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Comparative Safety and Attributable Healthcare Expenditures Following Inappropriate Versus Appropriate Outpatient Antibiotic Prescriptions Among Adults With Upper Respiratory Infections

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Background. Little is known about the clinical and financial consequences of inappropriate antibiotics. We aimed to estimate the comparative risk of adverse drug events and attributable healthcare expenditures associated with inappropriate versus appropriate antibiotic prescriptions for common respiratory infections.

Methods. We established a cohort of adults aged 18 to 64 years with an outpatient diagnosis of a bacterial (pharyngitis, sinusitis) or viral respiratory infection (influenza, viral upper respiratory infection, nonsuppurative otitis media, bronchitis) from 1 April 2016 to 30 September 2018 using Merative MarketScan Commercial Database. The exposure was an inappropriate versus appropriate oral antibiotic (ie, non-guideline-recommended vs guideline-recommended antibiotic for bacterial infections; any vs no antibiotic for viral infections). Propensity score-weighted Cox proportional hazards models were used to estimate the association between inappropriate antibiotics and adverse drug events. Two-part models were used to calculate 30-day all-cause attributable healthcare expenditures by infection type.

Results. Among 3 294 598 eligible adults, 43% to 56% received inappropriate antibiotics for bacterial and 7% to 66% for viral infections. Inappropriate antibiotics were associated with increased risk of several adverse drug events, including *Clostridioides difficile* infection and nausea/vomiting/abdominal pain (hazard ratio, 2.90; 95% confidence interval, 1.31–6.41 and hazard ratio, 1.10; 95% confidence interval, 1.03–1.18, respectively, for pharyngitis). Thirty-day attributable healthcare expenditures were higher among adults who received inappropriate antibiotics for bacterial infections ($18–$67) and variable (−$53 to $49) for viral infections.

Conclusions. Inappropriate antibiotic prescriptions for respiratory infections were associated with increased risks of patient harm and higher healthcare expenditures, justifying a further call to action to implement outpatient antibiotic stewardship programs.

Keywords. upper respiratory infections; antibiotics; comparative safety; healthcare expenditures; administrative data.

Antibiotics are prescribed during 13% of outpatient office visits in the United States, amounting to more than 154 million prescriptions annually [1]. The Centers for Disease Control and Prevention estimate that 30% of these prescriptions may be inappropriate, which is defined as prescribing antibiotics for viral infections and non-first-line antibiotics for bacterial infections [1,2].

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Inappropriate antibiotic prescriptions are harmful on a societal level because they contribute to costly and difficult to treat antibiotic-resistant infections [3]. Inappropriate antibiotics are harmful on an individual level because they may cause adverse drug events (ADEs) including allergic reactions (eg, anaphylaxis) and microbiome disruption-related conditions (eg, *Clostridioides difficile* infection [CDI]) [4–6]. Antibiotic-related ADEs result in additional healthcare utilization, including more than 145 000 emergency department visits among adults annually [4].

The Centers for Disease Control and Prevention guidance for antimicrobial stewardship programs (ASPs) in various healthcare settings recommends providing prescribers with educational resources for appropriate antibiotic use, feedback on their prescribing practices, and clinical decision support tools [7–9]. Although ASPs have been widely implemented in hospitals, adoption in outpatient settings has lagged because of limited resources, expertise, and staff [10–12]. Health systems and insurers are positioned to fill these gaps and support implementation of outpatient ASPs [13,14].

To warrant broader implementation of outpatient ASPs, evidence is needed about the clinical and economic consequences of inappropriate antibiotic prescriptions. Comprehensive estimates are not available on the risk of individual ADEs and attributable healthcare expenditures associated with inappropriate antibiotic prescriptions for common outpatient infections in adults [15,16]. We sought to evaluate the comparative safety and attributable healthcare expenditures of inappropriate outpatient antibiotic prescriptions for individual respiratory infections among US commercially insured adults.

METHODS

Data Source

We used the Merative MarketScan Commercial Database (2015–2018), consisting of longitudinal, patient-level data on enrollment, adjudicated inpatient and outpatient insurance claims, and outpatient pharmacy-dispensed medications. The database includes individuals with employer-sponsored commercial insurance and their spouses and dependents [17]. The institutional review board at Washington University School of Medicine deemed this study exempt from human subject review.

Study Design and Population

We identified adults aged 18 to 64 years diagnosed in an outpatient setting with a common bacterial (pharyngitis, sinusitis) or viral respiratory infection (influenza, viral upper respiratory infection [URI], nonsuppurative otitis media [OM], bronchitis) from 1 April 2016 to 30 September 2018. A cohort for each infection type was established based on categories developed by Fleming-Dutra et al [2]; we adapted definitions from the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes to ICD-10-CM codes using Centers for Medicare & Medicaid Services' general equivalence mappings [18] (Supplementary Table 1). The date of diagnosis (ignoring diagnostic/rule out claims) was considered the index date. We restricted the study population to otherwise healthy adults with no recent systemic antibiotic exposure (≤90 days before index), and required a single, index prescription with a typical antibiotic duration (5–14 days); we also applied a tiered approach to exclude index events with multiple, simultaneous, infection-related diagnoses of interest. Additional details are provided in the Supplementary Methods, Supplementary Tables 2–4 [19], and Supplementary Figure 1. Our methods were similar to those described previously by our team [20].

Antibiotic Exposure

We considered an oral antibiotic prescription dispensed on the index diagnosis date to be linked to the outpatient infection. We included 36 index oral antibiotics based on the 2016 "antibiotic utilization" quality measure in the Healthcare Effectiveness Data and Information Set (Supplementary Table 5) [21]. For bacterial infections, we categorized antibiotic exposure as appropriate (ie, first-line antibiotics; amoxicillin or penicillin for pharyngitis [22] and amoxicillin or amoxicillin-clavulanate for sinusitis [23]) or inappropriate (ie, non-first-line antibiotic), based on treatment guidelines. For viral infections, we categorized antibiotic exposure as appropriate if an antibiotic was not prescribed or inappropriate if an antibiotic was prescribed.

Safety Outcomes

We identified individual ADEs using ICD-10-CM diagnosis codes; the duration of follow-up (2–90 days) differed by outcome based on biologic plausibility and expert knowledge (Supplementary Table 6) [24,25]. To ensure identification of new-onset outcomes, we excluded index events coded for the outcome of interest in the 30 days before index for each respective ADE.

Healthcare Expenditure Outcomes

Healthcare expenditures were calculated as the sum of out-of-pocket patient expenditures (copayments, coinsurance, deductible) and health plan expenditures (negotiated fees paid to providers). We used 2 outcome definitions to calculate 30-day medical and pharmacy claim expenditures: (1) all-cause healthcare expenditures represented an "upper bound" by including expenditures recorded on all claims and (2) ADE-associated healthcare expenditures represented a "lower bound" by only including expenditures recorded on claims with antibiotic-related ADEs of interest. We included all claims with diagnosis codes for select ADEs if the initial ADE-related code occurred within the specified follow-up window. We analyzed total expenditures and expenditures by setting (inpatient, emergency department, outpatient, outpatient pharmacy). Expenditures were inflation adjusted to 2018 US dollars using the medical care component of the consumer price index [26].

Covariates

Covariates were defined during the 180-day baseline period before the index date. Potential confounders of the association between antibiotic exposure and ADE outcomes were identified a priori based on clinical knowledge, and included age, sex, health insurance plan type, urban/rural residence, geographic region, month and year of index, provider specialty, provider location, number of emergency department encounters, number of physician office visits, number of unique medication therapeutic groups, frailty markers (Supplementary Table 7), and comorbidities (Supplementary Table 8) [27–29].

Expenditure analyses additionally incorporated average monthly medical/prescription expenditures.

Statistical Analysis

Within each cohort, we used stabilized inverse probability of treatment weights to balance treatment groups with respect to potential confounding factors. We used logistic regression to estimate the propensity of appropriate (vs inappropriate) antibiotic agent, conditional on baseline covariates. Propensity scores were used to create weighted cohorts to estimate the treatment effects in the total population (the average treatment effect) (see Supplementary Methods) [30,31]. We assessed the balance of observed covariates between treatment groups; absolute standardized mean differences <10% in the weighted population were considered adequate [32].

To examine the relationship between inappropriate antibiotics and each ADE outcome, we used Cox proportional hazards models to estimate unadjusted and weighted hazard ratios. We used robust variance estimators to calculate 95% confidence intervals (CIs) [33]. Censoring events were defined as the earliest of: end of outcome-specific follow-up, end of continuous insurance coverage, subsequent different antibiotic prescription (Supplementary Table 5), hospitalization, or end-of-study period. We used ankle/knee sprain and motor vehicle accident as negative control outcomes because each is causally unrelated to the antibiotic exposure. In the absence of a biologically plausible mechanism for antibiotics to cause either outcome, estimates should be null in the absence of confounding [34].

We used 2-part models to estimate attributable expenditures. "Part 1" was a logistic regression of any versus no expenditures and "part 2" was a flexible model of healthcare expenditures from a generalized linear model with log-link and gamma distribution [35,36]. The total expenditure was estimated as the marginal effect (in dollars) that combines both parts. The attributable effect was defined as the difference in expenditures between the inappropriately and appropriately treated groups. We computed 95% CIs using a nonparametric bootstrap based on 250 resamples [37,38]. These analyses were restricted to adults with continuous health insurance coverage for 30 days of follow-up after index.

To determine the financial impact of inappropriate antibiotic prescriptions on the US healthcare system, we scaled the attributable expenditure estimates in the study cohort to the national employer-sponsored insurance population using MarketScan weights constructed from the American Community Survey, with respect to census division, age group, sex, and relationship to the insurance policy holder. We used the inverse probability of treatment–weighted all-cause attributable expenditures estimates to determine total national-level expenditures for inappropriate antibiotics.

Subgroup/Sensitivity Analysis

We conducted prespecified analyses for asthma—a noninfectious clinical condition frequently treated contrary to guidelines with antibiotic prescriptions—and subset analyses for asthma exacerbation, applying study inclusion/exclusion as per viral infections. As sensitivity analyses for all-cause expenditure analyses, we evaluated the effects of (1) redefining inappropriate antibiotic exposure as inappropriate agent or duration for bacterial infections (Supplementary Methods); (2) excluding beneficiaries with health maintenance organization and point of service with capitation plans; and (3) extending follow-up to 90 days.

RESULTS

A total of 1 656 960 bacterial infection index events (588 245 pharyngitis, 1 068 715 sinusitis) and 1 637 638 viral infection index events (266 464 influenza, 957 232 viral URI, 72 280 nonsuppurative OM, 341 662 bronchitis) were included (Supplementary Figure 1). The study cohort had a median age of 43 years (interquartile range, 31–54), 41% were male, and 48% resided in the South. The proportion of adults who received inappropriate antibiotics differed by infection cohort (bacterial infections: pharyngitis [56%], sinusitis [43%]; and viral infections: bronchitis [66%], nonsuppurative OM [52%], viral URI [32%], influenza [7%]). The distribution of antibiotics differed by infection type (Supplementary Table 9). Table 1 and Supplementary Table 10 summarize baseline characteristics by exposure group.

Adverse Drug Events

After propensity score weighting and outcome-specific exclusions (Supplementary Table 11), exposure groups had similar baseline characteristics, except for provider specialty and plan type in some cohorts (Supplementary Figure 2). For each infection-specific cohort, case counts, rates, and unadjusted and weighted hazard ratio estimates of each ADE outcome following appropriate versus inappropriate antibiotic prescriptions are presented in Figure 1, Supplementary Figure 3, and Supplementary Table 12. ADE rates varied widely, with lowest rates for Stevens-Johnson syndrome/toxic epidermal necrolysis and highest rates for nausea/vomiting/abdominal pain.

Among adults with bacterial infections, inappropriate antibiotics were consistently associated with higher risk of nausea/vomiting/abdominal pain and lower risk of vulvovaginal candidiasis/vaginitis and skin rash/urticaria. Inappropriate antibiotic prescriptions were associated with increased risk of CDI and non-*C. difficile* diarrhea in the pharyngitis cohort but decreased risk in the sinusitis cohort. Among adults with viral infections, inappropriate antibiotic prescriptions were associated with higher risk of non-*C. difficile* diarrhea (bronchitis), vulvovaginal candidiasis/vaginitis (viral URI and nonsuppurative OM), and unspecified allergy (viral URI, nonsuppurative OM, and bronchitis). In the negative control outcome analysis, we observed similar risks of ankle/knee sprain and motor vehicle accident among adults who received appropriate versus

Table 1. Selected Baseline Characteristics of Infections of Interest Among Adults (N = 3 294 598)[a,b]

	Bacterial Infections[c]		Viral Infections[d]	
	Appropriate Antibiotic n = 867 158 (%)	Inappropriate Antibiotic n = 789 802 (%)	Appropriate Antibiotic n = 1 053 612 (%)	Inappropriate Antibiotic n = 584 026 (%)
Age, mean (SD), y	40 (13)	41 (14)	41 (14)	45 (13)
Male	330 762 (38.1)	291 849 (37.0)	459 730 (43.6)	255 685 (43.8)
Urban residence	680 116 (78.4)	601 980 (76.2)	843 508 (80.1)	457 284 (78.3)
Geographic region				
Midwest	194 832 (22.5)	151 736 (19.2)	186 249 (17.7)	98 807 (16.9)
Northeast	148 526 (17.1)	139 019 (17.6)	196 341 (18.6)	114 047 (19.5)
South	410 506 (47.3)	409 784 (51.9)	501 753 (47.6)	304 579 (52.2)
West	113 294 (13.1)	89 263 (11.3)	169 269 (16.1)	66 593 (11.4)
Health insurance plan type				
Basic, comprehensive	113 188 (13.1)	92 446 (11.7)	138 800 (13.2)	69 385 (11.9)
CDHP	120 087 (13.9)	105 121 (13.3)	136 526 (13.0)	74 753 (12.8)
EPO or PPO	487 829 (56.3)	453 170 (57.4)	576 894 (54.8)	334 343 (57.3)
HMO	76 078 (8.8)	66 944 (8.5)	104 267 (9.9)	47 782 (8.2)
POS or POS with capitation	54 928 (6.3)	59 101 (7.5)	75 161 (7.1)	46 070 (7.9)
Unknown	15 048 (1.7)	13 020 (1.7)	21 964 (2.1)	11 693 (2.0)
Provider specialty				
Emergency medicine	29 310 (3.4)	26 088 (3.3)	64 580 (6.1)	21 608 (3.7)
Internal medicine	87 859 (10.1)	113 537 (14.4)	135 841 (12.9)	110 436 (18.9)
Allergy	1463 (0.2)	2306 (0.3)	3003 (0.3)	1002 (0.2)
Pulmonary	554 (0.1)	750 (0.1)	1764 (0.2)	1034 (0.2)
Cardiology	652 (0.1)	829 (0.1)	1533 (0.2)	1106 (0.2)
Pediatrics	19 015 (2.2)	16 016 (2.0)	20 192 (1.9)	5983 (1.0)
Family medicine	329 994 (38.1)	337 956 (42.8)	381 414 (36.2)	245 868 (42.1)
NP/PA	99 483 (11.5)	72 580 (9.2)	92 580 (8.8)	43 526 (7.5)
Other	108 777 (12.5)	83 444 (10.6)	131 225 (12.5)	53 710 (9.2)
Unknown (facilities)	190 061 (21.9)	136 294 (17.3)	221 480 (21.0)	99 753 (17.1)
Provider location				
Emergency department	4683 (0.5)	5505 (0.7)	56 422 (5.4)	6085 (1.0)
Office	704 115 (81.2)	652 474 (82.6)	804 247 (76.3)	478 217 (81.9)
Other/unknown	21 158 (2.4)	17 031 (2.2)	36 645 (3.5)	12 425 (2.1)
Retail clinic	7552 (0.9)	2623 (0.3)	5809 (0.6)	822 (0.1)
Urgent care center	129 650 (15.0)	112 169 (14.2)	150 489 (14.3)	86 477 (14.8)
Emergency department visit	52 408 (6.0)	49 831 (6.3)	70 461 (6.7)	35 666 (6.1)
No. of physician encounters, median (IQR)	1 (0–3)	1 (0–3)	1 (0–3)	1 (0–3)
No. of unique medication classes, median (IQR)	2 (0–3)	2 (1–3)	1 (0–3)	2 (1–3)
Index diagnosis				
Pharyngitis	256 700 (29.6)	331 545 (42.0)	0 (0.0)	0 (0.0)
Sinusitis	610 458 (70.4)	458 257 (58.0)	0 (0.0)	0 (0.0)
Influenza	0 (0.0)	0 (0.0)	249 033 (23.6)	17 431 (3.0)
Viral URI	0 (0.0)	0 (0.0)	653 986 (62.1)	303 246 (51.9)
Nonsuppurative OM	0 (0.0)	0 (0.0)	34 961 (3.3)	37 319 (6.4)
Bronchitis	0 (0.0)	0 (0.0)	115 632 (11.0)	226 030 (38.7)

Abbreviations: CDHP, consumer-directed health plans; EPO, exclusive provider organization; HMO, health maintenance organization; IQR, interquartile range; OM, otitis media; POS, point-of-service; PPO, preferred provider organization; URI, upper respiratory infection.

[a]Based on study inclusion and exclusion criteria, an adult could contribute 1 index event per individual infection type; therefore, a single adult can be represented more than once within the bacterial and viral infection overarching categories, respectively (eg, an adult with sinusitis and pharyngitis during the study period could contribute 2 index events to the bacterial infections columns). Baseline covariates were assessed on the index date. Emergency department visit, number of physician encounters, and number of unique medication classes were assessed in the 180-day baseline period before the index date.

[b]Results are expressed as N (%) unless otherwise indicated.

[c]For adults diagnosed with bacterial infections (ie, pharyngitis or sinusitis), antibiotic prescriptions were categorized as appropriate (ie, first-line antibiotic agent) or inappropriate (ie, non-first-line antibiotic agent); index events without an antibiotic prescription were excluded. First-line antibiotic agents were defined as amoxicillin or penicillin for pharyngitis; and amoxicillin or amoxicillin-clavulanate for sinusitis.

[d]For adults diagnosed with viral infections (ie, influenza, viral URI, nonsuppurative OM, or bronchitis), antibiotic prescriptions were categorized as appropriate (no antibiotic) or inappropriate (antibiotic).

	No. of events (Rate per 10,000 person-days)			
	Appropriate Agent	Inappropriate Agent	Weighted HR (95% CI)	Inappropriate agent nonharmful / Inappropriate agent harmful
Nausea/vomiting/abdominal pain				
Pharyngitis	1,558 (4.57)	2,218 (5.06)	1.10 (1.03, 1.18)	
Sinusitis	3,598 (4.41)	2,958 (4.87)	1.07 (1.02, 1.13)	
Influenza	1,959 (6.34)	127 (5.61)	0.86 (0.70, 1.06)	
Viral URI	3,891 (4.94)	1,733 (4.37)	0.90 (0.85, 0.96)	
Non-suppurative OM	188 (4.25)	190 (3.84)	0.84 (0.68, 1.03)	
Bronchitis	672 (5.04)	1,292 (4.30)	0.90 (0.81, 0.99)	
Non-C. difficile diarrhea				
Pharyngitis	788 (1.11)	1,376 (1.51)	1.31 (1.20, 1.43)	
Sinusitis	2,545 (1.51)	1,690 (1.35)	0.87 (0.82, 0.93)	
Influenza	930 (1.46)	76 (1.61)	1.03 (0.80, 1.32)	
Viral URI	2,100 (1.30)	1,072 (1.30)	1.02 (0.94, 1.10)	
Non-suppurative OM	110 (1.20)	126 (1.23)	0.97 (0.75, 1.26)	
Bronchitis	329 (1.21)	868 (1.40)	1.18 (1.03, 1.35)	
C. difficile infection				
Pharyngitis	8 (0.00)	29 (0.01)	2.90 (1.31, 6.41)	
Sinusitis	83 (0.02)	30 (0.01)	0.49 (0.32, 0.74)	
Influenza	8 (0.00)	0 (0.00)	NE	
Viral URI	19 (0.00)	15 (0.01)	1.57 (0.77, 3.18)	
Non-suppurative OM	3 (0.01)	3 (0.01)	NE	
Bronchitis	7 (0.01)	11 (0.01)	0.78 (0.30, 2.07)	
Vulvovaginal candidiasis or vaginitis				
Pharyngitis	1,418 (3.27)	1,627 (2.92)	0.92 (0.86, 0.99)	
Sinusitis	3,344 (3.24)	1,536 (1.92)	0.61 (0.57, 0.65)	
Influenza	558 (1.66)	37 (1.52)	0.85 (0.59, 1.22)	
Viral URI	1,698 (1.82)	1,011 (2.14)	1.24 (1.14, 1.34)	
Non-suppurative OM	116 (2.10)	173 (2.95)	1.39 (1.09, 1.77)	
Bronchitis	243 (1.61)	539 (1.59)	1.02 (0.87, 1.19)	
Anaphylaxis/angioedema/laryngeal edema				
Pharyngitis	21 (0.27)	46 (0.47)	1.30 (0.76, 2.20)	
Sinusitis	67 (0.37)	60 (0.44)	1.03 (0.72, 1.47)	
Influenza	5 (0.07)	2 (0.39)	NE	
Viral URI	155 (0.84)	26 (0.29)	0.49 (0.32, 0.76)	
Non-suppurative OM	5 (0.49)	4 (0.36)	NE	
Bronchitis	11 (0.34)	16 (0.24)	0.67 (0.31, 1.48)	
Skin rash/urticaria				
Pharyngitis	814 (2.37)	777 (1.76)	0.80 (0.72, 0.88)	
Sinusitis	1,088 (1.32)	718 (1.17)	0.89 (0.81, 0.98)	
Influenza	332 (1.06)	26 (1.13)	1.08 (0.66, 1.74)	
Viral URI	846 (1.07)	399 (1.00)	0.99 (0.87, 1.12)	
Non-suppurative OM	59 (1.32)	67 (1.34)	1.04 (0.73, 1.50)	
Bronchitis	123 (0.91)	287 (0.95)	1.05 (0.84, 1.31)	
Renal failure				
Pharyngitis	20 (0.06)	42 (0.09)	1.22 (0.70, 2.14)	
Sinusitis	57 (0.07)	54 (0.09)	1.13 (0.77, 1.64)	
Influenza	87 (0.28)	3 (0.13)	NE	
Viral URI	99 (0.12)	59 (0.15)	0.99 (0.70, 1.41)	
Non-suppurative OM	4 (0.09)	5 (0.10)	NE	
Bronchitis	25 (0.18)	68 (0.22)	1.12 (0.70, 1.81)	
Unspecified allergy				
Pharyngitis	298 (0.86)	279 (0.63)	0.78 (0.66, 0.92)	
Sinusitis	465 (0.56)	322 (0.52)	0.93 (0.80, 1.07)	
Influenza	95 (0.30)	10 (0.44)	1.10 (0.55, 2.21)	
Viral URI	189 (0.24)	160 (0.40)	1.66 (1.33, 2.08)	
Non-suppurative OM	11 (0.25)	44 (0.88)	3.60 (1.81, 7.16)	
Bronchitis	46 (0.34)	132 (0.43)	1.59 (1.12, 2.28)	

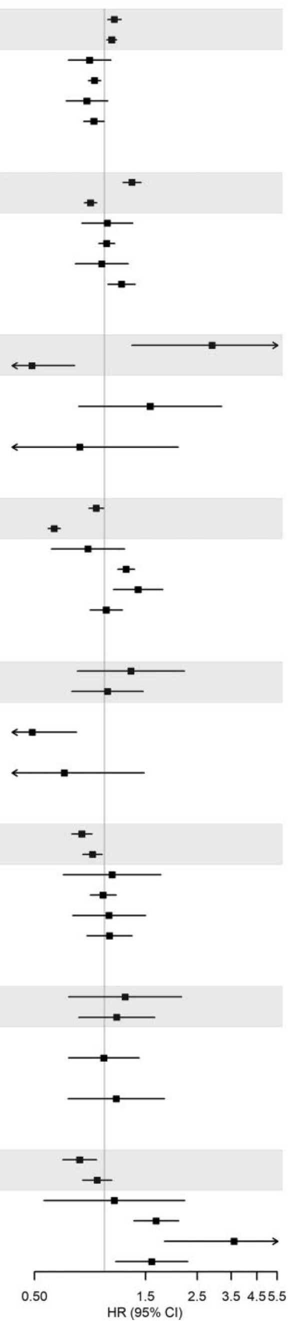

Figure 1. Inverse probability of treatment-weighted hazard ratio estimates of adverse drug events following inappropriate versus appropriate antibiotic prescriptions among adult patients with infections of interest.[a,b] Abbreviations: CI, confidence interval; HR, hazard ratio; OM, otitis media; URI, upper respiratory infection. [a] Presence of a shaded box denotes bacterial infection cohorts, whereas absence of a shaded box denotes viral infection cohorts. [b] Estimates for Stevens-Johnson syndrome/toxic epidermal necrolysis not shown because of the small number of observed events (<5 in all cohorts and exposure groups). The proportion of patients excluded for safety outcomes that occurred within 30 d before the index date ranged from 0.0% (*C. difficile* infection and anaphylaxis/angioedema/laryngeal edema, acute renal failure, and Stevens-Johnson syndrome/toxic epidermal necrolysis for all cohorts and unspecified allergy for pharyngitis and influenza cohorts) to 1.0% (nausea/vomiting/abdominal pain in the pharyngitis, sinusitis, nonsuppurative OM, and bronchitis cohorts) (Supplementary Table 11). For patients diagnosed with bacterial infections (ie, pharyngitis or sinusitis), antibiotic prescriptions were categorized as appropriate (ie, first-line antibiotic agent) or inappropriate (ie, non-first-line antibiotic agent); index events without an antibiotic prescription were excluded. First-line antibiotic agents were defined as amoxicillin or penicillin for pharyngitis and amoxicillin or amoxicillin-clavulanate for sinusitis. For patients diagnosed with viral infections (ie, influenza, viral URI, nonsuppurative OM, or bronchitis), antibiotic prescriptions were categorized as appropriate (no antibiotic) or inappropriate (antibiotic). Propensity score weighting was implemented using stabilized inverse probability of treatment (IPT) weights. For hazard ratio estimation, we required ≥5 adverse drug event cases in both the reference category (ie, appropriate antibiotic prescription) and the comparator group (ie, inappropriate antibiotic prescription) to ensure stability of the effect estimate.

Table 2. 30-Day Inverse Probability of Treatment-Weighted All-Cause Healthcare Utilization and Expenditure Estimates of Inappropriate Antibiotic Prescriptions Among Adults by Setting

Expenditure Category	Appropriate Utilization (%)	Inappropriate Utilization (%)	Appropriate Per Patient Expenditure Estimates, Mean (SD), $	Inappropriate Per Patient Expenditure Estimates, Mean (SD), $
Bacterial infections				
Pharyngitis				
Total	100.0	100.0	541 (2332)	692 (3128)
Inpatient medical	0.4	0.4	64 (1735)	87 (2356)
Emergency department	2.9	3.0	54 (503)	62 (575)
Outpatient medical	99.5	99.5	331 (1227)	403 (1638)
Outpatient pharmacy	100.0	100.0	92 (628)	141 (833)
Sinusitis				
Total	100.0	100.0	674 (3392)	746 (3404)
Inpatient medical	0.5	0.5	99 (2692)	105 (2538)
Emergency department	2.2	2.3	46 (487)	48 (477)
Outpatient medical	99.8	99.7	382 (1676)	414 (1753)
Outpatient pharmacy	100.0	100.0	147 (835)	179 (1095)
Viral infections				
Influenza				
Total	100.0	100.0	787 (3598)	868 (4000)
Inpatient medical	0.6	0.5	131 (3068)	154 (3588)
Emergency department	6.4	6.2	122 (702)	73 (643)
Outpatient medical	97.5	97.6	351 (1386)	392 (1008)
Outpatient pharmacy	85.9	100.0	182 (663)	249 (962)
Viral URI				
Total	100.0	100.0	721 (3558)	775 (3792)
Inpatient medical	0.5	0.5	114 (2897)	135 (3001)
Emergency department	3.5	3.4	75 (599)	51 (490)
Outpatient medical	99.2	99.1	403 (1564)	412 (1806)
Outpatient pharmacy	68.4	100.0	129 (867)	176 (1041)
Nonsuppurative OM				
Total	100.0	100.0	787 (2943)	740 (3128)
Inpatient medical	0.4	0.4	81 (1702)	87 (2345)
Emergency department	3.7	3.9	75 (549)	57 (497)
Outpatient medical	99.0	99.0	494 (1969)	436 (1700)
Outpatient pharmacy	61.6	100.0	137 (903)	159 (777)
Bronchitis				
Total	100.0	100.0	913 (4060)	813 (4031)
Inpatient medical	0.8	0.7	173 (3436)	165 (3457)
Emergency department	6.0	5.8	189 (828)	61 (493)
Outpatient medical	98.0	97.7	411 (1584)	399 (1648)
Outpatient pharmacy	73.3	100.0	140 (765)	188 (809)

Abbreviations: CI, confidence interval; OM, otitis media; SD, standard deviation; URI, upper respiratory infection.

inappropriate antibiotic prescriptions, irrespective of infection type (Supplementary Figure 3).

Attributable Expenditures and National Burden

After weighting, the exposure groups generally had similar baseline characteristics (Supplementary Table 13). Healthcare utilization and per-patient expenditure estimates are presented by infection type for all-cause (Table 2) and ADE-associated expenditures (Supplementary Table 14). For bacterial infections, the mean 30-day total attributable expenditure of an inappropriate antibiotic prescription was $67 (95% CI, $55–$85) for pharyngitis and $18 (95% CI, $6–$32) for sinusitis; for viral infections, the estimates ranged from −$53 (95% CI, −$78 to −$25) for bronchitis to $49 (95% CI, −$29 to $108) for influenza (Figure 2 and Supplementary Table 13). The 30-day ADE-associated attributable expenditure estimates of inappropriate antibiotics were elevated for pharyngitis ($6 [95% CI, $3–$8]); 95% CI estimates included the null for all other cohorts. The total attributable expenditure differences were largely driven by outpatient pharmacy and outpatient medical expenditures (Supplementary Table 13).

Total attributable expenditures of inappropriate antibiotics in the MarketScan study population are presented by infection type and setting in Supplementary Table 15. Table 3 presents

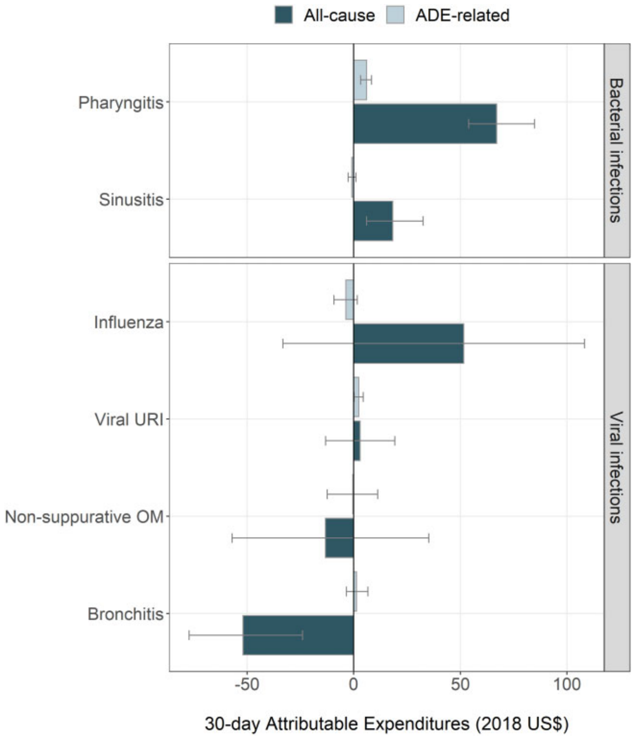

Figure 2. Inverse probability of treatment-weighted 30-day per patient attributable expenditure estimates of inappropriate antibiotic prescriptions among adults by infection type. Abbreviations: ADE, adverse drug event; OM, otitis media; URI, upper respiratory infection. Gray bars denote 95% confidence interval estimates.

the national annual expenditure estimates of inappropriate antibiotic treatment in the adult commercially insured population, which were highest for pharyngitis ($49.6 million), sinusitis ($19.1 million), and viral URI ($2.7 million).

Subgroup/Sensitivity Analyses

Results of the safety analyses for asthma were generally similar to results for viral infections, for which appropriate treatment was defined as the absence of an antibiotic prescription; results for asthma exacerbation were generally null or not estimable (Supplementary Tables 16–21 and Supplementary Figures 4–6). An antibiotic prescription to treat asthma or asthma exacerbation was associated with decreased expenditures (−$171 [95% CI, −$242 to −$118] and −$285 [95% CI, −$406 to −$172], respectively). We did not observe meaningful differences in calculated expenditures in sensitivity analyses that: (1) accounted for inappropriate antibiotic duration; (2) extended follow-up from 30 to 90 days (except higher 90-day expenditures for pharyngitis and viral URI); or (3) excluded health maintenance organization/point of service with capitation plans (Supplementary Table 22).

DISCUSSION

We performed a national cohort study to estimate the risk of ADEs and quantify attributable healthcare expenditures associated with inappropriate versus appropriate outpatient antibiotics prescribed to treat common respiratory infections among otherwise healthy, commercially insured US adults. Inappropriate antibiotic prescriptions were associated with higher risk of several individual ADEs including nausea/vomiting/abdominal pain (pharyngitis and sinusitis), non-*C. difficile* diarrhea (pharyngitis), CDI (pharyngitis), vulvovaginal candidiasis/vaginitis (viral URI and nonsuppurative OM), and unspecified allergy (viral URI, nonsuppurative OM, and bronchitis). The mean 30-day total attributable healthcare expenditures of inappropriate prescriptions were elevated for bacterial infections, indicating higher expenditures associated with broader spectrum antibiotics. The national annual estimates of attributable expenditures associated with inappropriate antibiotic prescriptions were $49.6 and $19.1 million for pharyngitis and sinusitis, respectively.

We observed substantial inappropriate antibiotic prescribing for bacterial and viral infections in adults, consistent with previous reports in pediatric and adult populations [1,2,20,39–44]. Additionally, our findings suggest that antibiotics are not benign, and that inappropriate antibiotics put patients at higher risk for ADEs. For viral infections, antibiotics are neither effective nor indicated, and our results suggest that reducing antibiotic prescriptions for viral infections may prevent cases of unspecified allergy and vulvovaginal candidiasis/vaginitis. For bacterial infections, our results suggest that efforts to shift prescribing from non-first-line to first-line antibiotics will involve safety-related tradeoffs, such as decreasing the risk of nausea/vomiting/abdominal pain, but increasing the risk of vulvovaginal candidiasis/vaginitis, skin rash/urticaria, and unspecified allergy. This is due in part to azithromycin, which is not indicated for any infections under study, yet is commonly prescribed to treat respiratory infections and associated with gastrointestinal side effects [45]. Moreover, penicillins—the first-line antibiotics for bacterial respiratory infections—frequently cause rashes and allergic reactions [46]. Additionally, amoxicillin-clavulanate—considered first-line therapy for sinusitis but not pharyngitis—is known to disrupt the microbiota, resulting in non-*C. difficile* diarrhea and CDI [23,47]. Balancing potential risks and benefits associated with different antibiotic agents remains challenging [48]; further research is warranted to determine the safest and most effective antibiotics for common conditions.

Inappropriate (vs appropriate) antibiotics for bacterial infections were associated with higher attributable expenditures, driven by subsequent emergency department encounters (pharyngitis only), outpatient medical encounters, and outpatient pharmacy expenditures. We suspect that some of these visits were for antibiotic-related ADEs, which have previously been shown to be undercoded [49]. Unlike other infections under study, patients with bronchitis inappropriately treated with antibiotics incurred lower 30-day total attributable expenditures than those who did not receive antibiotics, because of lower

Table 3. 30-Day Total Attributable Expenditures of Inappropriate Antibiotic Prescriptions, Standardized to the 2017 US Commercially Insured Adult Population

	Expenditures				
Index Diagnoses	Inpatient Medical	Emergency Department	Outpatient Medical	Outpatient Pharmacy	Total
Bacterial infections					
Pharyngitis	$5 998 537	$5 024 358	$25 527 802	$13 021 777	$49 575 060
Sinusitis	−$6 685 986	$1 069 528	$11 419 107	$13 308 669	$19 108 060
Viral infections					
Influenza	$201 981	−$338 135	$536 809	$1 293 271	$1 692 312
Viral URI	$4 603 233	−$5 187 609	−$7 893 105	$11 176 242	$2 682 337
Nonsuppurative OM	$113 167	−$424 563	−$1 809 507	$1 232 698	−$890 240
Bronchitis	−$2 184 838	−$17 388 596	−$17 393 273	$8 304 801	−$28 654 975

Abbreviations: OM, otitis media; URI, upper respiratory infection.

expenditures within outpatient and emergency department settings. Many of these follow-up encounters had diagnoses consistent with persistent bronchitis symptoms (rather than an undiagnosed bacterial infection), suggesting that providers need to better educate patients that bronchitis symptoms can last weeks, and antibiotics will not shorten duration of illness.

Although most published estimates of annual expenditures associated with inappropriate antibiotic prescribing are restricted to index antibiotic expenditures, our study additionally accounts for subsequent medical- and pharmacy-related expenditures within 30 days of infection diagnosis (eg, emergency department encounters for anaphylaxis; prescriptions for skin rash). Yet, our national attributable healthcare expenditure estimates of inappropriate outpatient antibiotic prescribing are substantially lower than previous estimates from national studies of adult influenza [15,50], acute respiratory infections [51], and pharyngitis [52]. Our estimates are likely conservative because the study restricted to younger, healthy, commercially insured adults without recent antibiotic exposures, and was conducted after increased outpatient utilization of rapid diagnostics for viral pathogens [3].

Altogether, the findings from this study and our recent companion pediatrics study [20] identify a clear opportunity to improve quality of care and reduce healthcare expenditures. The evidence serves as a call to action to establish outpatient antibiotic stewardship efforts including provider and patient education, incorporation of antibiotic prescribing metrics into quality reports, and financial and technical resources for outpatient stewardship activities [53].

Limitations

The primary limitation of our study is possible residual confounding because bias could occur if there are unmeasured or poorly measured variables associated with the exposure and outcome. For example, bias could be present if patients who inappropriately received antibiotics for viral infections were more likely to be treated by clinicians who routinely provide other unnecessary care associated with harms or additional expenditures (eg, opioid, benzodiazepine prescriptions). We implemented several established epidemiologic methods to mitigate confounding including an active comparator design for analyses of bacterial infections by restricting to patients prescribed an antibiotic [54–56]. We further restricted the study population to otherwise healthy adults [54] and applied propensity score methodology [57] to account for potential confounders. Last, we used negative control outcomes to assess the comparability of inappropriate versus appropriate antibiotic recipients within each infection-specific cohort, and the null results indicated that residual confounding was minimal [34].

Our results may be subject to additional limitations. First, eligibility for each infection-related cohort was based on the presence of infection diagnosis codes that have not been validated; thus, cohort eligibility may be subject to misclassification because of misdiagnosis or miscoding. However, we implemented strict eligibility criteria such as the absence of same-day codes for other bacterial/viral infections and required a same-day antibiotic dispensing for bacterial infection cohorts. Second, we classified adults treated for pharyngitis or sinusitis with first-line antibiotics as “appropriate,” even though many of these infections are viral and may not require antibiotics. Third, we did not account for history of antibiotic allergies or intolerances; therefore, some antibiotics deemed inappropriate may have been misclassified. Fourth, we did not attempt to study the long-term effects of antibiotic exposure (eg, dysbiosis [58,59], antibiotic-resistant infections [3]). Last, our results may not be generalizable to Medicaid-insured, Medicare-insured, or uninsured populations [60].

CONCLUSIONS

Our national study of adults with respiratory infections demonstrates that inappropriate outpatient antibiotic prescriptions are associated with increased risk of ADEs and substantial healthcare expenditures. These results support the need for increased outpatient antibiotic stewardship efforts to discourage antibiotic prescribing for viral infections, encourage appropriate selection of guideline-recommended antibiotics for bacterial infections, and reduce antibiotic-related harms and expenditures.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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