JAMA | Original Investigation

Amoxicillin-Clavulanate vs Amoxicillin for Acute Sinusitis in Adults

Timothy J. Savage, MD, MPH, MSc; Anne M. Butler, PhD, MS; Matthew P. Kronman, MD, MSCE; Michael J. Durkin, MD, MPH; Sushama Kattinakere Sreedhara, MBBS, MSPH; Sarah Kabbani, MD, MSc; Lauri A. Hicks, DO; Krista F. Huybrechts, MS, PhD

IMPORTANCE Acute sinusitis has the highest rate of antibiotic prescribing in adults younger than 65 years. There is no consensus regarding whether amoxicillin-clavulanate or amoxicillin should be first-line treatment for uncomplicated acute sinusitis in adults.

OBJECTIVE To compare the risk of treatment failure and adverse events between standard-dose amoxicillin-clavulanate vs standard-dose amoxicillin for acute sinusitis in adults.

DESIGN, SETTING, AND PARTICIPANTS New-user, active comparator retrospective cohort study using a nationwide health care utilization database comparing amoxicillin-clavulanate vs amoxicillin for adults aged 18 to 64 years with outpatient acute sinusitis. Patients with a new acute sinusitis diagnosis between January 1, 2018, and December 1, 2023, were eligible. Statistical analysis was conducted between July and November 2025. Propensity score matching was used to help mitigate confounding.

EXPOSURES Standard-dose amoxicillin-clavulanate (875 mg-125 mg twice daily) or standard-dose amoxicillin (875 mg twice daily or 500 mg 3 times daily).

MAIN OUTCOMES AND MEASURES The primary outcome was treatment failure, defined as the first occurrence of a new antibiotic dispensation (with or without an outpatient visit), emergency department or inpatient encounter for acute sinusitis, or inpatient encounter for a sinusitis complication assessed 1 to 14 days after treatment initiation. Antibiotic-associated adverse events and secondary infections were also assessed.

RESULTS The full cohort included 521 244 eligible patients. After propensity score matching, there were 234 608 patients (117 304 patients per group; 65.5% female; median [IQR] age, 43 [31-54] years). Treatment failure occurred in 3.1% of patients overall, with 0.03% requiring an emergency department or inpatient encounter. There was no observed difference in the risk of treatment failure between the amoxicillin-clavulanate vs amoxicillin groups (3.0% vs 3.1%; risk ratio [RR], 0.96 [95% CI, 0.92-1.01]), which was consistent across sensitivity analyses. There was no difference in antibiotic-associated adverse events (1.3% vs 1.2%; RR, 1.04 [95% CI, 0.97-1.12]). The risk of secondary infections was higher for amoxicillin-clavulanate vs amoxicillin, including yeast infections (1.1% vs 0.8%; RR, 1.40 [95% CI, 1.29-1.53]) and *Clostridioides difficile* infections (0.04% vs 0.02%; RR, 2.14 [95% CI, 1.29-3.54]).

CONCLUSIONS AND RELEVANCE In this observational study of patients aged 18 to 64 years with acute sinusitis treated in the outpatient setting with standard-dose amoxicillin-clavulanate or standard-dose amoxicillin, there was no observed difference in treatment failure. Amoxicillin-clavulanate was associated with a higher, albeit rare, risk of adverse events. These findings suggest standard-dose amoxicillin may be a preferred first-line treatment for adults with uncomplicated acute sinusitis.

JAMA. doi:10.1001/jama.2025.26902
Published online April 18, 2026.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Timothy J. Savage, MD, MPH, MSc, Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, 1620 Tremont St, Ste 3030, Boston, MA 02120 (tsavage@mgb.org).

Acute sinusitis is associated with the highest rate of antibiotic prescribing in the US among adults aged 18 to 65 years, with 2 visits per 100 adults resulting in 4 million antibiotic courses annually.[1-3] Amoxicillin-clavulanate and amoxicillin are the most frequently prescribed antibiotics, accounting for approximately 45% of prescriptions.[3] The Infectious Diseases Society of America makes a "weak" recommendation for amoxicillin-clavulanate as first-line treatment, rating the supporting evidence as low quality, while the American Academy of Otolaryngology-Head and Neck Surgery recommends either amoxicillin or amoxicillin-clavulanate.[4,5] Clavulanate is a β-lactamase inhibitor that extends antimicrobial coverage to organisms resistant to amoxicillin via β-lactamase production,[6] with the increased spectrum balanced against more adverse events and potential propagation of antimicrobial resistance.[7-10] Understanding whether there are differences in treatment failure or adverse events between amoxicillin-clavulanate and amoxicillin is essential to identify the optimal empiric antibiotic.

Bacteria are recovered in approximately 70% of patients meeting strict diagnostic criteria for acute sinusitis, with *Streptococcus pneumoniae*, nontypeable *Haemophilus influenzae*, and *Moraxella catarrhalis* most frequently isolated.[11,12] *S pneumoniae* resistance to amoxicillin is not mediated via a β-lactamase and thus amoxicillin-clavulanate adds no benefit. *H influenzae* β-lactamase expression occurs in up to 60% of isolates, although the clinical significance of this is unclear, as *H influenzae* is a less common cause of complicated sinusitis, suggestive of resolution even when an antibiotic without β-lactamase inhibition is administered.[13-15] *M catarrhalis* universally expresses a β-lactamase, although there is evidence that upper respiratory tract infections with this organism may resolve spontaneously.[16] Although there may be theoretical benefits to amoxicillin-clavulanate over amoxicillin, clinical data are lacking.

A prior study of nearly 200 000 children with acute sinusitis found no difference in treatment failure between amoxicillin-clavulanate and amoxicillin (risk ratio [RR], 1.10 [95% CI, 1.05-1.16]) and slightly increased adverse events with amoxicillin-clavulanate.[10] A study in Veterans Health Administration emergency department and urgent care settings with mostly male and older patients reported similar results.[17] To the study investigators' knowledge, no randomized clinical trial has compared the 2 treatments since a study of 188 children published in 2001, which found no difference in treatment failure.[18] This study aimed to compare the risk of treatment failure and adverse events for adults with acute sinusitis treated in the outpatient setting with amoxicillin-clavulanate vs amoxicillin.

Key Points

Question For acute sinusitis in adults younger than 65 years, is standard-dose amoxicillin-clavulanate associated with different risks of treatment failure and adverse events compared with standard-dose amoxicillin?

Findings In this retrospective cohort study of 521 244 adults with acute sinusitis, overall treatment failure was rare (3.1%). There was no observed difference in treatment failure between treatment groups and an elevated relative risk, corresponding to a small absolute increase in risk, of yeast infections and *Clostridioides difficile* infections among patients treated with amoxicillin-clavulanate.

Meaning These findings support standard-dose amoxicillin as a preferred empiric choice for adults younger than 65 years with uncomplicated acute sinusitis for whom an antibiotic is indicated.

Methods

Data Source

The Merative MarketScan Commercial database includes outpatient prescription medication dispensations, diagnoses, demographic information, health care encounters, and procedures.

Study Design and Population

This was a new-user, active comparator, nationwide retrospective cohort study of patients aged 18 to 64 years with new diagnoses of acute sinusitis between January 1, 2018, and December 1, 2023 (eFigure 1 in Supplement 1).[19,20] Cohort entry was defined as a dispensation of standard-dose amoxicillin-clavulanate (875 mg-125 mg twice daily) or standard-dose amoxicillin (875 mg twice daily or 500 mg 3 times daily), identified by National Drug Codes (eTable 1 in Supplement 1), for a 5-, 7-, or 10-day supply, with a same-day outpatient encounter with an *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) code for acute sinusitis (J01.×0).[21] Patients were excluded if they were younger than 18 years or 65 years or older; lacked 365 days of continuous insurance enrollment prior to cohort entry; received more than 1 antibiotic on cohort entry; or received any systemic antibiotic (oral, intravenous, or intramuscular route), acute sinusitis diagnosis, or were hospitalized in the 30 days prior to cohort entry. Patients were excluded for chronic sinus disease, a concurrent bacterial infection, influenza or COVID-19 within 7 days, or an immunization at the index encounter (see eTable 2 in Supplement 1 for exclusion definitions). Each patient contributed 1 treatment episode.

Exposures

Patients dispensed standard-dose amoxicillin-clavulanate were considered the exposed group; patients dispensed standard-dose amoxicillin were the referent group. Standard-dose formulations were chosen because a prior randomized clinical trial showed no difference in outcomes between standard- vs high-dose amoxicillin-clavulanate for acute sinusitis in adults.[22]

Outcomes

The primary treatment failure outcome was assessed 1 to 14 days after cohort entry. Treatment failure was defined as the

first occurrence of (1) a new antibiotic dispensation, different from the index antibiotic, in the absence of an outpatient encounter (eg, a prescription called in after an unbilled phone encounter); (2) a new antibiotic dispensation, different from the index antibiotic, with a same-day outpatient encounter for acute sinusitis; (3) an emergency department encounter for acute sinusitis; (4) an inpatient encounter for acute sinusitis; or (5) an inpatient encounter for a complication of sinusitis (see eTable 3 in Supplement 1 for outcome definitions). To attempt to capture treatment failure due to inadequate clinical response (rather than antibiotic-associated adverse events), we also required the following: no documentation of an alternative bacterial infection or chronic sinusitis between treatment start and outcome and, for outpatient and emergency department outcome components, no antibiotic-associated adverse events on the day of the outcome. Secondary analyses included the 5 component treatment failure outcomes individually.

We captured incident antibiotic-associated adverse events, including gastrointestinal, dermatologic, hypersensitivity, and kidney adverse events, as well as secondary infections, including yeast and *Clostridioides difficile* infections (see eTable 4 in Supplement 1 for definitions and follow-up windows). Adverse events were considered incident if there was no occurrence of the event in the 30 days prior to the outcome or 60 days prior for secondary infections.

Covariates

We prespecified potential confounders previously shown (or hypothesized) to be associated with both receipt of a broader antibiotic and occurrence of the outcomes, including age, chronic conditions (including immunocompromise and smoking), residence in the southern US, clinician specialty, and whether the patient was new or established with the practice (see eTables 5 and 6 in Supplement 1 for covariate definitions).[23-26] To mitigate confounding by indication, we included covariates potentially associated with acute sinusitis severity: antibiotic days' supply, coded symptoms at index visit, diagnostic testing at index visit, visit complexity level, patient comorbidities, and concurrent prescription medications. We captured whether patients took antibiotics in the year prior (before the 30-day washout window) due to the potential for infection with resistant organisms after extensive antibiotic exposure. We captured measures of health care utilization to account for health care access and health care-seeking behavior that could affect the likelihood of the primary outcome, including adherence to guideline-recommended cancer screening, number of previous health care encounters, number of distinct medications, and insurance plan type. In general, covariates were assessed during the 365 days prior to cohort entry (eTable 5 in Supplement 1).

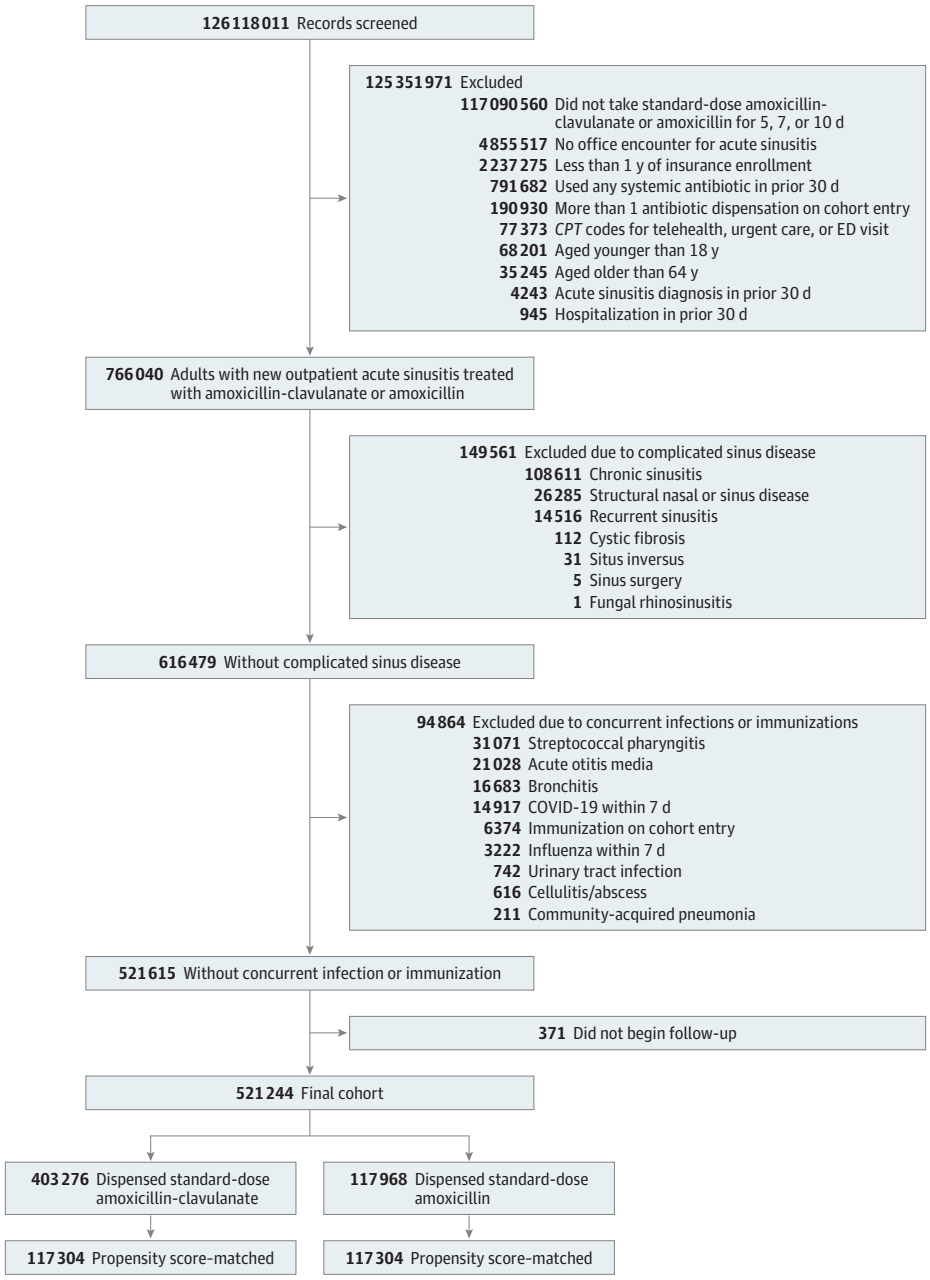
Analyses

Statistical analysis was conducted between July and November 2025. To achieve balance in measured covariates by exposure group, propensity scores for the likelihood to be dispensed amoxicillin-clavulanate were estimated using logistic regression, accounting for all prespecified covariates (eTable 5 in Supplement 1).[27,28] Propensity score nearest neighbor 1:1 matching with a maximum caliper of 1% was performed. Covariate balance between groups was assessed using absolute standardized differences, with differences greater than 0.1 indicating substantial imbalance.[29] Treatment effects were estimated without further adjustment because all covariates were balanced in the matched cohort. RRs were estimated using modified Poisson regression. Risk differences were estimated using generalized linear regression with an identity link function and normal error distribution. Cumulative incidence curves with 95% CIs were estimated using the cumulative incidence function, accounting for losses to follow-up (end of data, end of enrollment, and death). Subgroup analyses included age, sex, immunocompromised status, and amoxicillin dosing strategy (875 mg twice daily or 500 mg 3 times daily).[30]

Sensitivity analyses were conducted to assess the robustness of the primary results. First, high-dimensional propensity scores were estimated to capture additional confounders or proxies of confounders through a bias-ranking approach that incorporated covariate prevalence and strength of association with the exposure and outcome.[31] We accounted for up to 200 covariates, including prespecified and empirically identified covariates with the strongest potential for confounding.[32] Second, because antibiotic resistance risk increases with antibiotic exposure, we extended the washout period for previously taking antibiotics from 30 days to 90 days and 180 days.[33-35] Third, we extended the outcome assessment window from 14 days to 30 days to evaluate for both treatment failure and relapse of infection. Fourth, we included *ICD-10* codes for recurrent sinusitis (J01.×1) when defining treatment failure to address potential outcome misclassification. Fifth, to assess for residual confounding attributable to differences in health care-seeking behavior, we evaluated 4 negative control outcomes, which we anticipated would not differ between treatment groups: hemorrhoids, ingrown or fungal nail, tendinitis or tendinopathy, and wart removal (eTable 4 in Supplement 1).[36] These outcomes were selected because most cases could reasonably be cared for either at home or in the office and thus the presence of an office visit for 1 of these conditions could reflect an individual's propensity to seek health care. Therefore, differences in these outcomes between groups after propensity score matching would suggest residual confounding due to differences in health care-seeking behavior.

All analyses were prespecified and performed using Aetion Substantiate with R version 4.3.3 (R Foundation) integration.[37,38] We based interpretations of results on the magnitude of the point estimate and precision of the CI for each analysis, rather than dichotomizing *P* values into significant and not significant, consistent with American Statistical Association guidance.[39] The Brigham and Women's Hospital Institutional Review Board reviewed this study under 45 CFR part 46.101(c) and 21 CFR part 56; informed consent was waived due to the use of deidentified data. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[40,41]

Figure 1. Flow Diagram of Patient Cohort in a Study of Adults With Acute Sinusitis, 2018-2023



CPT indicates *Current Procedural Terminology*; ED, emergency department.

Results

Characteristics of the Study Cohort

The cohort included 521 244 patients after the application of inclusion and exclusion criteria (**Figure 1**). Before propensity score matching, the median (IQR) age was 44 (33-54) years and 327 269 patients (62.8%) were female (**Table**). Covariates were well-balanced before propensity score matching, with several exceptions. Compared with amoxicillin, patients treated with amoxicillin-clavulanate were more frequently from the West (10.8% vs 7.6%) and less frequently from the South (49.1% vs 55.3%) US Census Regions, were more likely to be treated concurrently with oral corticosteroids (15.1% vs 11.7%), were more likely to have had previous amoxicillin-clavulanate exposure (15.3% vs 10.5%) and less likely to have had previous amoxicillin exposure (12.6% vs 17.5%), and tended to have a higher copayment on the date of antibiotic dispensation (median of $5.00 vs $2.20) (eTable 7 in Supplement 1). Additionally, treatment with a 7-day supply was more frequent and treatment (31.3% vs 18.0%) with a 10-day supply was less frequent (66.3% vs 79.5%) among patients treated with amoxicillin-clavulanate. Patients were rarely treated with a 5-day supply (2.4% vs 2.5%). After propensity score matching,

Table. Baseline Demographic and Clinical Characteristics of the Study Cohort by Sinusitis Treatment

Characteristic	Unadjusted, No. (%)[a]			Propensity score–matched, No. (%)[a]		
	Amoxicillin-clavulanate (n = 403 276)	Amoxicillin (n = 117 968)	ASD	Amoxicillin-clavulanate (n = 117 304)	Amoxicillin (n = 117 304)	ASD
Demographics[b]						
Age, median (IQR), y	44 (33-54)	43 (31-54)	0.10	43 (31-53)	43 (31-54)	0.01
18-44	204 339 (50.7)	63 426 (53.8)	0.06	63 065 (53.8)	62 884 (53.6)	0
45-64	198 937 (49.3)	54 542 (46.2)	0.06	54 239 (46.2)	54 420 (46.4)	0
Sex						
Female	250 025 (62.0)	77 244 (65.5)	0.07	77 104 (65.7)	76 676 (65.4)	0.01
Male	153 251 (38.0)	40 724 (34.5)	0.07	40 200 (34.3)	40 628 (34.6)	0.01
Medical history[c]						
Hypertension	97 900 (24.3)	28 524 (24.2)	0	28 618 (24.4)	28 422 (24.2)	0
Obesity	80 428 (19.9)	23 512 (19.9)	0	23 649 (20.2)	23 411 (20.0)	0.01
Generalized anxiety disorder	74 654 (18.5)	21 732 (18.4)	0	21 905 (18.7)	21 594 (18.4)	0.01
Allergic rhinitis	57 139 (14.2)	17 388 (14.7)	0.02	17 705 (15.1)	17 232 (14.7)	0.01
Type 2 diabetes	38 693 (9.6)	10 763 (9.1)	0.02	10 891 (9.3)	10 729 (9.1)	0.01
Immunodeficiency	27 958 (6.9)	7589 (6.4)	0.02	7582 (6.5)	7561 (6.4)	0
Smoking	27 842 (6.9)	7578 (6.4)	0.02	7509 (6.4)	7559 (6.4)	0
Medications						
Oral corticosteroids, concurrent[b]	60 996 (15.1)	13 859 (11.7)	0.10	13 825 (11.8)	13 852 (11.8)	0
Nasal corticosteroids[d]	59 514 (14.8)	15 458 (13.1)	0.05	15 431 (13.2)	15 418 (13.1)	0
Influenza vaccine[e]	78 035 (19.4)	23 092 (19.6)	0.01	23 056 (19.7)	22 928 (19.5)	0
No. of prior amoxicillin courses[f]						
0	352 526 (87.4)	97 269 (82.5)	0.14	96 313 (82.1)	97 148 (82.8)	0.02
1	41 886 (10.4)	16 595 (14.1)	0.11	16 868 (14.4)	16 274 (13.9)	0.02
≥2	8864 (2.2)	4104 (3.5)	0.08	4123 (3.5)	3882 (3.3)	0.01
No. of prior amoxicillin-clavulanate courses[f]						
0	341 668 (84.7)	105 572 (89.5)	0.14	104 787 (89.3)	104 910 (89.4)	0
1	51 307 (12.7)	10 789 (9.1)	0.12	10 805 (9.2)	10 787 (9.2)	0
≥2	10 301 (2.6)	1607 (1.4)	0.09	1712 (1.5)	1607 (1.4)	0.01
Treatment characteristics[b]						
Days' supply of initial antibiotic dispensation						
10	267 407 (66.3)	93 728 (79.5)	0.30	93 195 (79.4)	93 070 (79.3)	0
7	126 147 (31.3)	21 282 (18.0)	0.31	21 147 (18.0)	21 281 (18.1)	0
5	9722 (2.4)	2958 (2.5)	0.01	2962 (2.5)	2953 (2.5)	0
Practice continuity						
Established patient	336 972 (83.6)	100 629 (85.3)	0.05	100 358 (85.6)	99 992 (85.2)	0.01
New patient	64 972 (16.1)	16 975 (14.4)	0.05	16 562 (14.1)	16 952 (14.5)	0.01
Unknown	1332 (0.3)	364 (0.3)	0	384 (0.3)	360 (0.3)	0

Abbreviation: ASD, absolute standardized difference.

[a] Unless otherwise noted.

[b] Assessed on cohort entry.

[c] Assessed using all data available for the duration of each patient's enrollment period.

[d] Assessed from 30 days prior to and including date of cohort entry.

[e] Assessed from 365 days prior to and including date of cohort entry.

[f] Assessed from 365 to 31 days prior to date of cohort entry.

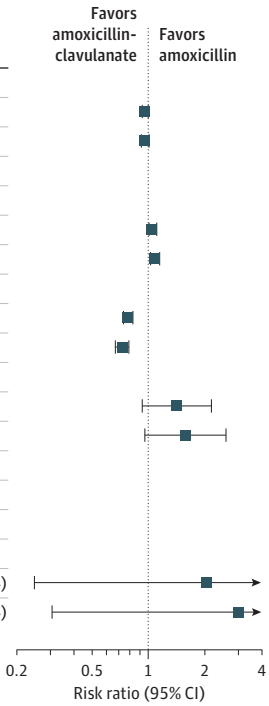
all covariates achieved balance between exposure groups (Table) (eTable 7 and eFigure 2 in Supplement 1).

Risk of Treatment Failure

After propensity score matching, treatment failure occurred in 3541 patients (3.0%) treated with amoxicillin-clavulanate and 3674 patients (3.1%) treated with amoxicillin (RR, 0.96 [95% CI, 0.92-1.01]) (**Figures 2** and **3**) (eTables 8 and 9 in Supplement 1). The most frequent reason for treatment failure was dispensation of a different antibiotic without an outpatient encounter, which occurred in 2582 patients (2.2%) treated with amoxicillin-clavulanate and 2377 patients (2.0%) treated with amoxicillin (RR, 1.09 [95% CI, 1.03-1.15]). Azithromycin was the most frequently dispensed

Figure 2. Forest Plot of Treatment Failure Before and After Propensity Score Matching

Outcome	No./total No. (%) Amoxicillin-clavulanate	Amoxicillin	Difference, % (95% CI)	Risk ratio (95% CI)
Treatment failure (primary outcome)[a]				
Unadjusted	12 197/403 276 (3.0)	3702/117 968 (3.1)	-0.11 (-0.23 to 0)	0.96 (0.93 to 1.00)
Propensity score-matched	3541/117 304 (3.0)	3674/117 304 (3.1)	-0.11 (-0.25 to 0.03)	0.96 (0.92 to 1.01)
Component treatment failure outcomes				
Antibiotic without same-day encounter				
Unadjusted	8662/403 276 (2.1)	2397/117 968 (2.0)	0.12 (0.02 to 0.21)	1.06 (1.01 to 1.11)
Propensity score-matched	2582/117 304 (2.2)	2377/117 304 (2.0)	0.18 (0.06 to 0.30)	1.09 (1.03 to 1.15)
Antibiotic with same-day acute sinusitis encounter				
Unadjusted	3550/403 276 (0.9)	1325/117 968 (1.1)	-0.24 (-0.31 to -0.18)	0.78 (0.74 to 0.83)
Propensity score-matched	962/117 304 (0.8)	1316/117 304 (1.1)	-0.30 (-0.38 to -0.22)	0.73 (0.67 to 0.79)
Acute sinusitis ED encounter				
Unadjusted	126/403 276 (<0.1)	26/117 968 (<0.1)	0.01 (0 to 0.02)	1.42 (0.93 to 2.16)
Propensity score-matched	41/117 304 (<0.1)	26/117 304 (<0.1)	0.01 (0 to 0.03)	1.58 (0.96 to 2.58)
Acute sinusitis inpatient encounter				
Unadjusted	1/403 276 (<0.1)	0/117 968	0	NA
Propensity score-matched	0/117 304 (0)	0/117 304	NA	NA
Acute sinusitis complication inpatient encounter				
Unadjusted	7/403 276 (<0.1)	1/117 968 (<0.1)	0	2.05 (0.25 to 16.64)
Propensity score-matched	3/117 304 (<0.1)	1/117 304 (<0.1)	0 (0 to 0.01)	3.00 (0.31 to 28.84)



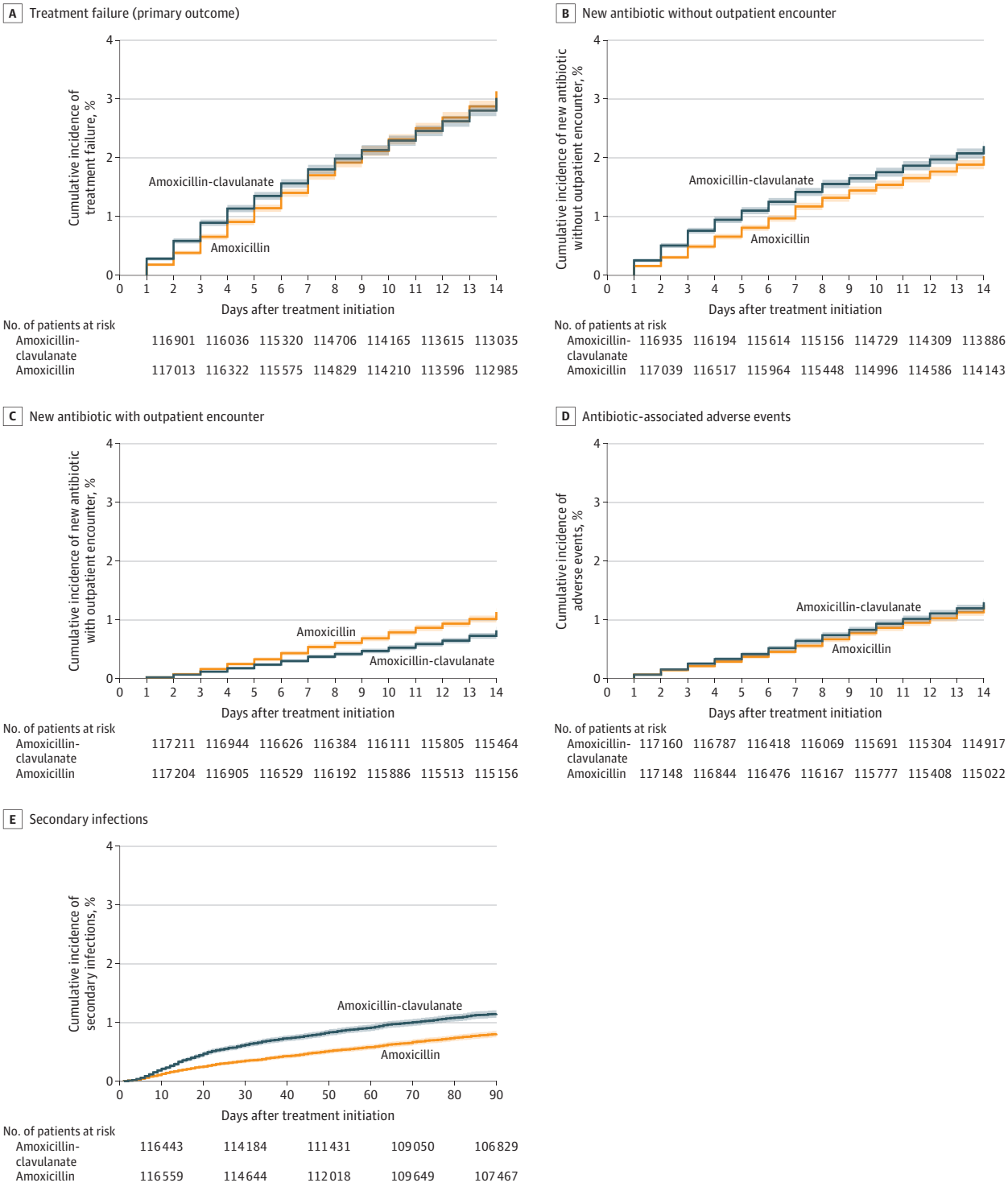
[a]Treatment failure was the first occurrence of any of the component outcomes: a new antibiotic dispensation, different from the index antibiotic, in the absence of an outpatient encounter (eg, a prescription called in after an unbilled phone encounter); a new antibiotic dispensation, different from the index antibiotic, with a same-day outpatient encounter for acute sinusitis; an ED encounter for acute sinusitis; an inpatient encounter for acute sinusitis; or an inpatient encounter for a complication of sinusitis. To attempt to capture treatment failure due to inadequate clinical response (rather than antibiotic-associated adverse events), the following was required as part of the outcome definitions: no documentation of an alternative bacterial infection or chronic sinusitis diagnosis between treatment start and the outcome and, for outpatient and ED outcome components only, no antibiotic-associated adverse events on the day of the outcome. ED indicates emergency department; NA, not applicable.

new antibiotic in both groups, followed by doxycycline among patients treated with amoxicillin-clavulanate and amoxicillin-clavulanate among patients treated with amoxicillin (eFigure 3 in Supplement 1). The second-most frequent reason for treatment failure was a return outpatient encounter with a new antibiotic dispensation, which occurred in 962 patients (0.8%) treated with amoxicillin-clavulanate and 1316 patients (1.1%) treated with amoxicillin (RR, 0.73 [95% CI, 0.67-0.79]). At return visits, patients treated with amoxicillin-clavulanate most often switched to doxycycline, while patients treated with amoxicillin most often switched to amoxicillin-clavulanate (eFigure 4 in Supplement 1). Treatment failure resulting in an emergency department encounter occurred in 41 patients (0.035%) treated with amoxicillin-clavulanate and 26 patients (0.022%) treated with amoxicillin (RR, 1.58 [95% CI, 0.96-2.58]). No treatment failure events were due to an inpatient encounter, with sinusitis as the principal diagnosis. There were 3 patients (0.003%) treated with amoxicillin-clavulanate and 1 patient (0.001%) treated with amoxicillin who had an inpatient encounter for a complication of sinusitis. This included 3 patients with bacterial meningitis and 1 patient with periorbital cellulitis with eyelid abscess.

Risk of Antibiotic-Associated Adverse Events and Secondary Infections

The risk of antibiotic-associated adverse events was similar among patients treated with amoxicillin-clavulanate (1522 [1.3%]) and patients treated with amoxicillin (1464 [1.2%]), corresponding to an RR of 1.04 (95% CI, 0.97-1.12) (Figures 3 and 4). The most frequent antibiotic-associated adverse events were gastrointestinal symptoms, occurring in 1092 patients (0.9%) treated with amoxicillin-clavulanate and 1049 patients (0.9%) treated with amoxicillin (RR, 1.04 [95% CI, 0.96-1.13]). Secondary infections were more frequent among patients treated with amoxicillin-clavulanate (1349 [1.2%]) than patients treated with amoxicillin (950 [0.8%]; RR, 1.42 [95% CI, 1.31-1.54]) (Figure 4) (eTable 10 in Supplement 1).[42] The most frequent adverse event was yeast infections, occurring in 1303 patients (1.1%) treated with amoxicillin-clavulanate and 928 patients (0.8%) treated with amoxicillin (RR, 1.40 [95% CI, 1.29-1.53]). *C difficile* infections were more frequent among patients treated with amoxicillin-clavulanate (47 [0.04%]) than patients treated with amoxicillin (22 [0.02%]; RR, 2.14 [95% CI, 1.29-3.54]), although the absolute risk difference was small (0.02% [95% CI, 0.01%-0.04%]).

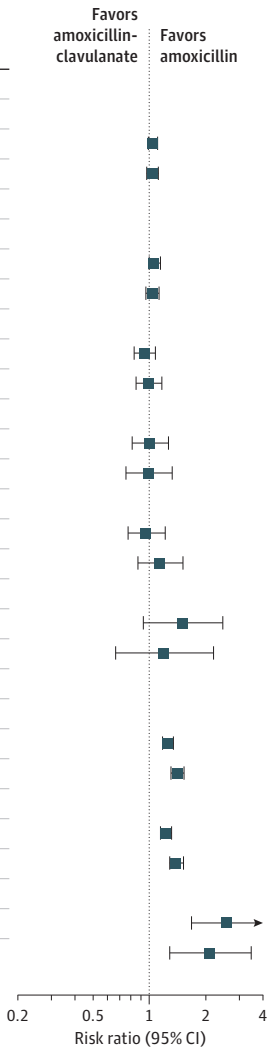
Figure 3. Cumulative Incidence Curve of Treatment Failure and Adverse Events After Propensity Score Matching



A, Treatment failure was first occurrence of new antibiotic dispensation, different from index, with no outpatient encounter (eg, prescription after unbilled phone encounter) (B); new antibiotic dispensation, different from index, with same-day outpatient encounter for acute sinusitis (C); emergency department encounter for acute sinusitis; inpatient encounter for acute sinusitis; or inpatient encounter for complication of sinusitis. To capture treatment failure due to inadequate clinical response (vs antibiotic-associated adverse events), the following was required: no documentation of alternative bacterial infection or chronic sinusitis between treatment start and outcome and, for outpatient and emergency department outcomes, no antibiotic-associated adverse events on day of outcome. D, Antibiotic-associated adverse events, first occurrence of gastrointestinal symptoms, skin and hypersensitivity reactions, antibiotic-associated event *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes, and acute kidney injury, through 14 days. E, Secondary infections, first occurrence of yeast or *Clostridioides difficile* infection, through 90 days.

Figure 4. Forest Plot of Antibiotic-Associated Adverse Events and Secondary Infections Before and After Propensity Score Matching

Outcome	No./total No. (%) Amoxicillin-clavulanate	Amoxicillin	Difference, % (95% CI)	Risk ratio (95% CI)
Antibiotic-associated adverse events[a]				
Overall				
Unadjusted	5271/403 276 (1.3)	1472/117 968 (1.2)	0.06 (-0.01 to 0.13)	1.05 (0.99 to 1.11)
Propensity score-matched	1522/117 304 (1.3)	1464/117 304 (1.2)	0.05 (-0.04 to 0.14)	1.04 (0.97 to 1.12)
Component outcomes				
Gastrointestinal symptoms[b]				
Unadjusted	3867/403 276 (1.0)	1055/117 968 (0.9)	0.07 (0 to 0.13)	1.07 (1.00 to 1.15)
Propensity score-matched	1092/117 304 (0.9)	1049/117 304 (0.9)	0.04 (-0.04 to 0.11)	1.04 (0.96 to 1.13)
Skin reactions[c]				
Unadjusted	1005/403 276 (0.2)	310/117 968 (0.3)	-0.01 (-0.05 to 0.02)	0.95 (0.83 to 1.08)
Propensity score-matched	307/117 304 (0.3)	308/117 304 (0.3)	0 (-0.04 to 0.04)	1.00 (0.85 to 1.17)
Hypersensitivity reactions[d]				
Unadjusted	332/403 276 (0.1)	96/118 037 (0.1)	0 (-0.02 to 0.02)	1.01 (0.81 to 1.27)
Propensity score-matched	96/117 375 (0.1)	96/117 375 (0.1)	0 (-0.02 to 0.02)	1.00 (0.75 to 1.33)
Antibiotic adverse event code[e]				
Unadjusted	304/403 276 (0.1)	92/117 968 (0.1)	0 (-0.02 to 0.02)	0.97 (0.77 to 1.22)
Propensity score-matched	106/117 304 (0.1)	92/117 304 (0.1)	0.01 (-0.01 to 0.04)	1.15 (0.87 to 1.52)
Acute kidney injury				
Unadjusted	99/403 276 (<0.1)	19/117 968 (<0.1)	0.01 (0 to 0.02)	1.52 (0.93 to 2.49)
Propensity score-matched	23/117 304 (<0.1)	19/117 304 (<0.1)	0 (-0.01 to 0.01)	1.21 (0.66 to 2.22)
Secondary infections[f]				
Overall				
Unadjusted	4157/403 276 (1.0)	965/117 968 (0.8)	0.21 (0.15 to 0.27)	1.26 (1.18 to 1.35)
Propensity score-matched	1349/117304 (1.2)	950/117 304 (0.8)	0.34 (0.26 to 0.42)	1.42 (1.31 to 1.54)
Yeast infection				
Unadjusted	3964/403 276 (1.0)	943/117 968 (0.8)	0.18 (0.12 to 0.25)	1.23 (1.15 to 1.32)
Propensity score-matched	1303/117 304 (1.1)	928/117 304 (0.8)	0.32 (0.24 to 0.40)	1.40 (1.29 to 1.53)
Clostridioides difficile infection				
Unadjusted	198/403 276 (<0.1)	22/117 968 (<0.1)	0.03 (0.02 to 0.04)	2.63 (1.69 to 4.09)
Propensity score-matched	47/117 304 (<0.1)	22/117 304 (<0.1)	0.02 (0.01 to 0.04)	2.14 (1.29 to 3.54)



Treatment-related adverse events and secondary infections were assessed as secondary outcomes.

[a]Measured from day 1 to day 14 after treatment initiation.

[b]First occurrence of nausea or vomiting, abdominal pain, or non–*Clostridioides difficile* diarrhea.

[c]First occurrence of skin rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, or urticaria.

[d]First occurrence of anaphylaxis, laryngeal edema, angioedema, unspecified allergy, or urticaria. Anaphylaxis, laryngeal edema, and angioedema were measured from day 0 to day 2 after treatment initiation, while unspecified allergy and urticaria were measured from day 1 to day 14 after treatment initiation.

[e]Antibiotic-associated adverse event *International Statistical Classification of Diseases and Related Health Problems, Tenth Edition* codes.

[f]Measured from day 1 to day 90 after treatment initiation.

Subgroup Analyses

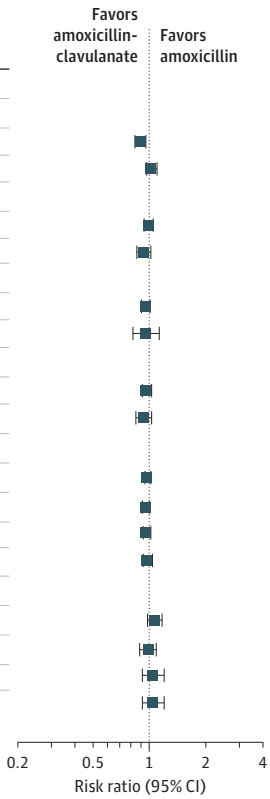
In age-stratified subgroups, there was a lower risk of treatment failure with amoxicillin-clavulanate among patients aged 18 to 44 years compared with amoxicillin (RR, 0.90 [95% CI, 0.84-0.96]). However, the absolute risk difference was small (−0.27% [95% CI, −0.45% to −0.10%]), with 365 patients needed to treat with amoxicillin-clavulanate to prevent 1 treatment failure with amoxicillin (**Figure 5**) (eTable 11 in Supplement 1). There was no observed difference in treatment failure risk among patients aged 45 to 64 years (RR, 1.03 [95% CI, 0.97-1.10]), in female (RR, 0.99 [95% CI, 0.94-1.05]) or male (RR, 0.94 [95% CI, 0.86-1.02]) patients, and in patients who were immunocompromised (RR, 0.96 [95% CI, 0.82-1.13]) or those who were not immunocompromised (RR, 0.96 [95% CI, 0.91-1.01]) (see eTable 6 in Supplement 1 for immunodeficiency definition). There was also no difference based on amoxicillin dosing strategy for 875 mg twice daily (RR, 0.97 [95% CI, 0.92-1.03]) and 500 mg 3 times daily (RR, 0.93 [95% CI, 0.85-1.03]).

Sensitivity Analyses and Negative Control Outcomes

The primary results were not sensitive to extending the antibiotic exclusion period to 90 days (RR, 0.97 [95% CI, 0.93-1.02]) or 180 days (RR, 0.98 [95% CI, 0.93-1.04]), nor to

Figure 5. Forest Plot of Subgroup Analyses, Sensitivity Analyses, and Negative Control Outcome Analyses After Propensity Score Matching

Outcome	No./total No. (%)		Difference, % (95% CI)	Risk ratio (95% CI)
	Amoxicillin-clavulanate	Amoxicillin		
Subgroup analyses				
Age, y				
18-44	1564/62 832 (2.5)	1736/62 832 (2.8)	-0.27 (-0.45 to -0.10)	0.90 (0.84 to 0.96)
45-64	2006/54 401 (3.7)	1939/54 401 (3.6)	0.12 (-0.10 to 0.35)	1.03 (0.97 to 1.10)
Sex				
Female	2552/76 731 (3.3)	2573/76 731 (3.4)	-0.03 (-0.21 to 0.15)	0.99 (0.94 to 1.05)
Male	1037/40 580 (2.6)	1104/40 580 (2.7)	-0.17 (-0.39 to 0.06)	0.94 (0.86 to 1.02)
Immune status				
Immunocompetent	3239/109 710 (3.0)	3375/109 710 (3.1)	-0.12 (-0.27 to 0.02)	0.96 (0.91 to 1.01)
Immunocompromised	289/7563 (3.8)	301/7563 (4.0)	-0.16 (-0.78 to 0.46)	0.96 (0.82 to 1.13)
Amoxicillin dosing[a]				
875 mg twice daily	2752/91 628 (3.0)	2823/91 628 (3.1)	-0.08 (-0.24 to 0.08)	0.97 (0.92 to 1.03)
500 mg 3 times daily	808/25 938 (3.1)	865/25 938 (3.3)	-0.22 (-0.52 to 0.08)	0.93 (0.85 to 1.03)
Sensitivity analyses				
30-d Outcome window[b]	5904/117 304 (5.0)	6014/117 304 (5.1)	-0.09 (-0.27 to 0.08)	0.98 (0.95 to 1.02)
Inclusion of recurrent sinusitis in outcome[c]	3645/117 304 (3.1)	3806/117 304 (3.2)	-0.14 (-0.28 to 0)	0.96 (0.92 to 1.00)
90-d Antibiotic exclusion[d]	3058/103 618 (3.0)	3141/103 618 (3.0)	-0.08 (-0.23 to 0.07)	0.97 (0.93 to 1.02)
180-d Antibiotic exclusion[e]	2427/85 402 (2.8)	2468/85 402 (2.9)	-0.05 (-0.21 to 0.11)	0.98 (0.93 to 1.04)
Negative control outcomes[f]				
Hemorrhoids	966/117 304 (0.8)	902/117 304 (0.8)	0.06 (-0.02 to 0.13)	1.07 (0.98 to 1.17)
Ingrown or fungal nail	760/117 304 (0.6)	769/117 304 (0.7)	-0.01 (-0.07 to 0.06)	0.99 (0.89 to 1.09)
Tendonitis	437/117 304 (0.4)	415/117 304 (0.4)	0.02 (-0.03 to 0.07)	1.05 (0.92 to 1.20)
Wart removal	418/117 304 (0.4)	398/117 304 (0.3)	0.02 (-0.03 to 0.07)	1.05 (0.92 to 1.20)



[a]Amoxicillin group restricted to the indicated dosing strategy. The amoxicillin-clavulanate group was unchanged from primary analysis.

[b]Assessed 1 to 30 days after treatment initiation.

[c]Includes *International Statistical Classification of Diseases and Related Health Problems, Tenth Edition* J01.×1 codes in outcome definition, along with J01.×0 codes of primary outcome definition.

[d]Extended antibiotic washout period from 30 days prior to treatment initiation of primary analysis to 90 days.

[e]Extended antibiotic washout period from 30 days prior to treatment initiation of primary analysis to 180 days.

[f]Assessed 1 to 90 days after treatment initiation.

changing the outcome definition to include *ICD-10* diagnostic codes for recurrent sinusitis (RR, 0.96 [95% CI, 0.92-1.00]) (Figure 5) (eTable 12 in Supplement 1). Extending the outcome window to 30 days after treatment initiation revealed no difference between groups (RR, 0.98 [95% CI, 0.95-1.02]). Compared with amoxicillin, amoxicillin-clavulanate had similar risks of all negative control outcomes after propensity score matching, including outpatient encounters for hemorrhoids (RR, 1.07 [95% CI, 0.98-1.17]), ingrown or fungal nails (RR, 0.99 [95% CI, 0.89-1.09]), tendinitis (RR, 1.05 [95% CI, 0.92-1.20]), and wart removal (RR, 1.05 [95% CI, 0.92-1.20]) (Figure 5) (eTable 13 in Supplement 1).

Discussion

In this nationwide retrospective cohort study of more than half a million US adults with acute sinusitis treated with standard doses of amoxicillin-clavulanate or amoxicillin, there was no observed difference in risk of treatment failure between groups; treatment failure characterized by an emergency department or inpatient encounter was rare. There was no difference in the risk of antibiotic-associated adverse events between treatment groups, although the risk of secondary infections was higher among patients dispensed amoxicillin-clavulanate.

Treatment failure was most frequently determined by a new antibiotic dispensation without a billed encounter, suggesting a patient may have called into the office to report persistent symptoms or intolerant adverse effects that resulted in a new prescription. The second-most frequent reason for treatment failure was an outpatient encounter for acute sinusitis with an antibiotic switch, which was less frequent among patients treated with amoxicillin-clavulanate, although the overall rare occurrence of this outcome meant that 331 patients would need to be treated with amoxicillin-clavulanate to prevent 1 patient treated with amoxicillin from returning to the clinic for a new antibiotic prescription. In the context of the association between broader-spectrum antibiotics and an increased risk of antimicrobial resistance, these findings do not support a clear preference for amoxicillin-clavulanate as first-line treatment, recommended by the Infectious Diseases Society of America guidelines.[4,43]

The American Academy of Otolaryngology-Head and Neck Surgery guidelines state that several conditions may benefit from amoxicillin-clavulanate rather than amoxicillin, including immunocompromised status. There was no difference in treatment failure risk among immunocompromised patients without a recent history of taking antibiotics or hospitalization.[5]

This study has several strengths. To the study investigators' knowledge, this is the largest study to compare amoxicillin-clavulanate with amoxicillin for the treatment of acute sinusitis and the first study of adults to include outpatient encounters, the most frequent setting where acute sinusitis is diagnosed. The findings are consistent with recent studies that compared amoxicillin-clavulanate with amoxicillin for acute sinusitis in children in the outpatient setting and in Veterans Health Administration emergency department and urgent care settings.[10,17] The large cohort size facilitated precise estimation of rare outcomes and included a range of geographic areas, reflecting a spectrum of prevalence of antimicrobial-resistant organisms. This study captured antibiotic dose alongside duration, enabling the comparison of standard-dose approaches to identify the preferred empiric treatment for uncomplicated acute sinusitis.

Limitations

This study has limitations. First, as with all nonrandomized studies, there is the potential for residual confounding. High-dimensional propensity score matching can mitigate this potential somewhat through inclusion of measured confounders that may have been missed in the a priori selected covariates, along with inclusion of proxies for unmeasured confounders. The high-dimensional propensity score analysis was consistent with the primary analysis, providing confidence in the validity of the findings. Second, this study captured medication dispensation, but did not evaluate medication adherence. However, treatment failure arising from nonadherence (eg, due to medication intolerance) is an important clinical factor captured in this study. Third, clinical guidelines recommend saline irrigation and corticosteroid nasal spray as adjunctive treatment, and while prescription corticosteroid nasal spray was captured, taking over-the-counter medication was not.[4,5] However, over-the-counter medications would only introduce bias if independently associated with the exposure and outcome. Negative control outcomes analyses suggest no difference in health care–seeking behavior, which could imply no difference in taking symptom-oriented over-the-counter medication. Fourth, the study did not capture microbiologic data and could not discern the etiology of acute sinusitis for each patient, although clinicians seldom incorporate microbiology data into the decision to treat or the choice of antibiotic. Fifth, excluding recent hospitalizations and antibiotic exposures likely led to conservative estimates of *C difficile* and yeast infection risk. Sixth, the study was limited to patients with commercial insurance. Although insurance type or status would not be anticipated to impact antibiotic effectiveness or adverse events, patients without insurance may present later to care, affecting disease severity, and surveillance rates for these outcomes may differ due to differential health care access, and thus absolute outcome risk may differ in different populations.[44] Seventh, information on patient race and ethnicity and socioeconomic status (apart from insurance plan type as a potential proxy) was not available. Previous studies suggest these factors could potentially be associated with the likelihood of receiving a sinusitis diagnosis, receipt of broad- vs narrow-spectrum antibiotics, and health care access. Although it would not be expected that relative risks would vary across these factors, future studies could examine whether absolute risks of treatment failure and adverse events vary within groups stratified by these factors.[45,46]

Conclusions

For adults with acute sinusitis treated with standard-dose amoxicillin-clavulanate or standard-dose amoxicillin in the outpatient setting, there was no difference in treatment failure and a slightly elevated risk of yeast and *C difficile* infections observed among patients treated with amoxicillin-clavulanate. Treatment failure resulting in an emergency department or inpatient encounter was rare. These findings support standard-dose amoxicillin as a preferred empiric treatment for adults with uncomplicated acute sinusitis without recent antibiotic exposure when antibiotics are indicated.

ARTICLE INFORMATION

Accepted for Publication: December 22, 2025.

Published Online: April 18, 2026. doi:10.1001/jama.2025.26902

Author Affiliations: Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts (Savage, Sreedhara, Huybrechts); Division of Infectious Diseases, Department of Pediatrics, Boston Children's Hospital, Boston, Massachusetts (Savage); Harvard Medical School, Boston, Massachusetts (Savage, Huybrechts); Division of Infectious Diseases, John T. Milliken Department of Medicine, Washington University School of Medicine, St Louis, Missouri (Butler, Durkin); Department of Surgery, Public Health Sciences Division, Washington University School of Medicine, St Louis, Missouri (Butler); Division of Infectious Disease, Department of Pediatrics, University of Washington, Seattle (Kronman); Division of Healthcare Quality Promotion, US Centers for Disease Control and Prevention, Atlanta, Georgia (Kabbani, Hicks).

Author Contributions: Dr Savage had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Savage, Butler, Kronman, Durkin, Hicks, Huybrechts.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Savage.
Critical review of the manuscript for important intellectual content: All authors.
Statistical analysis: Savage, Sreedhara.
Obtained funding: Savage.
Administrative, technical, or material support: Durkin.
Supervision: Durkin, Hicks, Huybrechts.

Conflict of Interest Disclosures: Dr Savage reported receiving grants to his institution from UCB and GSK outside the submitted work. Dr Kronman reported receiving travel support from Pediatric Infectious Diseases Society and personal fees from Scrudder Bass outside the submitted work. Dr Huybrechts reported receiving grants to her institution from Takeda, UCB, and GSK outside

the submitted work. No other disclosures were reported.

Funding/Support: This study was supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH) (T32HD040128, K08HD110600; Dr Savage) and the US Centers for Disease Control and Prevention (CDC) (U54CK000609; Drs Butler and Durkin).

Role of the Funder/Sponsor: The NICHD and CDC had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The findings and conclusions in this article are those of the authors and do not necessarily represent the official views or position of the NIH or the CDC.

Meeting Presentation: This article was presented at ESCMID Global 2026 of the European Society of Clinical Microbiology and Infectious Diseases; April 18, 2026; Munich, Germany.

Data Sharing Statement: See Supplement 2.

REFERENCES

1. Fleming-Dutra KE, Hersh AL, Shapiro DJ, et al. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010-2011. *JAMA*. 2016;315(17):1864-1873. doi:10.1001/jama.2016.4151

2. King LM, Sanchez GV, Bartoces M, Hicks LA, Fleming-Dutra KE. Antibiotic therapy duration in US adults with sinusitis. *JAMA Intern Med*. 2018;178(7):992-994. doi:10.1001/jamainternmed.2018.0407

3. Jin V, Chiu R, Patel M, Zhu A, Perez B, Lee V. Trends and frequencies of antibiotic prescriptions for acute sinusitis outpatient visits in adults. *Laryngoscope*. 2024;134(6):2622-2625. doi:10.1002/lary.31227

4. Chow AW, Benninger MS, Brook I, et al; Infectious Diseases Society of America. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *Clin Infect Dis*. 2012;54(8):e72-e112. doi:10.1093/cid/cis370

5. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): adult sinusitis. *Otolaryngol Head Neck Surg*. 2015;152(2)(suppl):S1-S39. doi:10.1177/0194599815572097

6. Weber DJ, Tolkoff-Rubin NE, Rubin RH. Amoxicillin and potassium clavulanate: an antibiotic combination mechanism of action, pharmacokinetics, antimicrobial spectrum, clinical efficacy and adverse effects. *Pharmacotherapy*. 1984;4(3):122-136. doi:10.1002/j.1875-9114.1984.tb03333.x

7. Gerber JS, Ross RK, Bryan M, et al. Association of broad- vs narrow-spectrum antibiotics with treatment failure, adverse events, and quality of life in children with acute respiratory tract infections. *JAMA*. 2017;318(23):2325-2336. doi:10.1001/jama.2017.18715

8. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States. Revised December 2019. Accessed December 29, 2025. https://www.cdc.gov/antimicrobial-resistance/media/pdfs/2019-ar-threats-report-508.pdf

9. Dantes R, Mu Y, Hicks LA, et al. Association between outpatient antibiotic prescribing practices and community-associated *Clostridium difficile* infection. *Open Forum Infect Dis*. 2015;2(3):ofv113. doi:10.1093/ofid/ofv113

10. Savage TJ, Kronman MP, Sreedhara SK, Lee SB, Oduol T, Huybrechts KF. Treatment failure and adverse events after amoxicillin-clavulanate vs amoxicillin for pediatric acute sinusitis. *JAMA*. 2023;330(11):1064-1073. doi:10.1001/jama.2023.15503

11. Wald ER, Applegate KE, Bordley C, et al; American Academy of Pediatrics. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. *Pediatrics*. 2013;132(1):e262-e280. doi:10.1542/peds.2013-1071

12. Wald ER, Reilly JS, Casselbrant M, et al. Treatment of acute maxillary sinusitis in childhood: a comparative study of amoxicillin and cefaclor. *J Pediatr*. 1984;104(2):297-302. doi:10.1016/S0022-3476(84)81018-5

13. Mulvey CL, Kiell EP, Rizzi MD, Buzi A. The microbiology of complicated acute sinusitis among pediatric patients: a case series. *Otolaryngol Head Neck Surg*. 2019;160(4):712-719. doi:10.1177/0194599818815109

14. Sawada S, Matsubara S. Microbiology of acute maxillary sinusitis in children. *Laryngoscope*. 2021;131(10):E2705-E2711. doi:10.1002/lary.29564

15. Shaikh N, Hoberman A, Shope TR, et al. Identifying children likely to benefit from antibiotics for acute sinusitis: a randomized clinical trial. *JAMA*. 2023;330(4):349-358. doi:10.1001/jama.2023.10854

16. Howie VM, Owen MJ. Bacteriologic and clinical efficacy of cefixime compared with amoxicillin in acute otitis media. *Pediatr Infect Dis J*. 1987;6(10):989-991. doi:10.1097/00006454-198710000-00040

17. Rovelsky SA, Remington RE, Nevers M, et al. Comparative effectiveness of amoxicillin versus amoxicillin-clavulanate among adults with acute sinusitis in emergency department and urgent care settings. *J Am Coll Emerg Physicians Open*. 2021;2(3):e12465. doi:10.1002/emp2.12465

18. Garbutt JM, Goldstein M, Gellman E, Shannon W, Littenberg B. A randomized, placebo-controlled trial of antimicrobial treatment for children with clinically diagnosed acute sinusitis. *Pediatrics*. 2001;107(4):619-625. doi:10.1542/peds.107.4.619

19. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol*. 2003;158(9):915-920. doi:10.1093/aje/kwg231

20. Sendor R, Stürmer T. Core concepts in pharmacoepidemiology: confounding by indication and the role of active comparators. *Pharmacoepidemiol Drug Saf*. 2022;31(3):261-269. doi:10.1002/pds.5407

21. Savage TJ, Wardell H, Huybrechts KF. Accuracy of identifying pediatric acute bacterial sinusitis diagnoses in outpatient claims data. *Pharmacoepidemiol Drug Saf*. 2023;32(8):918-923. doi:10.1002/pds.5617

22. Gregory J, Huynh B, Tayler B, et al. High-dose vs standard-dose amoxicillin plus clavulanate for adults with acute sinusitis: a randomized clinical trial. *JAMA Netw Open*. 2021;4(3):e212713. doi:10.1001/jamanetworkopen.2021.2713

23. Singer A, Fanella S, Kosowan L, et al. Informing antimicrobial stewardship: factors associated with inappropriate antimicrobial prescribing in primary care. *Fam Pract*. 2018;35(4):455-460. doi:10.1093/fampra/cmx118

24. Schmidt ML, Spencer MD, Davidson LE. Patient, provider, and practice characteristics associated with inappropriate antimicrobial prescribing in ambulatory practices. *Infect Control Hosp Epidemiol*. 2018;39(3):307-315. doi:10.1017/ice.2017.263

25. King LM, Kusnetsov M, Filippoupolitis A, et al. Using machine learning to examine drivers of inappropriate outpatient antibiotic prescribing in acute respiratory illnesses. *Infect Control Hosp Epidemiol*. 2023;44(5):786-790. doi:10.1017/ice.2021.476

26. Fleming-Dutra KE, Bartoces M, Roberts RM, Hicks LA. Characteristics of primary care physicians associated with high outpatient antibiotic prescribing volume. *Open Forum Infect Dis*. 2018;5(1):ofx279. doi:10.1093/ofid/ofx279

27. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Stürmer T. Variable selection for propensity score models. *Am J Epidemiol*. 2006;163(12):1149-1156. doi:10.1093/aje/kwj149

28. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1984;70(1):41-55. doi:10.1093/biomet/70.1.41

29. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat Simul Comput*. 2009;38(6):1228-1234. doi:10.1080/03610910902859574

30. Schröder W, Sommer H, Gladstone BP, et al. Gender differences in antibiotic prescribing in the community: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2016;71(7):1800-1806. doi:10.1093/jac/dkw054

31. Wyss R, Fireman B, Rassen JA, Schneeweiss S. Erratum: high-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology*. 2018;29(6):e63-e64. doi:10.1097/EDE.0000000000000886

32. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology*. 2009;20(4):512-522. doi:10.1097/EDE.0b013e3181a663cc

33. Levine OS, Farley M, Harrison LH, Lefkowitz L, McGeer A, Schwartz B. Risk factors for invasive pneumococcal disease in children: a population-based case-control study in North America. *Pediatrics*. 1999;103(3):E28. doi:10.1542/peds.103.3.e28

34. Magee JT, Pritchard EL, Fitzgerald KA, Dunstan FD, Howard AJ. Antibiotic prescribing and antibiotic resistance in community practice: retrospective study, 1996-8. *BMJ*. 1999;319(7219):1239-1240. doi:10.1136/bmj.319.7219.1239

35. Austin DJ, Kristinsson KG, Anderson RM. The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance. *Proc Natl Acad Sci U S A*. 1999;96(3):1152-1156. doi:10.1073/pnas.96.3.1152

36. Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. *Epidemiology*. 2010;21(3):383-388. doi:10.1097/EDE.0b013e3181d61eeb

37. Wang SV, Verpillat P, Rassen JA, Patrick A, Garry EM, Bartels DB. Transparency and reproducibility of observational cohort studies using large healthcare databases. *Clin Pharmacol Ther*. 2016;99(3):325-332. doi:10.1002/cpt.329

38. R: a language and environment for statistical computing. R Foundation for Statistical Computing. 2013. Accessed December 29, 2025. http://www.r-project.org

39. Wasserstein RL, Lazar NA. The ASA statement on *P* values: context, process, and purpose. *Am Stat*. 2016;70(2):129-133. doi:10.1080/00031305.2016.1154108

40. Vandenbroucke JP, von Elm E, Altman DG, et al; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *PLoS Med*. 2007;4(10):e297. doi:10.1371/journal.pmed.0040297

41. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med*. 2007;4(10):e296. doi:10.1371/journal.pmed.0040296

42. Altman DG. Confidence intervals for the number needed to treat. *BMJ*. 1998;317(7168):1309-1312. doi:10.1136/bmj.317.7168.1309

43. de Nies L, Kobras CM, Stracy M. Antibiotic-induced collateral damage to the microbiota and associated infections. *Nat Rev Microbiol*. 2023;21(12):789-804. doi:10.1038/s41579-023-00936-9

44. Bergmark RW, Ishman SL, Phillips KM, Cunningham MJ, Sedaghat AR. Emergency department use for acute rhinosinusitis: insurance dependent for children and adults. *Laryngoscope*. 2018;128(2):299-303. doi:10.1002/lary.26671

45. Gerber JS, Prasad PA, Localio AR, et al. Racial differences in antibiotic prescribing by primary care pediatricians. *Pediatrics*. 2013;131(4):677-684. doi:10.1542/peds.2012-2500

46. Schwandt H, Currie J, von Wachter T, Kowarski J, Chapman D, Woolf SH. Changes in the relationship between income and life expectancy before and during the COVID-19 pandemic, California, 2015-2021. *JAMA*. 2022;328(4):360-366. doi:10.1001/jama.2022.10952