycin, tedizolid, tetracycline, trimethoprim-sulfamethoxazole	Excluded day -30 to CED

^aInternational Classification of Diseases – 10th Edition codes unless otherwise noted.

^bIdentified via generic names

eTable 2. Outcome Definitions

Outcome	Definition
A new antibiotic dispensation, different from the index antibiotic, in the absence of an outpatient encounter	No outpatient encounter with the same-day dispensation of one of the following antibiotics: azithromycin, cefaclor, cefadroxil, cefdinir, cefditoren, cefixime, cefpodoxime, cefprozil, cefuroxime, ceftibuten, cephalexin, ciprofloxacin, clarithromycin, clindamycin, delafloxacin, dicloxacillin, erythromycin, levofloxacin, linezolid, moxifloxacin, penicillin V, telithromycin, tedizolid, trimethoprim-sulfamethoxazole, doxycycline, tetracycline, (amoxicillin if initially dispensed amoxicillin-clavulanate, amoxicillin-clavulanate if initially dispensed amoxicillin)
A new antibiotic dispensation, different from the index antibiotic, with a same-day outpatient encounter for acute sinusitis	Outpatient acute sinusitis encounter (ICD-10 code J01.x0) with the same-day dispensation of one of the following antibiotics: azithromycin, cefaclor, cefadroxil, cefdinir, cefditoren, cefixime, cefpodoxime, cefprozil, cefuroxime, ceftibuten, cephalexin, ciprofloxacin, clarithromycin, clindamycin, delafloxacin, dicloxacillin, erythromycin, levofloxacin, linezolid, moxifloxacin, penicillin V, telithromycin, tedizolid, trimethoprim-sulfamethoxazole, doxycycline, tetracycline, (amoxicillin if initially dispensed amoxicillin-clavulanate, amoxicillin-clavulanate if initially dispensed amoxicillin)
An emergency department encounter for acute sinusitis	Emergency department encounter with an ICD-10 code J01.x0
An inpatient encounter for acute sinusitis	Inpatient encounter with an ICD-10 code J01.x0
An inpatient encounter for a complication of sinusitis	<p><u>Nasal/sinus endoscopy</u> Inpatient encounter with procedure code (CPT and HCPC) in the principal position: 31233, 31235, 31237, 31238, 31239, 31240, 31241, 31253, 31254, 31255, 31256, 31257, 31259, 31267, 31276, 31287, 31288, 31290, 31291, 31292, 31293, 31294, 31295, 31296, 31297, 31298, S2344</p> <p><u>Intracranial abscess</u> Inpatient encounter with an ICD-10 code in the principal position: G06.0, G06.2</p> <p><u>Intracranial thrombosis</u> Inpatient encounter with an ICD-10 code in the principal position: G08, I67.6</p> <p><u>Meningitis</u> Inpatient encounter with an ICD-10 code in the principal position: A39.0, G00.0-G00.9, G01, G03.8, G03.9</p> <p><u>Neurosurgery</u> Inpatient encounter with procedure code (CPT and HCPC) in the principal position: 61304, 61305, 61320, 61321, 61322, 61150, 61151, 61522</p> <p><u>Orbital cellulitis</u> Inpatient encounter with ICD-10 code in the principal position: H05.01x</p> <p><u>Orbital osteomyelitis</u> Inpatient encounter with ICD-10 code in the principal position: H05.02x</p>

eTable 3. Adverse and Control Outcome Definitions

Adverse Drug Event	Follow up duration relative to cohort entry date	ICD-10-CM Diagnosis codes
Dermatologic		
Skin Rash	1-14 days	R21
Stevens-Johnson Syndrome	1-14 days	L51.1
Toxic epidermal necrolysis	1-14 days	L51.2, L51.3
Urticaria	1-14 days	L50.0, L50.1, L50.6-L50.9
Gastrointestinal		
Abdominal pain	1-14 days	R10.0-R10.33, R10.84-R10.9
Nausea/vomiting	1-14 days	R11.0-R11.12, R11.2
Non- <i>C. difficile</i> diarrhea	1-14 days	K52.29-K52.3, K52.831-K52.9, R19.7
Hypersensitivity		
Anaphylaxis	0-2 days	T78.2XXA, T88.6XXA
Angioedema	0-2 days	H02.841-H02.849, T78.3XXA
Laryngeal edema	0-2 days	J38.4
Unspecified allergy	1-14 days	T78.40XA, T78.49XA
Secondary infections		
<i>C. difficile</i> infection	1-90 days	A04.7-A04.72
Yeast infection	1-90 days	B37, B37.0-B37.9
Kidney		
Acute kidney injury	1-14 days	N00.0- N00.9, N00.A, N17.0-N17.9, N19, R94.4
Control Outcomes		
Ingrown nail	1-90 days	L60.0
Tendonitis/tendinopathy	1-90 days	M66.20, M66.221-M66.80, M66.821-M66.9, M75.120-M75.122, M76.50-M76.62, M76.811-M76.829, M77.9
Wart removal	1-90 days	17110 ^a

^aCPT code

eTable 4. Comprehensive Patient Characteristics

Covariate	Unadjusted			Propensity score matched		
	Amoxicillin-clavulanate (n= 117,659)	Amoxicillin (n= 202,482)	Absolute standardized difference	Amoxicillin-clavulanate (n= 99,471)	Amoxicillin (n= 99,471)	Absolute standardized difference
Year						
2017	36,607 (31.1)	63,960 (31.6)	0.01	30,989 (31.2)	31,039 (31.2)	0.00
2018	28,450 (24.2)	48,408 (23.9)	0.01	24,008 (24.1)	23,936 (24.1)	0.00
2019	29,086 (24.7)	48,462 (23.9)	0.02	24,480 (24.6)	24,476 (24.6)	0.00
2020	10,475 (8.9)	17,070 (8.4)	0.02	8,762 (8.8)	8,809 (8.9)	0.00
2021	13,041 (11.1)	24,582 (12.1)	0.03	11,232 (11.3)	11,211 (11.3)	0.00
Demographics						
Age, median (IQR)	13 (7,16)	8 (4,13)	0.52	12 (6, 15)	12 (6, 15)	0.01
Age						
0 – 5 years	23,812 (20.2)	74,677 (36.9)	0.38	22,656 (22.8)	22,411 (22.5)	0.01
6 – 11 years	27,480 (23.4)	61,676 (30.5)	0.16	26,046 (26.2)	26,103 (26.2)	0.00
12 – 17 years	66,367 (56.4)	66,129 (32.7)	0.49	50,769 (51.0)	50,957 (51.2)	0.00
Female	59,087 (50.2)	103,135 (50.9)	0.01	50,094 (50.4)	50,246 (50.5)	0.00
Male	58,572 (49.8)	99,347 (49.1)	0.01	49,377 (49.6)	49,225 (49.5)	0.00
Census Region						
Northeast	18,961 (16.1)	29,503 (14.6)	0.04	15,538 (15.6)	15,504 (15.6)	0.00
North Central	22,693 (19.3)	43,768 (21.6)	0.06	19,848 (20.0)	19,671 (19.8)	0.01
South	60,584 (51.5)	109,056 (53.9)	0.05	52,003 (52.3)	52,152 (52.4)	0.00
West	15,098 (12.8)	19,666 (9.7)	0.10	11,808 (11.9)	11,861 (11.9)	0.00
Unknown	323 (0.3)	489 (0.2)	0.02	274 (0.3)	283 (0.3)	0.00
State			0.32			0.16
Metropolitan Statistical Area			0.56			0.21
Medical History						
Allergic rhinitis	21,016 (17.9)	31,651 (15.6)	0.06	16,964 (17.1)	17,066 (17.2)	0.00
Anxiety	11,091 (9.4)	12,792 (6.3)	0.13	8,527 (8.6)	8,524 (8.6)	0.00

Asthma	6,268 (5.3)	9,190 (4.5)	0.04	5,037 (5.1)	5,046 (5.1)	0.00
Chronic rhinitis	2,909 (2.5)	4,916 (2.4)	0.00	2,345 (2.4)	2,342 (2.4)	0.00
Diabetes mellitus, type 1	549 (0.5)	613 (0.3)	0.03	411 (0.4)	414 (0.4)	0.00
Diabetes mellitus, type 2	431 (0.4)	438 (0.2)	0.03	325 (0.3)	313 (0.3)	0.00
Any malignancy	245 (0.2)	315 (0.2)	0.01	196 (0.2)	186 (0.2)	0.00
Primary immunodeficiency	425 (0.4)	431 (0.2)	0.28	300 (0.3)	281 (0.3)	0.00
Bone marrow transplant	22 (0.0)	24 (0.0)	0.01	15 (0.0)	13 (0.0)	0.00
Solid organ transplant	45 (0.0)	58 (0.0)	0.01	35 (0.0)	30 (0.0)	0.00
Overweight or obese	9,629 (8.2)	15,222 (7.5)	0.03	8,064 (8.1)	8,119 (8.2)	0.00
Underweight/failure to thrive	1,480 (1.3)	3,525 (1.7)	0.04	1,346 (1.4)	1,339 (1.3)	0.01
Inflammatory bowel disease	185 (0.2)	255 (0.1)	0.01	157 (0.2)	151 (0.2)	0.00
Irritable bowel syndrome	427 (0.4)	519 (0.3)	0.02	337 (0.3)	339 (0.3)	0.00
Constipation	5,165 (4.4)	10,382 (5.1)	0.04	4,504 (4.5)	4,482 (4.5)	0.00
Pediatric comorbidity index ^{a,b}	1.34 (2.09)	1.03 (1.76)	0.16	1.24 (1.97)	1.24 (1.99)	0.00
Prior infectious disease ^a						
Acute sinusitis ^c	0.43 (1.38)	0.30 (1.07)	0.03	0.36 (1.22)	0.35 (1.22)	0.00
Upper respiratory tract infection ^d	1.06 (2.59)	1.20 (2.68)	0.01	1.06 (2.57)	1.06 (2.61)	0.00
Community acquired pneumonia ^d	0.11 (1.15)	0.11 (1.19)	0.00	0.10 (1.09)	0.10 (1.36)	0.02
Acute otitis media ^d	0.65 (2.61)	0.73 (2.59)	0.00	0.64 (2.49)	0.65 (2.66)	0.01
Group A Strep pharyngitis ^d	1.58 (3.30)	1.44 (3.06)	0.01	1.52 (3.18)	1.51 (3.25)	0.00
COVID-19 ^e	355 (0.3)	519 (0.3)	0.00	291 (0.3)	286 (0.3)	0.00
Medications						
Influenza vaccine ^d	44,219 (37.6)	88,773 (43.8)	0.13	38,559 (38.8)	38,575 (38.8)	0.00
Nasal corticosteroids ^f	14,310 (12.2)	16,666 (8.2)	0.13	10,877 (10.9)	10,904 (11.0)	0.00
Oral corticosteroids ^f	12,082 (10.3)	13,226 (6.5)	0.14	8,655 (8.7)	8,657 (8.7)	0.00
Inhaled corticosteroids	2,859 (2.4)	4,015 (2.0)	0.03	2,264 (2.3)	2,276 (2.3)	0.00
Proton pump inhibitors ^e	1,389 (1.2)	1,673 (0.8)	0.04	1,078 (1.1)	1,088 (1.1)	0.00
H2-Receptor Antagonists ^e	884 (0.8)	1,531 (0.8)	0.00	708 (0.7)	699 (0.7)	0.00
Number of distinct prescriptions ^{d,g}	2 (1,5)	2 (0,4)	0.19	2 (1,4)	2 (1,4)	0.00
No. prior amox uses ^{a,c}	0.36 (0.70)	0.51 (0.84)	0.19	0.38 (0.73)	0.39 (0.72)	0.01

No. prior amox/clav uses ^{a,c}	0.26 (0.66)	0.13 (0.43)	0.23	0.19 (0.52)	0.19 (0.53)	0.00
No. prior broad antibiotics ^{a,h}	0.37 (0.80)	0.31 (0.73)	0.08	0.34 (0.76)	0.34 (0.78)	0.00
Days' supply of initial antibiotic dispensation						
Fewer than 4 days	210 (0.2)	449 (0.2)	0.00	190 (0.2)	207 (0.2)	0.00
5 – 7 days	13,335 (11.3)	9,781 (4.8)	0.24	8,112 (8.2)	8,042 (8.1)	0.00
8 – 9 days	390 (0.3)	714 (0.4)	0.02	348 (0.3)	350 (0.4)	0.02
10 days	91,977 (78.2)	173,585 (85.7)	0.20	81,148 (81.6)	81,288 (81.7)	0.00
11 – 14 days	8,838 (7.5)	14,800 (7.3)	0.01	7,431 (7.5)	7,374 (7.4)	0.00
More than 15 days	2,909 (2.5)	3,153 (1.6)	0.06	2,242 (2.3)	2,210 (2.2)	0.01
Care setting						
Office	101,895 (86.6)	184,682 (91.2)	0.15	87,700 (88.2)	87,673 (88.1)	0.00
Urgent care	11,316 (9.6)	12,005 (5.9)	0.14	8,329 (8.4)	8,367 (8.4)	0.00
Retail health clinic	718 (0.6)	579 (0.3)	0.04	454 (0.5)	453 (0.5)	0.00
Emergency room	901 (0.8)	707 (0.3)	0.07	601 (0.6)	568 (0.6)	0.00
Other/missing/unknown	2,829 (2.4)	4,509 (2.2)	0.01	2,387 (2.4)	2,410 (2.4)	0.00
Prescribing provider type						
Pediatrician	58,149 (49.4)	124,927 (61.7)	0.25	52,611 (52.9)	52,671 (53.0)	0.00
Family Medicine	16,887 (14.4)	22,898 (11.3)	0.09	13,718 (13.8)	13,672 (13.7)	0.00
Nurse practitioner	8,126 (6.9)	11,143 (5.5)	0.06	6,495 (6.5)	6,449 (6.5)	0.00
Physician's assistant	2,706 (2.3)	3,194 (1.6)	0.05	2,064 (2.1)	2,072 (2.1)	0.00
Peds Emergency Med	104 (0.1)	158 (0.1)	0.00	91 (0.1)	90 (0.1)	0.00
Emergency Med	3,631 (3.1)	4,458 (2.2)	0.06	2,772 (2.8)	2,754 (2.8)	0.00
All others	28,056 (23.8)	35,704 (17.6)	0.15	21,720 (21.8)	21,763 (21.9)	0.00
Healthcare Utilization ^{a,d}						
Outpatient nurse encounters	0.05 (0.79)	0.04 (0.55)	0.02	0.05 (0.76)	0.05 (0.71)	0.00
Outpatient encounters	5.25 (4.62)	5.07 (4.31)	0.04	5.08 (4.43)	5.07 (4.51)	0.00
Emergency department encounters	0.27 (0.73)	0.25 (0.69)	0.02	0.26 (0.71)	0.26 (0.71)	0.00
Inpatient encounters	0.11 (1.48)	0.09 (1.48)	0.02	0.10 (1.43)	0.10 (1.40)	0.00
Bacterial conjunctivitis at time of cohort entry	3,124 (2.7)	3,686 (1.8)	0.06	2,435 (2.4)	2,453 (2.5)	0.01

Insurance plan type						
Comprehensive	1,973 (1.7)	4,056 (2.0)	0.02	1,737 (1.7)	1,672 (1.7)	0.00
EPO	1,038 (0.9)	1,520 (0.8)	0.01	847 (0.9)	865 (0.9)	0.00
HMO	12,146 (10.3)	21,625 (10.7)	0.01	10,406 (10.5)	10,463 (10.5)	0.00
POS	7,405 (6.3)	10,622 (5.2)	0.05	5,932 (6.0)	5,872 (5.9)	0.00
PPO	60,509 (51.4)	103,829 (51.3)	0.00	51,059 (51.3)	50,960 (51.2)	0.00
PPO with capitation	572 (0.5)	953 (0.5)	0.00	490 (0.5)	499 (0.5)	0.00
HDHP	15,274 (13.0)	27,110 (13.4)	0.01	13,086 (13.2)	13,142 (13.2)	0.00
CDHP	17,139 (14.6)	30,263 (14.9)	0.01	14,589 (14.7)	14,670 (14.7)	0.00
Missing	1,603 (1.4)	2,504 (1.2)	0.02	1,325 (1.3)	1,328 (1.3)	0.00
Pharmacy copays, USD ^a	9.32 (22.61)	8.72 (24.11)	0.03	9.23 (22.15)	9.30 (27.04)	0.00

All values are number (%) unless otherwise noted. All patient characteristics were assessed in the year preceding cohort entry, unless otherwise noted (age was included as a continuous variable). All listed covariates were included in estimation of the propensity score.

^aMean (sd).

^bPediatric comorbidity index predicts the one-year risk of hospitalization in children based upon 24 conditions assessed via ICD-10 codes and was developed and validated using the MarketScan database. The score ranges from 0 to 29, with each point increase associated with 1.39 increased odds of hospitalization. [add appropriate numerical citation here]

^cAssessed 365 to 30 days prior to cohort entry

^dAssessed in 365 days prior to cohort entry

^eAssessed in 90 days prior to cohort entry

^fAssessed in 30 days prior to and including day of cohort entry

^gMedian (IQR)

^hIncludes cefdinir, cefpodoxime, cefixime, azithromycin, levofloxacin, moxifloxacin.

eTable 5. Counts of Complications of Sinusitis Among Patients Who Experienced Treatment Failure in The Primary Analysis

Complication of Sinusitis	Amoxicillin-clavulanate	Amoxicillin
Orbital cellulitis	10	3
Intracranial abscess	2	1
Meningitis	2	0
Functional Endoscopic Sinus Surgery	0	0
Intracranial thrombosis	0	0
Neurosurgery	0	0
Orbital osteomyelitis	0	0
Other acute osteomyelitis	0	0

eTable 6. Treatment Failure

Outcome	No. / total No. (%)		Difference (95% CI), %	Relative risk (95% CI)
	Amoxicillin-clavulanate Exposure	Amoxicillin Referent		
Overall Composite Treatment Failure Outcome (primary outcome)				
Unadjusted	3,784 / 117,659 (3.2)	5,710 / 202,482 (2.8)	0.4 (0.27, 0.52)	1.15 (1.10, 1.19)
Propensity score matched	3,209 / 99,471 (3.2)	2,928 / 99,471 (2.9)	0.28 (0.13, 0.43)	1.10 (1.05, 1.16)
High dimensional propensity score matched	3,194 / 99,183 (3.2)	2,973 / 99,183 (3.0)	0.22 (0.07, 0.38)	1.08 (1.02, 1.13)
Component outcomes				
New antibiotic dispensation without an outpatient encounter ^a				
Unadjusted	2,523 / 117,659 (2.1)	2,961 / 202,482 (1.5)	0.68 (0.59, 0.78)	1.48 (1.40, 1.56)
Propensity score matched	2,179 / 99,471 (2.2)	1,550 / 99,471 (1.6)	0.63 (0.51, 0.75)	1.42 (1.33, 1.51)
High dimensional propensity score matched	2,165 / 99,180 (2.2)	1,538 / 99,180 (1.6)	0.63 (0.51, 0.75)	1.42 (1.33, 1.51)
New antibiotic dispensation with outpatient sinusitis encounter ^a				
Unadjusted	1,238 / 117,659 (1.1)	2,790 / 202,482 (1.4)	-0.33 (-0.40, -0.25)	0.76 (0.71, 0.82)
Propensity score matched	1,010 / 99,471 (1.0)	1,405 / 99,471 (1.4)	-0.40 (-0.49, -0.30)	0.72 (0.66, 0.78)
High dimensional propensity score matched	1,005 / 99,135 (1.0)	1,418 / 99,135 (1.4)	-0.42 (-0.51, -0.32)	0.71 (0.65, 0.77)
Emergency department encounter for acute sinusitis				
Unadjusted	74 / 117,659 (0.1)	67 / 202,482 (0.0)	0.03 (0.01, 0.05)	1.90 (1.37, 2.65)
Propensity score matched	58 / 99,471 (0.1)	33 / 99,471 (0.0)	0.03 (0.01, 0.04)	1.76 (1.15, 2.70)
High dimensional propensity score matched	56 / 99,104 (0.1)	43 / 99,104 (0.0)	0.01 (-0.01, 0.03)	1.30 (0.88, 1.94)
Inpatient encounter for acute sinusitis				
Unadjusted	6 / 117,659 (0.0)	3 / 202,482 (0.0)	0.00 (-0.00, 0.01)	3.44 (0.86, 13.76)
Propensity score matched	5 / 99,471 (0.0)	1 / 99,471 (0.0)	0.00 (0.00, 0.01)	5.00 (0.58, 42.80)
High dimensional propensity score matched	5 / 99,216 (0.0)	2 / 99,216 (0.0)	0.00 (-0.00, 0.01)	2.50 (0.49, 12.89)
Inpatient encounter for sinusitis complications				
Unadjusted	16 / 117,659 (0.0)	6 / 202,482 (0.0)	0.01 (0.00, 0.02)	4.59 (1.80, 11.73)
Propensity score matched	14 / 99,471 (0.0)	4 / 99,471 (0.0)	0.01 (0.00, 0.02)	3.50 (1.15, 10.63)
High dimensional propensity score matched	15 / 99,146 (0.0)	5 / 99,146 (0.0)	0.01 (0.00, 0.02)	3.00 (1.09, 8.25)
Serious treatment failure^b				

Unadjusted	87 / 117,659 (0.1)	71 / 202,482 (0.0)	0.04 (0.02, 0.06)	2.11 (1.54, 2.88)
Propensity score matched	70 / 99,471 (0.1)	35 / 99,471 (0.0)	0.04 (0.01, 0.06)	2.00 (1.33, 3.00)
High dimensional propensity score matched	66 / 99,123 (0.1)	39 / 99,123 (0.0)	0.03 (0.01, 0.05)	1.69 (1.14, 2.52)

Treatment failure is the first occurrence of any of: a new, different antibiotic dispensation without a same-day outpatient encounter, a new, different antibiotic dispensation with a same-day outpatient acute sinusitis encounter, an ED or inpatient encounter for acute sinusitis, and an inpatient encounter for complications of sinusitis. Serious treatment failure is the first occurrence of an ED encounter for acute sinusitis, inpatient encounter for acute sinusitis, or inpatient encounter for a complication of sinusitis.

eTable 7. Adverse Outcomes

Outcome	No. / total No. (%)		Mean difference (95% CI), %	Relative risk (95% CI)
	Amoxicillin-clavulanate Exposure	Amoxicillin Referent		
Any adverse event				
Unadjusted	2,642 / 117,659 (2.2)	4,300 / 202,482 (2.1)	0.12 (0.02, 0.23)	1.06 (1.02, 1.11)
PS matched	2,249 / 99,471 (2.3)	1,970 / 99,471 (2.0)	0.28 (0.15, 0.41)	1.15 (1.08, 1.22)
HdPS matched	2,216 / 99,302 (2.2)	2,024 / 99,302 (2.0)	0.19 (0.07, 0.32)	1.10 (1.03, 1.17)
Gastrointestinal symptoms^{a,b}				
Unadjusted	1,383 / 117,659 (1.2)	1,944 / 202,482 (1.0)	0.22 (0.14, 0.29)	1.22 (1.14, 1.31)
PS matched	1,160 / 99,471 (1.2)	1,014 / 99,471 (1.0)	0.14 (0.06, 0.24)	1.15 (1.05, 1.25)
HdPS matched	1,141 / 99,244 (1.2)	1,004 / 99,244 (1.0)	0.14 (0.05, 0.23)	1.14 (1.05, 1.24)
Yeast infection^c				
Unadjusted	516 / 117,659 (0.4)	705 / 202,482 (0.3)	0.09 (0.04, 0.14)	1.26 (1.12, 1.41)
PS matched	443 / 99,471 (0.4)	333 / 99,471 (0.3)	0.11 (0.06, 0.17)	1.33 (1.16, 1.54)
HdPS matched	447 / 99,140 (0.5)	313 / 99,140 (0.3)	0.14 (0.08, 0.19)	1.43 (1.24, 1.65)
Skin reactions^a				
Unadjusted	406 / 117,659 (0.3)	898 / 202,482 (0.4)	-0.10 (-0.14, -0.05)	0.78 (0.69, 0.87)
PS matched	356 / 99,471 (0.4)	331 / 99,471 (0.3)	0.02 (-0.03, 0.08)	1.08 (0.93, 1.25)
HdPS matched	361 / 99,270 (0.4)	355 / 99,270 (0.4)	0.01 (-0.05, 0.06)	1.02 (0.88, 1.18)
Hypersensitivity reactions^d				
Unadjusted	416 / 117,659 (0.4)	943 / 202,482 (0.5)	-0.11 (-0.16, -0.07)	0.76 (0.68, 0.85)
PS matched	361 / 99,471 (0.4)	375 / 99,471 (0.4)	-0.01 (-0.07, 0.04)	0.96 (0.83, 1.11)
HdPS matched	352 / 99,167 (0.4)	401 / 99,167 (0.4)	-0.05 (-0.10, 0.01)	0.88 (0.76, 1.01)
<i>C. difficile</i> infection^c				
Unadjusted	29 / 117,659 (0.0)	24 / 202,482 (0.0)	0.01 (0.00, 0.02)	2.08 (1.21, 3.57)
PS matched	22 / 99,471 (0.0)	12 / 99,471 (0.0)	0.01 (0.00, 0.02)	1.83 (0.91, 3.71)
HdPS matched	24 / 99,191 (0.0)	14 / 99,191 (0.0)	0.01 (-0.00, 0.02)	1.71 (0.89, 3.31)
Acute kidney injury^a				
Unadjusted	9 / 117,659 (0.0)	10 / 202,482 (0.0)	0.00 (-0.00, 0.01)	1.55 (0.63, 3.81)
PS matched	8 / 99,471 (0.0)	2 / 99,471 (0.0)	0.00 (-0.00, 0.01)	4.00 (0.85, 18.84)
HdPS matched	9 / 99,206 (0.0)	6 / 99,206 (0.0)	0.00 (-0.01, 0.01)	1.50 (0.53, 4.21)

^aMeasured from day 1 to day 14 after cohort entry date.

^bThe first occurrence of: nausea/vomiting, abdominal pain, non-*C. difficile* diarrhea.

^cMeasured from day 1 to day 90 after cohort entry date.

^dThe first occurrence of: anaphylaxis, laryngeal edema, angioedema, unspecified allergy, and urticaria. Anaphylaxis, laryngeal edema, and angioedema were measured from day 0 to day 2 after cohort entry date, while unspecified allergy and urticaria were measured from day 1 to day 14 after cohort entry date.

eTable 8. Treatment Failure and Adverse Events by Age

Outcome	Amoxicillin-clavulanate, No. / total No. (%)	Amoxicillin, No. / total No. (%)	Mean difference (95% CI), %	Relative risk (95% CI)
Ages 0 – 5 years				
Treatment Failure				
Unadjusted	930 / 23,816 (3.9)	2,122 / 74,685 (2.8)	1.10 (0.81, 1.32)	1.39 (1.29, 1.50)
Propensity Score Matched	869 / 22,573 (3.9)	725 / 22,573 (3.2)	0.64 (0.30, 0.98)	1.21 (1.09, 1.33)
Adverse Events				
Unadjusted	799 / 23,816 (3.4)	2,139 / 74,685 (2.9)	0.49 (0.23, 0.75)	1.17 (1.08, 1.27)
Propensity Score Matched	759 / 22,573 (3.4)	622 / 22,573 (2.8)	0.61 (0.29, 0.92)	1.23 (1.10, 1.37)
Ages 6 – 11 years				
Treatment Failure				
Unadjusted	860 / 27,483 (3.1)	1,536 / 61,677 (2.5)	0.64 (0.41, 0.87)	1.27 (1.16, 1.38)
Propensity Score Matched	798 / 25,975 (3.1)	690 / 25,975 (2.7)	0.42 (0.13, 0.70)	1.16 (1.05, 1.29)
Adverse Events				
Unadjusted	553 / 27,483 (2.0)	988 / 61,677 (1.6)	0.41 (0.21, 0.61)	1.26 (1.13, 1.39)
Propensity Score Matched	512 / 25,975 (2.0)	433 / 25,975 (1.7)	0.30 (0.07, 0.53)	1.19 (1.04, 1.35)
Ages 12 – 17 years				
Treatment Failure				
Unadjusted	1,994 / 66,360 (3.0)	2,052 / 66,120 (3.1)	-0.10 (-0.28, 0.09)	0.97 (0.91, 1.03)
Propensity Score Matched	1,489 / 49,582 (3.0)	1,564 / 49,582 (3.2)	-0.15 (-0.37, 0.06)	0.95 (0.88, 1.02)
Adverse Events				
Unadjusted	1,290 / 66,360 (1.9)	1,173 / 66,120 (1.8)	0.17 (0.02, 0.32)	1.10 (1.01, 1.19)
Propensity Score Matched	937 / 49,582 (1.9)	903 / 49,582 (1.8)	0.07 (-0.10, 0.24)	1.04 (0.95, 1.14)

The sum of patients across strata does not equal the total number of patients in the primary analyses due to propensity score estimation and matching occurring after patients were stratified by age.

eTable 9. Sensitivity Analyses

Outcome	No. / total No. (%)		Mean difference (95% CI), %	Relative risk (95% CI)
	Amoxicillin-clavulanate	Amoxicillin		
Primary analysis	3,209 / 99,471 (3.2)	2,928 / 99,471 (2.9)	0.28 (0.13, 0.43)	1.10 (1.05, 1.16)
Washout: -1 to -180 days ^a	2,042 / 69,448 (2.9)	1,823 / 69,448 (2.6)	0.32 (0.14, 0.49)	1.12 (1.05, 1.20)
Washout: -1 to -365 days ^a	1,326 / 47,498 (2.8)	1,145 / 47,498 (2.4)	0.38 (0.18, 0.58)	1.16 (1.07, 1.26)
Outcome misclassification ^b	3,268 / 99,471 (3.3)	3,016 / 99,471 (3.03)	0.25 (0.1, 0.41)	1.09 (1.03, 1.14)
Failure and relapse ^c	5,146 / 99,471 (5.2)	4,981 / 99,471 (5.01)	0.17 (-0.03, 0.36)	1.03 (0.99, 1.08)
10-day supply only ^d	2,585 / 81,483 (3.2)	2,391 / 81,483 (2.9)	0.24 (0.07, 0.41)	1.08 (1.02, 1.15)

Treatment failure sensitivity analyses after 1:1 propensity score matching. Note that 10-day supply and Bacterial infections only analyses were identified post-hoc, while all other analyses were prespecified.

^aWashout period is exclusion window for (1) any antibiotic dispensation and (2) an ICD-10 code for acute sinusitis, inpatient or outpatient, extended as indicated from baseline washout period of 30 days in primary analysis.

^bOutcome misclassification analysis is same as primary analysis, with exception of outcome measure, which includes ICD-10 codes for both acute sinusitis (as in primary analysis) and recurrent sinusitis.

^cMeasured 1 to 30 days after cohort entry

^dCohort limited to only patients who were dispensed 10-day supplies of index antibiotic. Analysis was then same as primary analysis.

eTable 10. Control Outcomes

Outcome	No. / total No. (%)		Mean difference (95% CI), %	Relative Risk (95% CI)
	Amoxicillin-clavulanate	Amoxicillin		
Ingrown nail				
Unadjusted	416 / 117,659 (0.4)	406 / 202,482 (0.2)	0.15 (0.11, 0.19)	1.76 (1.54, 2.02)
Propensity score matched	313 / 99,471 (0.3)	266 / 99,471 (0.3)	0.05 (-0.09, 0.10)	1.18 (1.00, 1.39)
HdPS matched	302 / 99,299 (0.3)	283 / 99,299 (0.3)	0.02 (-0.03, 0.07)	1.07 (0.91, 1.26)
Tendonitis/tendinopathy				
Unadjusted	373 / 117,659 (0.3)	366 / 202,482 (0.2)	0.14 (0.10, 0.17)	1.75 (1.52, 2.03)
Propensity score matched	284 / 99,471 (0.3)	263 / 99,471 (0.3)	0.02 (-0.03, 0.07)	1.08 (0.91, 1.28)
HdPS matched	263 / 99,330 (0.3)	261 / 99,330 (0.3)	0.00 (-0.10, 0.05)	1.01 (0.85, 1.20)
Wart removal				
Unadjusted	1,094 / 117,659 (0.9)	1,549 / 202,482 (0.8)	0.17 (0.10, 0.23)	1.22 (1.13, 1.31)
Propensity score matched	906 / 99,471 (0.9)	887 / 99,471 (0.9)	0.02 (-0.06, 0.10)	1.02 (0.93, 1.12)
HdPS matched	876 / 99,184 (0.9)	899 / 99,184 (0.9)	-0.02 (-0.10, 0.06)	0.97 (0.89, 1.07)

Outcomes were assessed on days +1 through +90 after cohort entry to evaluate for differences in health seeking behavior between group