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Comparative Safety of Different Antibiotic Regimens for the Treatment of Outpatient Community-Acquired Pneumonia Among Otherwise Healthy Adults

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Abstract

Background. Evidence is limited on the comparative safety of antibiotic regimens for treatment of community-acquired pneumonia (CAP). We compared the risk of adverse drug events (ADEs) associated with antibiotic regimens for CAP treatment among otherwise healthy, nonelderly adults.

Methods. We conducted an active-comparator new-user cohort study (2007–2019) of commercially insured adults aged 18–64 years diagnosed with outpatient CAP, evaluated via chest X-ray, and dispensed a same-day CAP-related oral antibiotic regimen. ADE follow-up duration ranged from 2 to 90 days (eg, renal failure [14 days]). We estimated risk differences [RDs] per 1000 treatment episodes and risk ratios using propensity score–weighted Kaplan-Meier functions. Ankle/knee sprain and influenza vaccination were considered as negative control outcomes.

Results. Of 145 137 otherwise healthy CAP patients without comorbidities, 52% received narrow-spectrum regimens (44% macrolide, 8% doxycycline) and 48% received broad-spectrum regimens (39% fluoroquinolone, 7% β -lactam, 3% β -lactam + macrolide). Compared with macrolide monotherapy, each broad-spectrum antibiotic regimen was associated with increased risk of several ADEs (eg, β -lactam: nausea/vomiting/abdominal pain [RD per 1000, 3.20; 95%

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CI, 0.99–5.73]; non-*Clostridioides difficile* diarrhea [RD per 1000, 4.61; 95% CI, 2.47–6.82]; vulvovaginal candidiasis/vaginitis [RD per 1000, 3.57; 95% CI, 0.87, 6.88]). Narrow-spectrum antibiotic regimens largely conferred similar risk of ADEs. We generally observed similar risks of each negative control outcome, indicating minimal confounding.

Conclusions. Broad-spectrum antibiotics were associated with increased risk of ADEs among otherwise healthy adults treated for CAP in the outpatient setting. Antimicrobial stewardship is needed to promote judicious use of broad-spectrum antibiotics and ultimately decrease antibiotic-related ADEs.

Keywords

administrative data; adverse drug events; antibiotic safety; antimicrobial stewardship; community-acquired pneumonia

Community-acquired pneumonia (CAP) is a common indication for outpatient antibiotic prescriptions in otherwise healthy adults in the United States [1]. Evidence-based clinical practice guidelines on the management of adult outpatients with CAP recommend empiric antibiotic therapy. Broad-spectrum regimens have better empiric coverage and have been recommended for patients with risk factors for antibiotic-resistant pathogens or select comorbidities [2, 3]. Narrow-spectrum regimens have been recommended for otherwise healthy patients in low-antibiotic-resistance regions. These treatment recommendations are based on efficacy and safety evidence from randomized clinical trials (RCTs), observational studies, and data on antimicrobial resistance and antibiotic spectrum of action.

Knowledge about the safety of different oral antibiotic regimens is particularly relevant to inform CAP prescribing choices, given the absence of differences in efficacy. Existing studies of efficacy provide little evidence of superiority or equivalence of 1 antibiotic regimen over another [2-6]. Recent Cochrane meta-analyses of RCTs reported no difference in clinical effectiveness between different antibiotic regimens in outpatients with CAP [4, 6]. A network meta-analysis of 24 RCTs comparing empiric oral antibiotic regimens in adults with mild-moderate CAP observed trends toward a better clinical response and lower mortality for quinolones, but found no conclusive evidence of any antibiotic regimen being clearly more effective than another [7]. Non-experimental studies on effectiveness are limited and have been inconclusive due to small sample size [3]. Furthermore, clinical practice guidelines highlight the paucity of evidence on the risk of adverse events related to oral antibiotic therapy for the treatment of CAP in the outpatient setting, and call for additional research [3, 6]. Non-experimental safety studies of patients with other common infections report that non-first-line agents are frequently associated with higher risk of several individual adverse drug events (ADEs) and potential microbiome-related adverse events including non-*Clostridioides difficile* diarrhea, *C difficile* infection (CDI), vaginitis/vulvovaginal candidiasis, and more [8-10].

Uncertainty about the risks and benefits of different antibiotic regimens has resulted in wide variation in antibiotic prescribing for CAP in outpatient settings [11]. For example, broad-spectrum agents (eg, fluoroquinolones) are commonly prescribed for the treatment of CAP among otherwise healthy patients in the outpatient setting. These prescribing

practices are contrary to guidelines [3, 6] and antimicrobial stewardship guidance from the Centers for Disease Control and Prevention to use narrow-spectrum agents when possible to treat bacterial infections [12, 13]. Using national data from a large commercial insurance database, we performed an active-comparator new-user study to estimate the comparative risk of several individual ADEs between different antibiotic regimens to treat outpatient CAP among otherwise healthy, nonelderly adults in the United States.

METHODS

Data Source

We used the Merative MarketScan Commercial Database (2006–2019), which includes longitudinal, patient-level data on enrollment, adjudicated inpatient and outpatient medical insurance claims, and outpatient pharmacy-dispensed medications. The database includes individuals with employer-sponsored commercial insurance and their spouses and dependents [14]. The Washington University School of Medicine Institutional Review Board deemed this study exempt from human subjects review.

Study Design and Population

We identified a cohort of adults aged 18–64 years with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), or an International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM), diagnosis code for pneumonia (Supplementary Table 1) (ignoring diagnostic/rule-out claims) diagnosed in an outpatient setting from 1 July 2007 to 30 November 2019. We required same-day treatment (index date) with a guideline-recommended oral antibiotic (see “Antibiotic Exposure” section) per the 2007 and 2019 Infectious Diseases Society of America / American Thoracic Society (IDSA/ATS) CAP guidelines [2, 3]. We also required continuous medical and prescription drug insurance enrollment during the 180-day baseline period before the index date. We implemented several exclusion criteria to create a final cohort of otherwise healthy adults with CAP that was unlikely to be caused by a multidrug-resistant pathogen (Supplementary Tables 1-6) [2, 3, 15-20]. The Supplementary Methods provide additional details on these exclusions.

Antibiotic Exposure

We categorized antibiotic regimens in accordance with the 2007 and 2019 IDSA/ATS guidelines on the clinical management of adults with CAP [2, 3]. We included antibiotic regimens recommended in both guidelines (macrolide, doxycycline, respiratory fluoroquinolones, β -lactam plus macrolide, β -lactam plus doxycycline) and added β -lactam monotherapy, given common real-world prescribing for CAP. We did not include amoxicillin monotherapy in the primary analysis, as this new recommendation from the 2019 guidelines [3] occurred very late in the study period. Rather, amoxicillin initiators were included with β -lactam monotherapy in the main analysis, and further studied in subgroup analyses. We additionally categorized antibiotic regimens by coverage type, defined as narrow-spectrum (macrolide, doxycycline) or broad-spectrum (respiratory fluoroquinolones, β -lactam monotherapy, β -lactam plus macrolide, β -lactam plus doxycycline) [2]. Supplementary Table 5 presents antibiotic generic names and coverage by antibiotic regimen category.

Safety Outcomes

We used ICD-9-CM and ICD-10-CM diagnosis codes to identify individual ADE outcomes, including nausea/vomiting/abdominal pain, rash/urticaria, non-*C difficile* diarrhea, vulvovaginal candidiasis/vaginitis, unspecified allergy, renal failure, tendinopathy (including tendon rupture), CDI, and anaphylaxis/angioedema/laryngeal edema [21]. This approach captures ADEs that are serious enough for the patient to seek medical care. Outcome-specific follow-up periods ranged from 2 to 90 days, based on expert knowledge of anticipated onset after antibiotic initiation (Supplementary Table 7) [9, 10, 22]. We also used negative-control outcomes—ankle/knee sprain and influenza vaccination—which have been used previously to assess the comparability of treatment groups (Supplementary Table 7) [9, 23]. Each negative-control outcome met the criteria of being (1) causally unrelated to the treatment under study and (2) sharing common confounding structures with the treatments and outcomes of interest (ie, the same confounders affect the negative control as the outcome of interest) [24, 25]. To ensure identification of new-onset outcomes, we excluded index events coded for the outcome of interest within 30 days before the index event date, except for influenza vaccination.

Covariates

Potential confounders of the association between antibiotic exposure and ADE outcomes were identified a priori based on clinical knowledge. The following patient- and provider-level characteristics were assessed at the index event date: age, sex, geographic region, health insurance plan type, urban residence (ie, residence in a metropolitan statistical area), calendar month, calendar year, provider specialty, provider outpatient location (ie, office, emergency department, urgent care center, other), and ceftriaxone administration on the date of CAP diagnosis (since patients with CAP frequently receive a one-time dose of intravenous [IV] ceftriaxone). The presence of baseline emergency department encounters, number of physician office visits (0, 1, 2, 3+), number of unique medication therapeutic groups (0, 1, 2, 3+), and frailty markers (Supplementary Table 8) were assessed during the 180-day baseline period [26]. Comorbidities (other than those used to exclude adults with comorbidities per CAP treatment guidelines) were captured using an all-available look-back period (Supplementary Table 6) [18, 19].

Statistical Analysis

Baseline covariates were summarized by antibiotic regimen. We used an as-treated approach to evaluate the association between antibiotic regimens and ADE outcomes. We estimated the weighted cumulative incidence of individual ADE outcomes using Kaplan-Meier methods. Adults were followed until the first occurrence of the ADE outcome or a censoring event (health insurance disenrollment, diagnosis of a non-CAP bacterial or viral infection, diagnosis of viral pneumonia or pneumonia due to a rare organism, influenza diagnosis or oseltamivir prescription, hospitalization, end-of-outcome-specific follow-up period, or end-of-study period on 31 December 2019). In as-treated analyses, adults are considered to be exposed to the initial treatment until changes in treatment. We censored for diagnosis of non-CAP infections as a proxy for treatment changes, given the possibility of ADE outcomes related to other infections (eg, nausea/vomiting/abdominal pain, rash/urticaria) or

medication use not recorded in the database (eg, over-the-counter medication, prescription paid out-of-pocket). To account for potential confounding, we used standardized mortality ratio (SMR) weights applied to the Kaplan-Meier estimator. SMR weights standardize the covariate distribution of a comparator cohort (eg, doxycycline initiators) to a reference cohort (ie, macrolide initiators), resulting in unconfounded treatment comparisons, assuming no unmeasured confounding [27]. For each macrolide/comparator contrast, SMR weights were calculated using propensity scores (p) estimated from multivariable logistic regression, where p represents the probability of initiating macrolides versus each other antibiotic of interest, accounting for baseline covariates. Age was modeled with restricted cubic splines. We used absolute standardized mean differences to assess the balance of measured covariates between treatment groups, with values less than 0.10 considered adequate [28]. If balance was not initially achieved for all covariates, we applied asymmetric trimming of the propensity score as needed to account for areas of non-overlap. We estimated both absolute and relative effect measures to assess the association between different antibiotic regimens and ADE outcomes. Risk differences (RDs) per 1000 treatment episodes and risk ratios (RRs) of the cumulative incidence functions were calculated over follow-up for each ADE outcome, with corresponding 95% confidence intervals (CIs) calculated using nonparametric bootstrap sampling with replacement ($N = 1000$). The number needed to harm (NNH) was calculated by inverting the weighted RD.

We conducted prespecified subgroup analyses for broad- and narrow-spectrum β -lactam monotherapy, with amoxicillin and ampicillin considered narrow-spectrum and other β -lactam agents considered broad-spectrum (Supplementary Table 5). We used analogous methods to evaluate the association between macrolides (vs comparator regimen) and the risk of negative-control outcomes, wherein each outcome is causally unrelated to the antibiotic exposure. In the absence of a biologically plausible mechanism for antibiotics to cause each negative-control outcome, effect estimates should be null in the absence of confounding [29]. Analyses were conducted using SAS software version 9.4 (SAS Institute, Inc.) and R Statistical Software version 4.3 (R Core Team) with R packages dplyr, forestplot, ggplot2, and patchwork.

RESULTS

Study Cohort

After applying eligibility criteria, the outpatient CAP cohort included initiators of macrolides ($n = 63\,474$), doxycycline ($n = 11\,301$), fluoroquinolones ($n = 56\,388$), β -lactam monotherapy ($n = 9652$), β -lactam + macrolide ($n = 4322$), and β -lactam + doxycycline ($n = 612$) (see the flow diagram in Figure 1). Due to rare use, the β -lactam + doxycycline treatment group was excluded from further analyses. Thus, the final study sample included 145 137 otherwise healthy adults with outpatient CAP. The distribution of antibiotic regimens was as follows: macrolides (44%), doxycycline (8%), fluoroquinolones (39%), β -lactam monotherapy (7%), and β -lactam + macrolide (3%). Overall, adults with CAP had a mean (SD) age of 44 (13) years and 47% were female. The majority were seen in an office setting (69%), as well as the emergency department (16%) or urgent care (11%). Baseline characteristics are reported by antibiotic regimen in Table 1. The distribution of

antibiotic agents within each antibiotic treatment group is presented in Supplementary Table 9.

Adverse Drug Events

After exclusions for ADE outcomes occurring in the 30 days before antibiotic initiation (Supplementary Table 10) and propensity score weighting, all measured characteristics were well balanced between antibiotic treatment groups (Supplementary Figure 1). The crude risk of ADEs observed during follow-up varied widely (Figure 2, Supplementary Table 11). *Clostridioides difficile* infection and anaphylaxis/angioedema/laryngeal edema were rare (Supplementary Table 12); thus, no further analyses were conducted for these outcomes. Figure 3 and Supplementary Figure 2 present the weighted cumulative incidence curves for individual ADEs by antibiotic regimen and type of coverage.

Of the narrow-spectrum antibiotic regimens (doxycycline vs macrolide), we observed similar risks for most individual ADEs, including rash/urticaria, non-*C difficile* diarrhea, vulvovaginal candidiasis/vaginitis, unspecified allergy, and tendinopathy; the exception was nausea/vomiting, which was associated with increased risk in doxycycline users (weighted RD per 1000 treatment episodes, 2.18; 95% CI, .17–4.54) (Figure 2). The NNH suggests that 1 additional case of nausea/vomiting/abdominal pain would occur during a 14-day follow-up period for every 455 doxycycline treatment episodes.

In contrast, each broad-spectrum antibiotic regimen was associated with increased risk of several individual ADEs, compared with a macrolide. Specifically, fluoroquinolones were associated with increased risk of nausea/vomiting/abdominal pain and unspecified allergy; β -lactam monotherapy was associated with increased risk of nausea/vomiting/abdominal pain, rash/urticaria, non-*C difficile* diarrhea, and vulvovaginal candidiasis/vaginitis; and β -lactam + macrolide use was associated with increased risk of non-*C difficile* diarrhea and vulvovaginal candidiasis/vaginitis (Figure 2). On the absolute scale, the highest increased risk of individual ADEs was observed for vulvovaginal candidiasis/vaginitis, among users of β -lactam monotherapy (NNH = 278) or combination therapy with a macrolide (NNH = 204); and for non-*C difficile* diarrhea, among users of β -lactam monotherapy (NNH = 217) or combination therapy with a macrolide (NNH = 175). The interpretation of crude and weighted results was consistent for analyses on the absolute and relative scales, with few exceptions (Supplementary Table 11).

Subgroup and Sensitivity Analyses

Analyses restricted to β -lactam broad-spectrum monotherapy revealed similar results as the primary analysis that included all β -lactam monotherapy (Supplementary Figure 3, Supplementary Table 13). The number of ADE outcomes among adults treated with narrow-spectrum β -lactam monotherapy was small; thus, the effects of this antibiotic regimen on most ADEs were not estimable.

In analyses of negative-control outcomes, the effects were not estimable for 3 of 15 comparisons due to small sample size (Figure 4). Otherwise, weighted RD estimates were null for all treatment comparisons for ankle/knee sprain outcomes and all treatment

comparisons for influenza vaccination, except for β -lactam + macrolide versus macrolide (weighted RD per 1000 treatment episodes, 7.71; 95% CI, 1.40–14.90).

DISCUSSION

In this large, population-based study implementing an active-comparator, new-user cohort design, otherwise healthy adults treated for CAP in the outpatient setting who initiated a broad-spectrum antibiotic regimen experienced a higher risk of several individual antibiotic-related ADEs compared with initiators of narrow-spectrum macrolide monotherapy. In contrast, we observed similar risk between initiators of the 2 narrow-spectrum antibiotic regimens—doxycycline and macrolide monotherapy—for most individual ADEs, including rash/urticaria, non-*C difficile* diarrhea, vulvovaginal candidiasis/vaginitis, unspecified allergy, and tendinopathy. The findings of sensitivity analyses were consistent with the primary results.

Evidence is limited on the comparative safety of different oral antibiotic regimens for the treatment of CAP in the outpatient setting, as noted by existing treatment guidelines [3]. However, our findings are consistent with previous studies that found that broader spectrum antibiotic regimens for common outpatient conditions are associated with increased risks of adverse effects in both adults and children [8-10]. Results of the present study add to accumulating evidence suggesting that efforts to shift prescribing from broader-spectrum antibiotics to narrower-spectrum antibiotics may prevent ADEs. Unlike the 2007 guidelines, the updated 2019 guidelines give a strong recommendation for routine use of doxycycline, based on limited data, mostly involving small numbers of patients [3]. Our findings of a similar risk of ADEs compared with macrolide monotherapy support the safety of doxycycline for the treatment of outpatient CAP. Additionally, the updated guidelines newly recommend amoxicillin monotherapy [3]. Although use in the present study was too rare to evaluate the effects, future research on the safety of amoxicillin monotherapy is warranted. These new recommendations provide alternatives to broad-spectrum antibiotic regimens, such as fluoroquinolones, which have been increasingly linked to safety warnings by the US Food and Drug Administration [30]. Ultimately, knowledge about antibiotic-related harms can help patients, prescribers, and stewardship programs make judicious decisions about antibiotic utilization [31].

The selection of antibiotic regimen should balance benefits and risks. Prescribing clinicians ought to consider the risk of treatment failure, based, in part, on local prevalence of antibiotic resistance. For example, due to increasing concern for macrolide-resistant *Streptococcus pneumoniae* [32], the updated 2019 guidelines no longer give a strong recommendation for routine use of macrolide monotherapy. Ironically, macrolide resistance may be largely driven by inappropriate prescribing for viral upper respiratory tract infections. Specifically, a major unintended consequence of overprescribing antibiotics for viral conditions—which providers often justify as “just in case”—is the need for more toxic antibiotic regimens for bacterial conditions. Other unintended consequences include ADEs, as demonstrated by the present study. Ideally, clinicians should educate patients about the trade-offs of antibiotic exposure for low-yield conditions and antibiotic resistance [33].

Limitations

Our results are subject to several possible limitations. First, the effect estimates may be subject to residual confounding given the nonrandomized study design. The unadjusted and weighted estimates were generally similar, indicating little confounding by measured factors. However, our analysis was not able to account for certain risk factors for ADE outcomes that are unmeasured or poorly measured in health insurance claims data (eg, common noninfectious causes of rash/urticaria). Bias may be present if patients with these risk factors experienced differential exposure to the antibiotic regimens under study, although we expect this to be unlikely. To mitigate measured and unmeasured confounding, we implemented several established epidemiologic methods, including an active-comparator new-user design by restricting the cohort to a homogeneous population with indication for treatment [34, 35]. We further restricted the study population to otherwise healthy adults [36] and applied propensity score methodology to account for potential confounders [37]. Last, we used negative-control outcomes to assess the comparability of initiators of different CAP-related antibiotics under study; the results were generally null, indicating that residual confounding was minimal [29].

Second, study inclusion was based on diagnosis codes for pneumonia that have not been validated in the outpatient setting, and there is general diagnostic uncertainty related to pneumonia [38]. To further refine the study population, we required a same-day chest X-ray and CAP-related antibiotic prescription, as well as the absence of codes for other bacterial and viral infections within 30 days before the CAP diagnosis. Despite possible inclusion of patients without true CAP, our results are useful because they generalize to adults treated for CAP in the outpatient setting, all of whom are at risk of antibiotic-related ADEs. Third, the antibiotic exposure was based on pharmacy-dispensing billing claims. While this is the gold standard of prescription drug ascertainment, information on adherence was not available and failure to consume the medication could result in bias toward the null. Fourth, our claims-based algorithms to identify ADEs have been used in previous studies [8-10] but have not been validated. While claims databases typically have excellent ascertainment of serious events, milder safety events are less likely to be reported to providers, as demonstrated by a study that identified 10 times more ADEs via telephone calls to families versus manual review of electronic health record data [39]. It is unlikely that outcome misclassification would be differential by exposure. Fifth, we did not have the statistical power to evaluate the effect of narrow-spectrum β -lactam monotherapy (ie, amoxicillin or ampicillin monotherapy) on the risk of individual ADEs. Subgroup analyses restricted to β -lactam broad-spectrum monotherapy revealed similar results as the primary analysis that included all β -lactam monotherapy. Sixth, we did not have the statistical power to evaluate the effect of antibiotic duration on ADEs. Last, the study was restricted to otherwise healthy, commercially insured adults aged 18–64 years; thus, results may not be generalizable to other populations such as adults with comorbidities who may be at increased risk of ADEs due to underlying health conditions or drug interactions.

Conclusions

Among otherwise healthy, nonelderly adults treated for CAP in the outpatient setting, broad-spectrum antibiotics were associated with increased risk of ADEs compared with narrow-spectrum antibiotics. Antimicrobial stewardship efforts are needed to promote the judicious use of broad-spectrum antibiotics, and ultimately decrease antibiotic-related ADEs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability.

Data are not publicly available through authors; data can be licensed through Merative.

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;315:1864–73. [PubMed: 27139059]
2. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007;44(Suppl 2): S27–72. [PubMed: 17278083]
3. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med* 2019;200:e45–67. [PubMed: 31573350]
4. Bjerre LM, Verheij TJ, Kochen MM. Antibiotics for community acquired pneumonia in adult outpatients. *Cochrane Database Syst Rev* 2009;CD002109. [PubMed: 19821292]
5. Maimon N, Nopmaneejumrulers C, Marras TK. Antibacterial class is not obviously important in outpatient pneumonia: a meta-analysis. *Eur Respir J* 2008;31:1068–76. [PubMed: 18216053]
6. Pakhale S, Mulpuru S, Verheij TJ, Kochen MM, Rohde GG, Bjerre LM. Antibiotics for community-acquired pneumonia in adult outpatients. *Cochrane Database Syst Rev* 2014;2014:CD002109. [PubMed: 25300166]
7. Kurotschka PK, Bentivegna M, Hulme C, Ebell MH. Identifying the best initial oral antibiotics for adults with community-acquired pneumonia: a network meta-analysis. *J Gen Intern Med* 2024;39:1214–26. [PubMed: 38360961]
8. Butler AM, Brown DS, Durkin MJ, et al. Association of inappropriate outpatient pediatric antibiotic prescriptions with adverse drug events and health care expenditures. *JAMA Network Open* 2022;5:e2214153. [PubMed: 35616940]
9. Butler AM, Brown DS, Newland JG, et al. Comparative safety and attributable health care expenditures following inappropriate versus appropriate outpatient antibiotic prescriptions among adults with upper respiratory infections. *Clin Infect Dis* 2022; 76:986–95.

10. Butler AM, Durkin MJ, Keller MR, Ma Y, Powderly WG, Olsen MA. Association of adverse events with antibiotic treatment for urinary tract infection. *Clin Infect Dis* 2022;74:1408–18. [PubMed: 34279560]
11. Nickel KB, Durkin MJ, Olsen MA, et al. Utilization of broad- versus narrow-spectrum antibiotics for the treatment of outpatient community-acquired pneumonia among adults in the United States. *Pharmacoepidemiol Drug Saf* 2024;33:e5779. [PubMed: 38511244]
12. Sanchez GV, Fleming-Dutra KE, Roberts RM, Hicks LA. Core elements of outpatient antibiotic stewardship. *MMWR Recomm Rep* 2016;65:1–12.
13. Healthcare Infection Control Practices Advisory Committee. Antibiotic Stewardship Statement for Antibiotic Guidelines—The Recommendations of the Healthcare Infection Control Practices Advisory Committee (HICPAC). 2016. Available at: <https://www.cdc.gov/hicpac/media/pdfs/antibiotic-stewardship-statement-508.pdf>.
14. Merative. MarketScan Research Databases for life sciences researchers. 2023. Available at: <https://www.merative.com/content/dam/merative/documents/brief/marketscan-research-databases-for-life-sciences-researchers.pdf>. Accessed 29 October 2024.
15. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005;171:388–416. [PubMed: 15699079]
16. Dubberke ER, Olsen MA, Stwalley D, et al. Identification of Medicare recipients at highest risk for *Clostridium difficile* infection in the US by population attributable risk analysis. *PLoS One* 2016;11:e0146822. [PubMed: 26859403]
17. van der Sluijs KF, van der Poll T, Lutter R, Juffermans NP, Schultz MJ. Bench-to-bedside review: bacterial pneumonia with influenza—pathogenesis and clinical implications. *Crit Care* 2010;14:219. [PubMed: 20459593]
18. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care* 1998;36:8–27. [PubMed: 9431328]
19. Agency for Healthcare Research and Quality. HCUP Elixhauser Comorbidity Software. Healthcare Cost and Utilization Project (HCUP). Available at: www.hcup-us.ahrq.gov/toolssoftware/comorbidity/comorbidity.jsp. Accessed 21 December 2020.
20. Metlay JP, Kapoor WN, Fine MJ. Does this patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination. *JAMA* 1997;278:1440–5. [PubMed: 9356004]
21. Centers for Medicare and Medicaid Services. General Equivalence Mappings: ICD-9-CM to and from ICD-10-CM and ICD-10-PCS. 2009. Available at: https://www.cms.gov/medicare/coding/icd10/downloads/icd-10_gem_fact_sheet.pdf. Accessed 14 January 2021.
22. Layton JB, McGrath LJ, Sahrman JM, et al. Comparative safety of high-dose versus standard-dose influenza vaccination in patients with end-stage renal disease. *Vaccine* 2020;38:5178–86. [PubMed: 32565346]
23. Levintow SN, Nielson CM, Hernandez RK, et al. Pragmatic considerations for negative control outcome studies to guide non-randomized comparative analyses: a narrative review. *Pharmacoepidemiol Drug Saf* 2023;32:599–606. [PubMed: 36965103]
24. Shi X, Miao W, Nelson JC, Tchetgen EJT. Multiply robust causal inference with double-negative control adjustment for categorical unmeasured confounding. *J R Stat Soc Series B Stat Methodol* 2020;82:521–40. [PubMed: 33376449]
25. Tchetgen Tchetgen E. The control outcome calibration approach for causal inference with unobserved confounding. *Am J Epidemiol* 2014;179:633–40. [PubMed: 24363326]
26. IBM Watson Health. IBM(R) Micromedex(R) RED BOOK(R) Flat File. Available at: <https://www.ibm.com/products/micromedex-red-book>. Accessed 1 August 2021.
27. Sato T, Matsuyama Y. Marginal structural models as a tool for standardization. *Epidemiology* 2003;14:680–6. [PubMed: 14569183]
28. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009;28:3083–107. [PubMed: 19757444]

29. Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. *Epidemiology* 2010;21:383–8. [PubMed: 20335814]
30. US Food and Drug Administration. Fluoroquinolone antimicrobial drugs information. Available at: <https://www.fda.gov/drugs/information-drug-class/fluoroquinolone-antimicrobial-drugs-information>. Accessed 2 May 2024.
31. Cherian JP, Helsel TN, Jones GF, et al. Understanding the role of antibiotic-associated adverse events in influencing antibiotic decision-making. *Antimicrob Steward Healthc Epidemiol* 2024;4:e13. [PubMed: 38415083]
32. Olson G, Davis AM. Diagnosis and treatment of adults with community-acquired pneumonia. *JAMA* 2020;323:885–6. [PubMed: 32027358]
33. Merenstein DJ, Barrett B, Ebell MH. Antibiotics not associated with shorter duration or reduced severity of acute lower respiratory tract infection. *J Gen Intern Med* 2024; 39:1887–94. [PubMed: 38619737]
34. Lund JL, Richardson DB, Stürmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. *Curr Epidemiol Rep* 2015;2:221–8. [PubMed: 26954351]
35. D’Arcy M, Stürmer T, Lund JL. The importance and implications of comparator selection in pharmacoepidemiologic research. *Curr Epidemiol Rep* 2018;5: 272–83. [PubMed: 30666285]
36. Schneeweiss S, Patrick AR, Stürmer T, et al. Increasing levels of restriction in pharmacoepidemiologic database studies of elderly and comparison with randomized trial results. *Med Care* 2007;45:S131–42. [PubMed: 17909372]
37. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70:41–55.
38. Jones BE, Chapman AB, Ying J, et al. Diagnostic discordance, uncertainty, and treatment ambiguity in community-acquired pneumonia : a national cohort study of 115 U.S. veterans affairs hospitals. *Ann Intern Med* 2024; 177:1179–1189. 10.7326/M23-2505 [PubMed: 39102729]
39. 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;318:2325–36. [PubMed: 29260224]

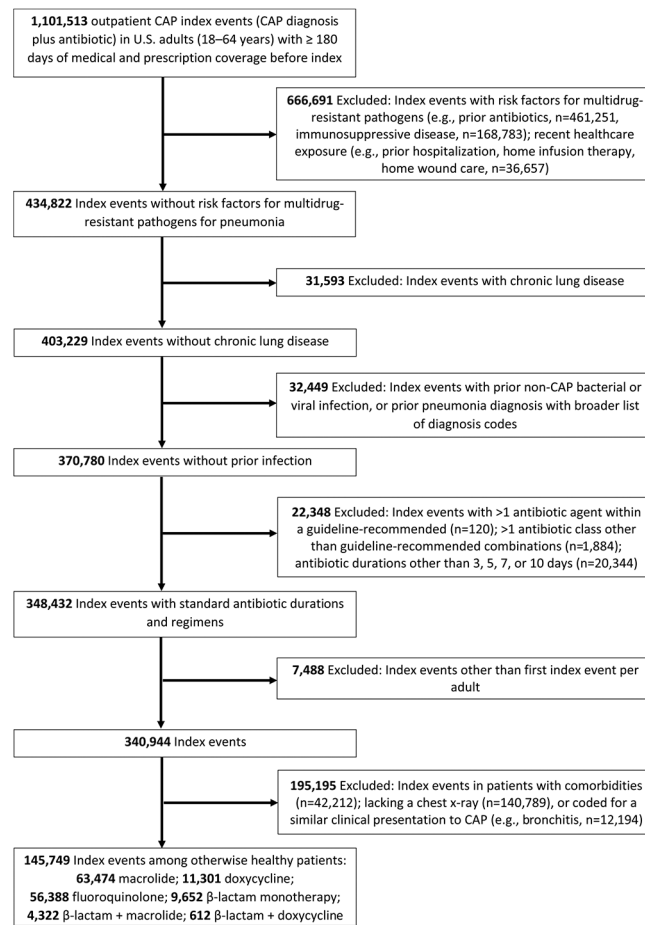
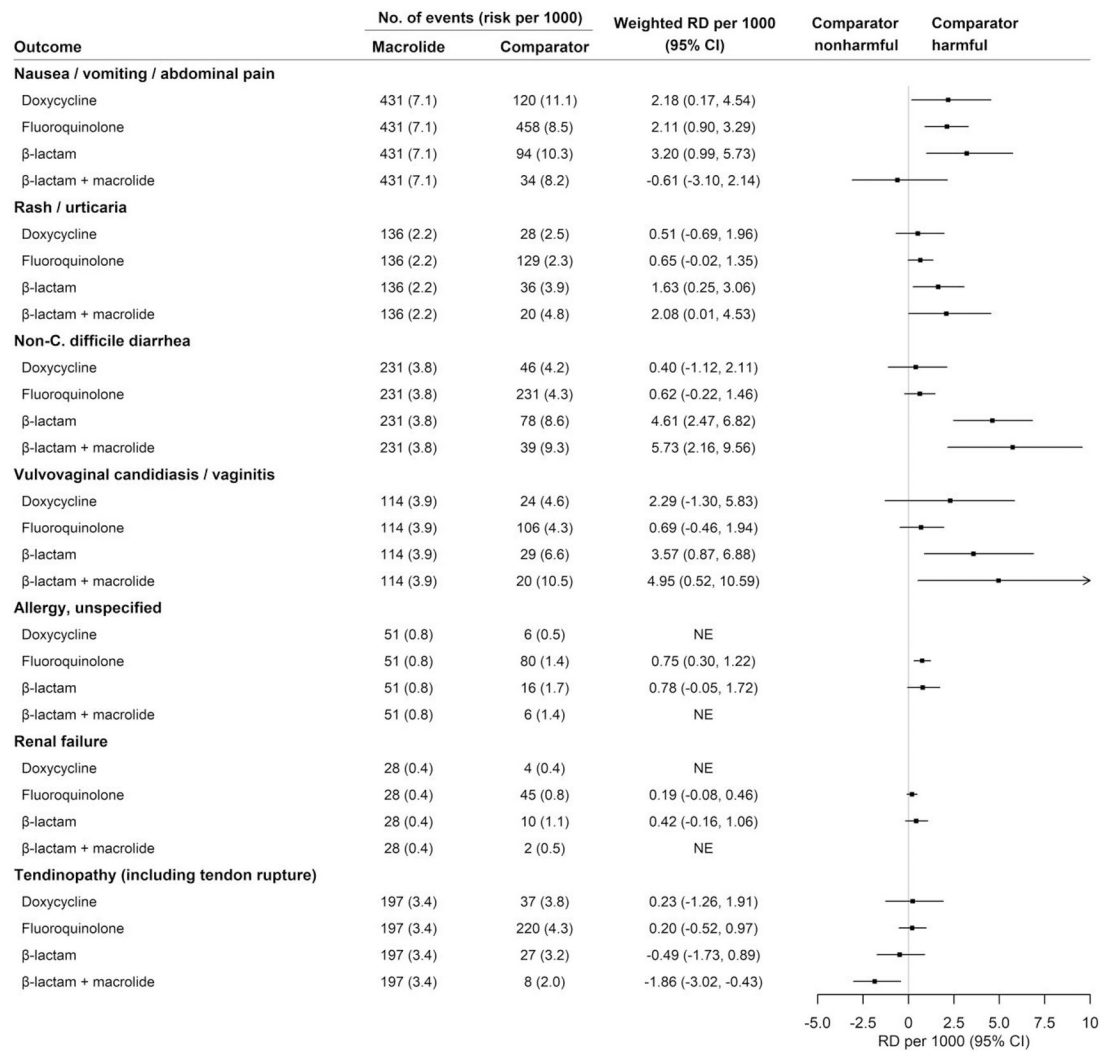


Figure 1. Derivation of the cohort of adults with outpatient community-acquired pneumonia in the MarketScan Commercial Database (index events 1 July 2007 to 30 November 2019). Abbreviation: CAP, community-acquired pneumonia.

**Figure 2.**

Weighted RDs per 1000 of adverse drug events by antibiotic regimen versus macrolide (reference) among adults treated for community-acquired pneumonia in the outpatient setting. Standardized mortality ratio-weighted RD was calculated on the last day of outcome-specific follow-up (14 days for nausea/vomiting/abdominal pain, rash/urticaria, unspecified allergy, renal failure; 30 days for non-*C. difficile* diarrhea, vulvovaginal candidiasis; 90 days for tendinopathy). 95% CIs were calculated via nonparametric bootstrap sampling with replacement ($N = 1000$). We required ≥ 8 adverse drug event cases in both the reference category (ie, macrolide) and the comparator group to ensure stability of the effect estimate. Abbreviations: *C. difficile*, *Clostridioides difficile*; CI, confidence interval; NE, not estimable; RD, risk difference.

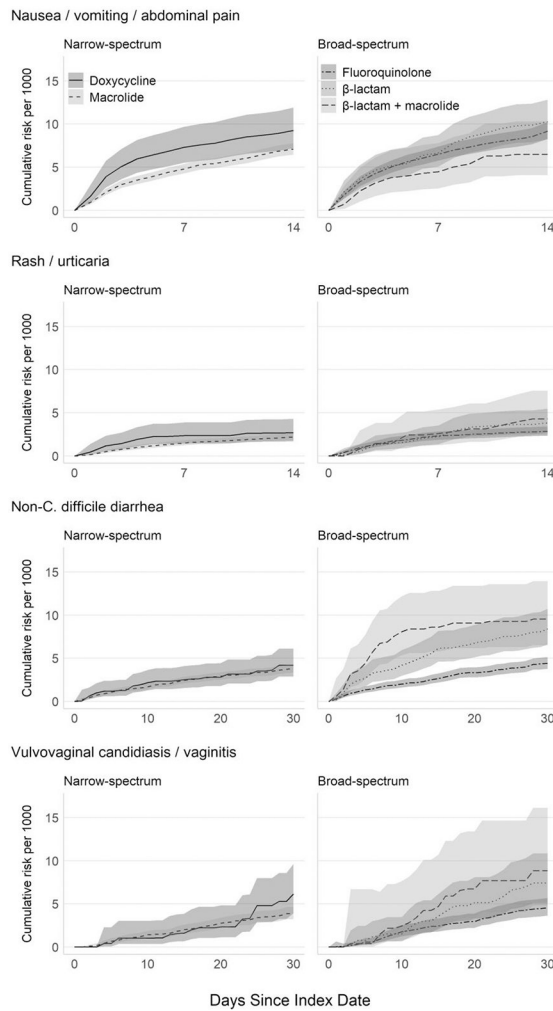
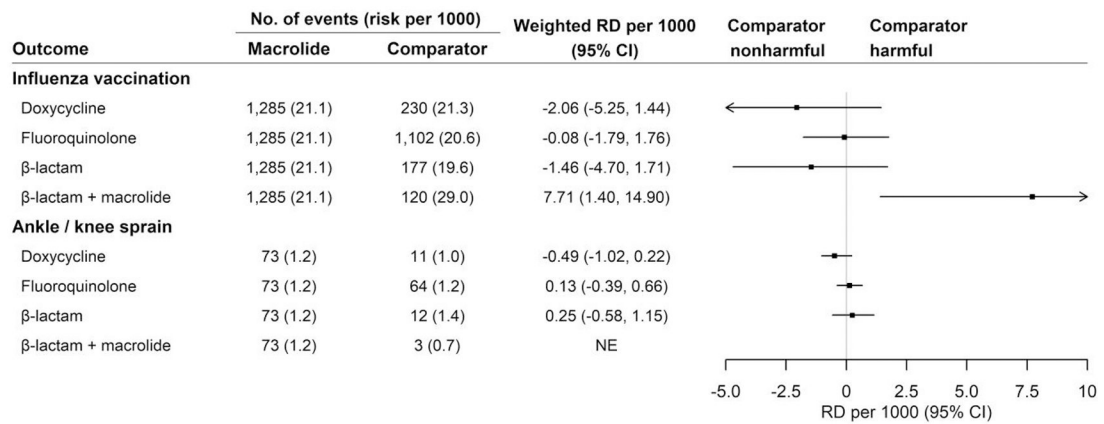


Figure 3. Weighted cumulative incidence curves of select adverse drug events by antibiotic agent among adults treated for community-acquired pneumonia in the outpatient setting. The lines represent the standardized mortality ratio-weighted cumulative incidence estimate; shaded bands represent corresponding 95% confidence intervals. Abbreviation: *C. difficile*, *Clostridioides difficile*.

**Figure 4.**

Weighted RDs per 1000 negative-control outcomes by antibiotic regimen versus macrolide (reference) among adults treated for community-acquired pneumonia in the outpatient setting. Standardized mortality ratio–weighted risk difference represents the risk difference on the last day of follow-up (day 30). 95% CIs were calculated via nonparametric bootstrap sampling with replacement ($N = 1000$). We required ≥ 8 cases in both the reference category (ie, macrolide) and the comparator group to ensure stability of the effect estimate. Abbreviations: CI, confidence interval; NE, not estimable; RD, risk difference.

Table 1.
Select Baseline Characteristics Among Adults Treated for Community-Acquired Pneumonia in the Outpatient Setting, by Index Antibiotic Regimen

	Macrolide n = 63 474%	Doxycycline n = 11 301%	Fluoroquinolone n = 56 388%	β -lactam n = 9652%	β -lactam + macrolide n = 4322%
Demographic characteristics					
Age, mean (SD), y	42 (13)	44 (13)	45 (12)	43 (13)	42 (13)
Male sex	52.0	51.4	54.4	51.4	53.8
Urban residence	86.2	84.7	85.4	82.1	79.3
Geographic region					
Midwest	28.2	22.1	25.5	28.1	23.2
Northeast	16.4	17.3	14.3	15.6	11.7
South	28.4	32.5	44.6	38.6	38.4
West	26.9	28.1	15.5	17.8	26.7
Provider characteristics					
Provider specialty					
Emergency medicine	13.8	14.9	11.9	9.2	12.6
Internal medicine and specialties					
MD/DO NEC	11.5	7.7	15.3	13.0	10.4
Family practice	12.2	10.9	11.1	10.1	9.1
NP/PA	36.9	30.5	38.4	41.8	37.3
Urgent care	5.2	8.2	3.6	4.4	4.7
Facility	8.3	16.8	9.6	9.2	15.8
Other/missing	6.1	5.1	5.1	5.0	4.6
Provider location					
Emergency department	6.0	5.8	4.9	7.2	5.4
Office	17.9	14.4	14.2	11.5	12.7
Urgent care	67.5	60.1	71.9	73.9	68.1
Other	10.4	22.1	10.2	10.5	16.0
	4.2	3.4	3.7	4.1	3.2
CAP management					
IV ceftriaxone receipt on date of CAP diagnosis	11.5	9.8	16.9	18.7	21.6
Health care utilization in the previous 180 days					
Emergency department visit	6.2	6.2	5.9	6.3	5.5

	Macrolide n = 63 474%	Doxycycline n = 11 301%	Fluoroquinolone n = 56 388%	β-lactam n = 9652%	β-lactam + macrolide n = 4322%
No. of physician encounters, median (IQR)	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)
No. of unique medication therapeutic groups, median (IQR)	1 (0–2)	1 (0–3)	1 (0–3)	1 (0–3)	1 (0–2)
Elixhauser comorbidities					
Cerebrovascular disease	0.1	0.1	0.1	0.1	0.0
Coagulopathy	0.3	0.2	0.3	0.3	0.5
Deficiency anemias	1.3	1.7	1.3	1.4	1.5
Depression	5.2	7.5	4.4	5.6	5.2
Drug abuse	0.9	1.2	0.8	0.9	0.9
Hypertension	11.3	14.0	14.8	14.6	13.5
Hypothyroidism	3.4	4.7	3.9	4.0	3.9
Neurological disorders affecting movement	0.2	0.4	0.4	0.4	0.3
Neurological disorders, dementia	0.0	0.0	0.0	0.0	0.0
Neurological disorders, other	0.3	0.4	0.3	0.5	0.6
Neurological disorders, seizures and epilepsy	0.5	0.7	0.5	0.9	0.7
Obesity	8.7	14.4	7.9	9.1	11.8
Paralysis	0.1	0.1	0.1	0.3	0.2
Psychoses	3.7	4.6	3.7	4.1	3.4
Pulmonary circulation disease	0.2	0.3	0.2	0.3	0.3
Rheumatoid arthritis / collagen vascular disease	0.5	0.7	0.6	0.6	0.2
Thyroid disorders (other than hypothyroidism)	1.2	1.4	1.3	1.1	1.4
Weight loss	1.1	1.4	1.1	1.7	1.4
Frailty markers					
Oxygen equipment	0.1	0.1	0.2	0.3	0.1
Home hospital bed	0.0	0.0	0.0	0.0	0.0
Mobility aids	0.1	0.1	0.1	0.2	0.1
Ambulance / life support	0.9	1.2	1.0	0.9	0.8
Non-SNF-related rehabilitation services	6.2	6.5	5.9	6.4	5.3
Timing of index date					
Month					
January–March	28.6	27.8	28.3	28.5	26.1
April–June	17.7	19.2	17.7	19.0	19.0

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	Macrolide n = 63 474%	Doxycycline n = 11 301%	Fluoroquinolone n = 56 388%	β -lactam n = 9652%	β -lactam + macrolide n = 4322%
July–September	21.5	21.3	21.7	20.1	21.8
October–December	32.2	31.7	32.2	32.4	33.1
Year					
2007–2011	42.4	20.6	49.2	41.2	26.3
2012–2015	33.9	25.8	35.2	33.5	33.9
2016–2019	23.7	53.6	15.6	25.3	39.8

Abbreviations: CDHP, Consumer Directed Health Plans; EPO, Exclusive Provider Organization; HMO, Health Maintenance Organization; IQR, interquartile range; MD/DO NEC, doctor of medicine / doctor of osteopathic medicine not elsewhere classified; NP/PA, nurse practitioner / physician assistant; POS, Point-of-Service; PPO, Preferred Provider Organization; SNF, skilled nursing facility; SD, standard deviation.