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Clostridium difficile and other adverse events from overprescribed antibiotics for acute upper respiratory infection

Harris Carmichael[1,2,3], Steven M. Asch[1,4] & Eran Bendavid[1,3]

From the [1]Division of Primary Care and Population Health, Stanford University School of Medicine, Stanford, California, USA; [2]Intermountain Healthcare Delivery Institute, Intermountain Healthcare, Murray, Utah, USA; [3]Center for Health Policy, Center for Primary Care and Outcomes Research, Stanford University, Stanford, California, USA; and [4]Center for Innovation to Implementation, VA Palo Alto Health Care System, Menlo Park, California, USA

Abstract. Carmichael H, Asch SM, Bendavid E. *Clostridium difficile* and other adverse events from overprescribed antibiotics for acute upper respiratory infection. *J Intern Med.* 2023;**293**:470–480.

Background. Guidelines widely recommend avoiding antibiotics for many acute upper respiratory infections (aURIs) to avert adverse events in the absence of likely benefit. However, the extent of harm from these antibiotics remains a subject of debate and could inform patient-centered decision-making. Prior estimates finding a number needed to harm (NNH) between 8 and 10 rely on patient-reported adverse events of any severity. In this analysis, we sought to estimate adverse events by only measuring comparatively severe events that require subsequent clinical evaluation.

Methods. We constructed a retrospective cohort, including 51 million patient encounters. Using logistic regression models, we determined the adjusted odds ratio (aOR) of clinically detectable adverse events following antibiotic use compared with events among unexposed individuals with aURIs. Our outcomes included candidiasis, diarrhea, *Clostridium difficile* infection (CDI), and a composite outcome.

Findings. From our analysis, 62.4% of the population received antibiotics in an aURI encounter. Observed adverse events in the antibiotic-exposed group were 54,279 and 46,936 for diarrhea and candidiasis, respectively, yielding an aOR of 1.24 and 1.61, and an NNH of 3,126 and 1,975. Observed events of CDI in the exposed group were 30,133, and aORs of isolated CDI and combined adverse events were 1.07 and 1.30, resulting in an NNH of 17,695 and 1,150, respectively. Females were more likely to be diagnosed with any adverse event. Overall antibiotics were found to result in 5.7 additional cases of CDI per 100,000 outpatient prescriptions following an upper respiratory tract infection.

Interpretation. Despite higher NNH than previous methods of analysis, we find substantial iatrogenic harm associated with prescribing antibiotics in aURIs.

Keywords: antibacterial agents, antibiotic stewardship, drug-related side effects and adverse reactions, respiratory tract infections

Introduction

The overuse of antibiotics is widely recognized [1, 2]. One study finds that while there are enough antibiotics prescribed for acute upper respiratory infections (aURIs; e.g., sinusitis, otitis media, and bronchitis; see Supplementary Information) to cover 22% of the US population annually, only half of those prescriptions were considered necessary [3]. The majority of antibiotic prescriptions not recommended in aURI guidelines are for viral or bacterial etiologies that do not benefit clinically from antibiotics [2, 4]. Still other researchers have found that nearly half of antibiotic prescriptions were written without an associated infectious diagnosis susceptible to antibiotics [5]. A recent Cochrane Review found that antibiotics have a

lower number needed to harm (NNH) than number needed to treat in rhinosinusitis, meaning that antibiotics were more likely to cause harm than benefit in this analysis [6]. Unnecessary antibiotic utilization can lead to increased antibiotic resistance, healthcare costs, and adverse drug reactions with little clinical benefit. The NNH for common antibiotics in aURIs has been reported as low as 8–10 for diarrhea and 27 for candidiasis [6, 7].

Our current estimations for the frequency of harms associated with the use of antibiotics in aURIs come predominately from studies that rely on patient-reported symptoms. These estimates make no distinction regarding the severity of adverse events and do not include diagnoses clinically validated by a physician. Despite the well-documented increase in the rates of symptoms in these randomized trials, observable adverse event rates requiring subsequent clinical evaluation have not been studied in large patient datasets. One study in pediatric populations found a nearly 10-fold increase in patient-reported adverse events compared with those captured in provider documentation [8]. Identifying the observable adverse events following the outpatient prescription of antibiotics will allow us to quantify some of the excess cost associated with the widespread inappropriate use of antibiotics in terms of clinically significant patient harm, healthcare utilization, and financial costs. We will assess these adverse events in aURIs for which the overutilization of antibiotics has already been identified in prior analyses. In this analysis, we aim to quantify the observable nonallergic clinical harms following antibiotic utilization for aURIs for which the appropriateness of antibiotics has already been assessed.

Methods

Data

Optum's deidentified Clinformatics Data Mart Database is derived from a large adjudicated claims data warehouse [9]. Data include Medicare Advantage and commercially insured patients in all 50 states in the United States, inpatient and outpatient administrative claims, pharmaceutical claims, and patient demographics for beneficiaries seen between December 2002 and December 2017.

Sample selection

The dataset includes information on approximately 58 million distinct patients, whereas our analysis focused on outpatient aURIs. aURIs were assessed on diagnostic categories of antibiotic appropriateness using the tiered criteria established by Fleming-Dutra [3]. Tier 1 diagnoses are encounters in which antibiotics are almost always indicated (e.g., pneumonia) and were thus excluded from this study. Tier 2 diagnoses are those for which antibiotics may be indicated (e.g., pharyngitis), and Tier 3 diagnoses are those in which antibiotics are not indicated (e.g., bronchitis). This analysis focused on the adverse events associated with antibiotics in Tier 2 and Tier 3 diagnostic conditions for which there is evidence of antibiotic overutilization, limited clinical benefit, and risk for severe adverse events. aURIs were defined as sinusitis, suppurative and nonsuppurative otitis media, pharyngitis, laryngitis, bronchitis and bronchiolitis, common cold, and unspecified URI (Supplementary Information) [3]. The diagnostic codes to identify these diagnoses have been previously found to have an overall specificity of 99% and PPV of 93% [10].

Patients were included if they had an outpatient encounter with an aURI diagnosis without a previous aURI identified within the preceding 60 days and were at least 1 year of age at the time of the encounter. Index events were excluded if there was missing, or verifiably inaccurate, demographic data (e.g., date of visit prior to date of birth), a superseding Tier 1 diagnosis, a superseding respiratory diagnosis (e.g., COPD), or a diagnosis of one of our primary or secondary outcomes. Patients were allowed more than one aURI diagnostic episode in the analysis. Control patients were those with a qualifying index visit and without a pharmaceutical claim for antibiotics within 14 days of the index visit.

Antibiotic exposure

We determined the exposure group through pharmaceutical claims demonstrating the patient received an oral antibiotic following a diagnosis of aURI. We assessed all oral antibiotics that accounted for at least 0.25% of antibiotics prescribed, yielding 15 antibiotics from the 101 total antibiotics identified. In total, these antibiotics accounted for >98% of all antimicrobial prescriptions in our dataset. Antibiotics assessed in the final analysis included amoxicillin, amoxicillin/clavulanate, azithromycin, cefdinir, cefprozil, cefuroxime, cephalexin, ciprofloxacin, clarithromycin, clindamycin, doxycycline, levofloxacin, moxifloxacin, penicillin V, and trimethoprim/

sulfamethoxazole. All exposed patients filled a prescription for at least one of the above antibiotics within 5 days following the index visit. The encounter was excluded if the patient received antibiotics up to 5 days before the index visit, or between day 5 and day 14 of follow-up period monitoring for adverse events.

Outcomes

We identified two primary and two secondary outcomes for this analysis. Primary study outcomes were diagnosis of either (1) diarrhea or (2) candidiasis. Secondary outcomes were diagnosis of (1) *Clostridium difficile* infection (CDI) or (2) a composite outcome of any primary outcome or CDI. Both primary and secondary outcomes were identified using ICD codes for encounters occurring within 14 days of antibiotic exposure. We defined CDI by diagnostic codes up to 1 year following the index aURI visit (Supplementary Information).

Statistical analyses

The data were analyzed using logistic regression, and each outcome was modeled separately. The main parameter of interest was an indicator variable for antibiotic exposure. The (exponentiated) coefficient of the model can then be interpreted as the odds of an adverse event following receipt of antibiotics for aURIs. Adjusted odds ratios (aORs) and 95% confidence intervals are reported. All main models included the following set of controls: age (grouped into five categories of 20 years), sex, Elixhauser comorbidity index (count variable), and any hospitalization during the follow-up period (indicator variable).

In addition to the primary analysis, we conducted several additional analyses. First, we tested differential effects in the pediatric and adult populations (defined at 18 years of age). In these analyses, age was assessed as an integer variable. Second, we replaced the indicator variable for receiving any antibiotic with each antibiotic as an independent predictor variable in both the overall model and each of the pediatric and adult models. Finally, we conducted a staged analysis by sequentially adding all predictor variables in the main analysis as well as indicator variables for a CDI diagnosis in the year prior to the index visit, and an indicator variable for no healthcare claims in the 60 days prior to the index visit. The Supplementary Information section includes the exact model specifications.

We did not include any other outcomes in this analysis. Although they are often reported in chart reviews, allergic drug reactions (e.g., rash, anaphylaxis, or unspecified adverse drug effect) were not included in this analysis as researchers have assessed ICD-9 coding for these adverse events and found poor individual reliability in identifying allergic drug reactions (Supplementary Information).

STATA v14.2 was used in this data analysis. We report our results in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

This study was conducted in accordance with all guidelines from Clinformatics and the World Medical Association Declaration of Helsinki. The deidentified data assessed did not meet requirements for patient-informed consent and was IRB approved.

Results

We identified 55.9 million outpatient provider encounters with a diagnosis code for aURIs, and 50.9 million met our criteria for inclusion in this analysis representing 23 million unique patients (Fig. 1). Of all encounters for aURI, 62.4% were followed by a filled prescription for antibiotics. Following the index visit, 26.0% of encounters had an outpatient visit of any kind within 14 days, and 0.6% recorded an adverse event. Our patient population closely reflected racial demographics in the United States nationally; however, it trended more affluent than the US population average.

In our analysis, those receiving antibiotics were more likely to be older, female, have insurance claims within the last 2 months, have follow-up visits within 14 days, and have more Elixhauser comorbidities (Table 1). The entire cohort was disproportionately female (57.7%), and females were more likely to receive antibiotics after adjusting for visit frequency, consistent with prior studies [11]. The number of Elixhauser comorbidities observed per patient ranged from 0 to 25, with an average of 0.9 and standard deviation of 1.5. We observed an average age of 31.8 (SD 22.3), ranging from 1 to 99. Of our cohort, 40.6% had no insurance claims within 2 months prior to the index visit.

Antibiotic prescription for aURIs increased from 2003 to 2010, stabilizing at a maximum of 66%

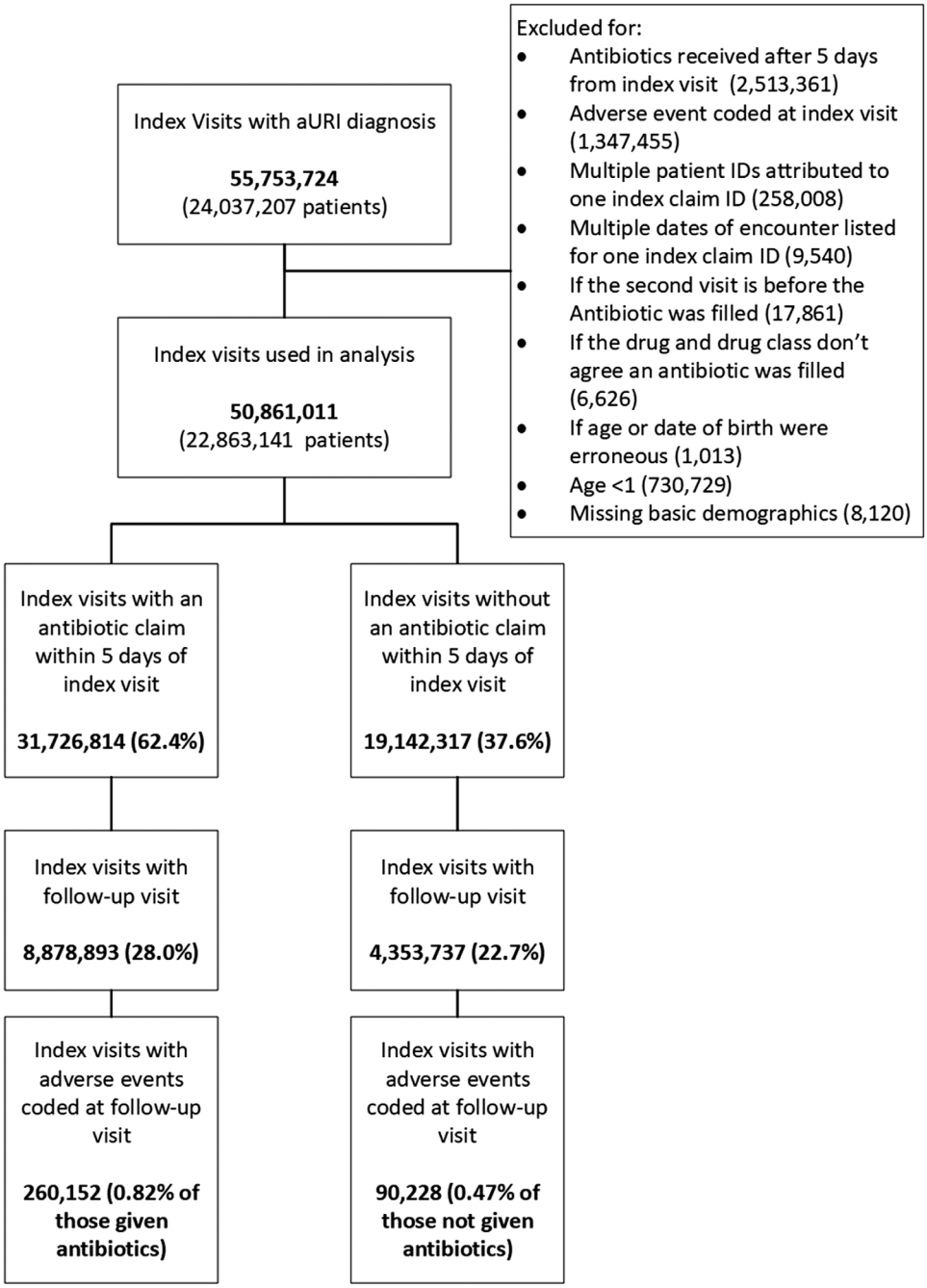

Fig. 1 *Study flow diagram.*

until 2013, when prescribing rates then declined slightly to an average of 63.4% from 2013 to 2017. We found that azithromycin, amoxicillin, and amoxicillin/clavulanate were the most common antibiotics prescribed, representing 34.2% (10.9 million), 22.5% (7.1 million), and 15.0% (4.8 million), respectively.

Encounters with adverse events by antibiotic exposure are displayed in Fig. 2. The absolute risk

Table 1. *Demographics*

	All	Antibiotics	No antibiotics
	(n = 50,861,011)	(n = 31,722,698)	(n = 19,138,313)
	n (%)	n (%)	n (%)
Age			
1–19	19,004,571 (37.4)	10,010,249 (31.6)	8994,322 (47.0)
20–39	12,237,757 (24.1)	8113,498 (25.6)	4124,259 (21.5)
40–59	13,094,079 (25.7)	9342,071 (29.4)	3752,008 (19.6)
60–79	5759,606 (11.3)	3825,239 (12.1)	1934,367 (10.1)
80–100	764,998 (1.5)	431,641 (1.4)	333,357 (1.7)
Sex			
Female	29,378,160 (57.8)	18,561,154 (58.5)	10,817,006 (56.5)
Male	21,482,851 (42.2)	13,161,544 (41.5)	8321,307 (43.5)
Race			
White	32,346,254 (63.6)	20,539,684 (64.7)	11,806,570 (61.7)
Hispanic	4041,373 (7.9)	2455,167 (7.7)	1586,206 (8.3)
Black	3405,121 (6.7)	2099,191 (6.6)	1305,930 (6.8)
Asian	1641,852 (3.2)	876,946 (2.8)	764,906 (4.0)
Unknown	9426,411 (18.5)	5751,710 (18.1)	3674,701 (19.2)
Household Income			
Unknown	16,525,729 (32.5)	9866,168 (31.1)	6659,561 (34.8)
<$40,000	4868,034 (9.6)	3171,232 (10.0)	1696,802 (8.9)
$40,000–$49,000	2048,830 (4.0)	1331,696 (4.2)	717,134 (3.7)
$50,000–$59,000	2245,241 (4.4)	1465,304 (4.6)	779,937 (4.1)
$60,000–$74,000	3395,094 (6.7)	2216,837 (7.0)	1178,257 (6.2)
$75,000–$99,000	5431,239 (10.7)	3533,251 (11.1)	1897,988 (9.9)
>$100,000	16,346,844 (32.1)	10,138,210 (32.0)	6208,634 (32.4)
No visit 60 days prior to index visit	20,661,017 (40.6)	13,133,170 (41.4)	7527,847 (39.3)
Next visit within 14 days of index visit	13,230,414 (26.0)	8877,656 (28.0)	4352,758 (22.7)
Hospitalized within 14 days of index visit	2655,860 (5.2)	1766,421 (5.6)	889,439 (4.6)
Adverse events			
Diarrhea	79,831 (0.2)	54,279 (0.2)	25,552 (0.1)
Candidiasis	62,845 (0.1)	46,936 (0.1)	15,909 (0.1)
CDI	44,955 (0.1)	30,133 (0.1)	14,822 (0.1)
	M (SD)	*M (SD)*	*M (SD)*
Elixhauser comorbidity index	0.9 (1.5)	0.9 (1.5)	0.7 (1.4)

Abbreviation: CDI, *Clostridium difficile* infection.

associated with our primary endpoints—diarrhea and candidiasis—in the unexposed population was 13.4 and 8.3 events per 10,000 encounters, respectively. The absolute risk associated with our primary endpoints in the exposed population was 17.1 and 14.8 events per 10,000 encounters for diarrhea and candidiasis, respectively. The aORs for antibiotics in these events were 1.24 (95% CI, 1.23–1.26, $p < 0.001$) and 1.61 (95% CI, 1.59–1.64, $p < 0.001$), resulting in an NNH of 3126 (95% CI, 2885–3262) and 1975 (95% CI, 1882–2042) for diarrhea and candidiasis, respectively (Table 2). The absolute risk associated with our secondary endpoints—CDI over the year following the index visit and combined adverse event—in the unexposed population was 7.7 and 29 events per 10,000 encounters, respectively. The aORs of CDI and combined events were 1.07 (95% CI, 1.05–1.09, $p < 0.001$) and 1.30 (95% CI, 1.29–1.31, $p < 0.001$), resulting in an NNH of 17,695 (95% CI, 13,742–24,841) and 1150 (95% CI, 1102–1202), respectively.

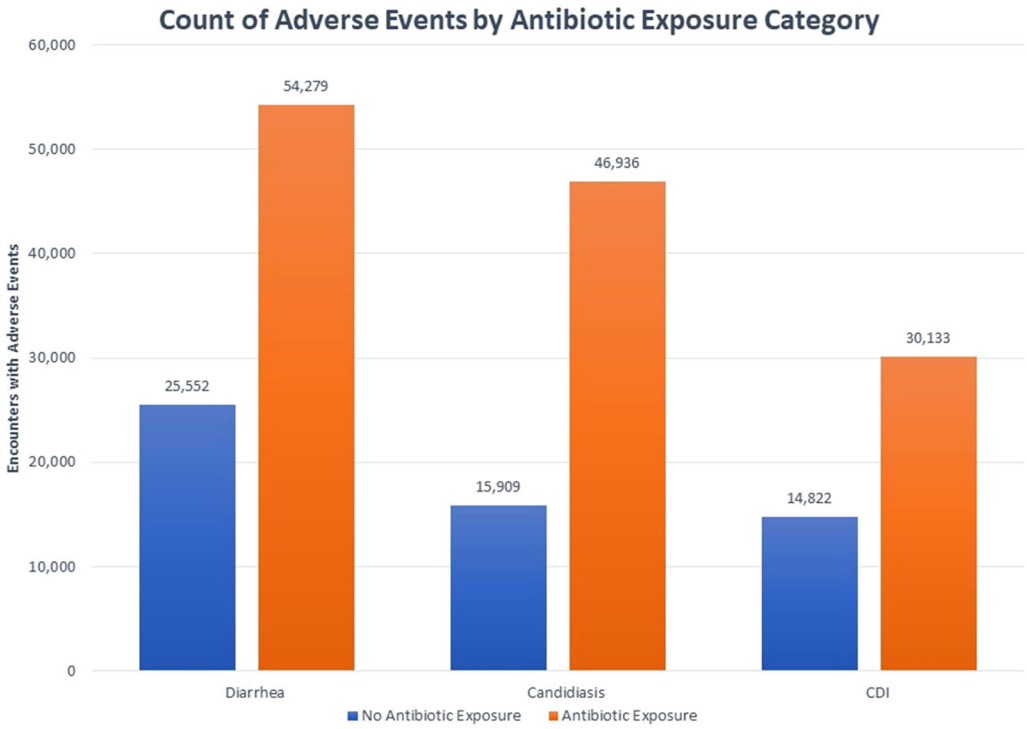

Fig. 2 *Adverse events by antibiotic exposure category.*

Table 2. *Main regression analysis*

	Diarrhea	Candidiasis	CDI	All adverse events
Received antibiotics	1.24*** (0.00956)	1.61*** (0.0150)	1.07*** (0.0109)	1.30*** (0.00670)
Female sex	1.13*** (0.00834)	2.82*** (0.0288)	1.24*** (0.0125)	1.51*** (0.00772)
Age 1–19 (reference group)	Ref	Ref	Ref	Ref
Age 20–39	0.89*** (0.00887)	1.74*** (0.0195)	1.91*** (0.0376)	1.27*** (0.00871)
Age 40–59	0.80*** (0.00797)	1.26*** (0.0149)	2.68*** (0.0479)	1.11*** (0.00764)
Age 60–79	0.96*** (0.0116)	1.24*** (0.0186)	4.85*** (0.0892)	1.42*** (0.0114)
Age 80–100	1.20*** (0.0251)	1.13*** (0.0336)	8.90*** (0.196)	2.07*** (0.0256)
Was the patient hospitalized within 14 days after the index visit	4.93*** (0.0431)	2.64*** (0.0304)	3.08*** (0.0356)	3.57*** (0.0216)
Elixhauser comorbidity index	1.13*** (0.00205)	1.12*** (0.00248)	1.25*** (0.00203)	1.18*** (0.00127)
Observations	50,861,011			

Note: Regression results for primary and secondary endpoints with any antibiotic. Exponentiated coefficients; standard errors in parentheses.
Abbreviation: CDI, *Clostridium difficile* infection.
*p < 0.05; **p < 0.01; ***p < 0.001.

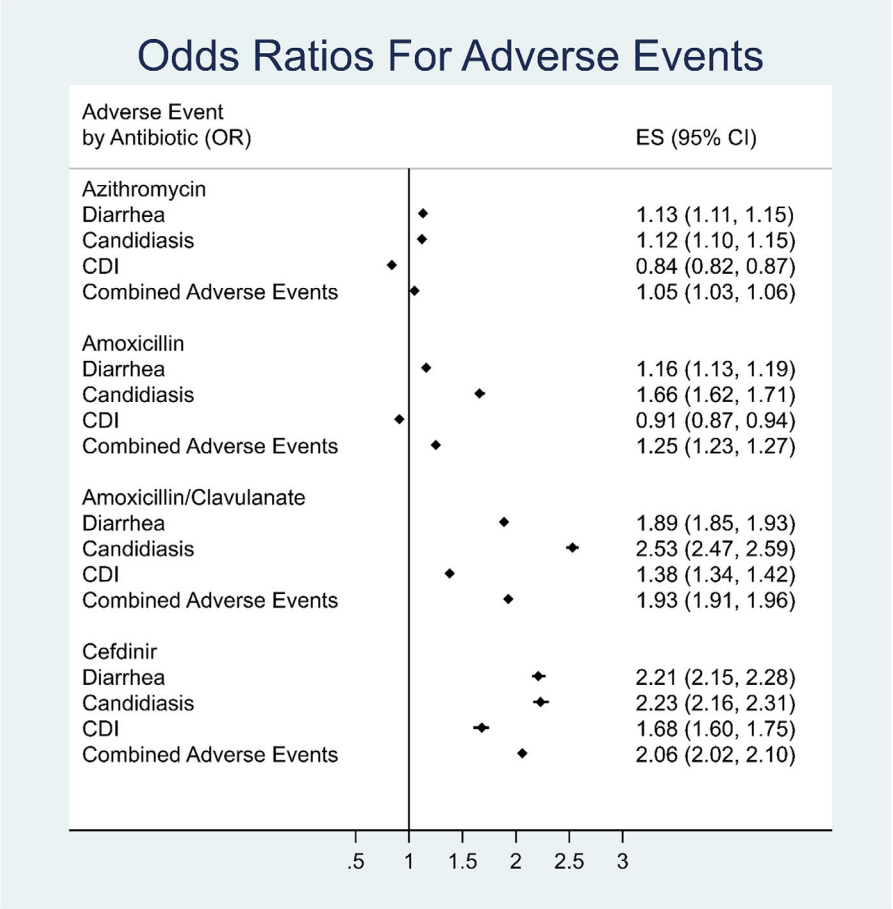

Fig. 3 *Odds of adverse events.*

We found odds of diarrhea to have a bimodal age distribution. Those over age 80 had the highest aOR for diarrhea as an adverse event, followed by the pediatric population. We also identified that the aOR of candidiasis was highest in the 21–40 age group and reduced with age thereafter, and the pediatrics having the lowest aOR. Lastly, the odds of CDI increased dramatically with age. Patients over 80 had an almost ninefold increase in the odds of CDI compared to our reference pediatric population. Female sex increased the odds of all adverse events in our main analysis.

In the most prescribed antibiotics—azithromycin, amoxicillin, and amoxicillin/clavulanate—we observed a combined adverse event aOR of 1.05, 1.25, and 1.93, respectively (Fig. 3). Clindamycin had the highest aOR of combined adverse events at 2.30 (Table S1). Cefdinir, the fourth most prescribed antibiotic, had the second highest aOR for combined adverse events—2.06. Based on this analysis, the NNH attributed to cefdinir for all adverse events is 327. Ciprofloxacin followed by cefdinir had the highest aOR of causing diarrhea—2.38 and 2.21. Clindamycin and amoxicillin/clavulanate had the highest aOR of causing candidiasis—2.61 and 2.53. Clindamycin and cefdinir had the highest aOR for CDI at 2.65 and 1.68, respectively. Penicillin V was the only antibiotic not to increase the odds for a primary endpoint (diarrhea) and the only antibiotic to have a non-statistically significant finding in the main analysis.

In the pediatric population (age < 18), we identified an aOR after receiving any antibiotic of 1.28 (95% CI, 1.25–1.31, $p < 0.001$) and 1.94 (95% CI, 1.87–2.01, $p < 0.001$) for diarrhea and

candidiasis, respectively. The odds of all outcomes decreased with age in the pediatric population. In this population, the fluoroquinolones—consisting of moxifloxacin, ciprofloxacin, and levofloxacin—had the highest odds for combined adverse events, with aORs of 5.17, 4.63, and 4.12, respectively (Table S2). Notably, all fluoroquinolones profoundly increased the odds for candidiasis, with levofloxacin having the highest aOR of 14.3 for pediatric candidiasis. In the adult population, we identified an aOR of 1.24 (95% CI, 1.22–1.27, $p < 0.001$) and 1.54 (95% CI, 1.51–1.57, $p < 0.001$) for diarrhea and candidiasis, respectively (Table S3). Increasing age in the adult population increased the risk for all outcomes except candidiasis, where it was found to be protective.

The aOR of CDI was increased by 24% when the patient was female, validated by prior literature describing the same phenomenon of female predilection [12]. When controlling for all antibiotics assessed, the aORs of CDI for azithromycin, amoxicillin, and amoxicillin/clavulanate were 0.84, 0.91, and 1.38, respectively. The antibiotics with the highest aORs for CDI were clindamycin, cefdinir, and ciprofloxacin—2.65, 1.68, and 1.48, respectively. The order of antibiotics most highly associated with CDI is consistent with a previous analysis assessing antibiotics on their propensity to cause CDI [13]. ORs for the adverse event of CDI were higher in the pediatric population—1.27; however, a lower unexposed risk of 2 per 10,000 visits was observed. In a sensitivity analysis, we included an indicator variable for patients who had previously had an ICD code for CDI that was associated with an aOR of 6.75 for a diagnosis of CDI following antibiotics, but did not substantially change the odds of adverse event at the index encounter (Table S2).

Females had higher aORs of adverse events in all analyses except pediatric CDI, for which there was no statistically significant finding, and pediatric diarrhea for which females had a 12% reduction in the odds of diarrhea. The addition of confounding estimates to our main model in the staged analysis did not profoundly alter the odds of our predictor variable (Table S5). Potential confounders in this analysis were considered as age, sex, patient comorbidities, recent utilization of healthcare prior to the index encounter, and recent initiation of new medication use. We adjusted for these considerations where possible. We also assessed possible contributions of race and income in our main model (Table S6).

Discussion

The goal of this analysis was to quantify the clinical harms severe enough to require subsequent medical encounters following antibiotic utilization in aURIs that are often inappropriate. In this analysis, the NNH for observable adverse events of diarrhea and candidiasis were 3074 and 1962, respectively. The NNH for CDI and combined adverse events were 17,695 and 1150, respectively. These are known adverse events of antibiotics; however, until this analysis, the extent of the severe harm in the use of these medications was unknown. With millions of visits for aURI in the United States annually, the extent of these severe adverse events in the population is significant. Combining our conservative estimates on adverse events and recent evidence [3], we estimate that over the timeline contained in this analysis, there would have been 154,515 cases of diarrhea and 242,119 cases of candidiasis severe enough to warrant a subsequent medical visit resulting only from unnecessary antibiotics. This would also represent 26,846 cases of CDI due only to antibiotics that have previously been reported as inappropriate for aURIs.

It is notable that in addition to the overprescribing of antibiotics, there is also overuse of broad-spectrum antibiotics when narrow spectrum antibiotics are recommended by guidelines. Cefdinir was also the antibiotic with the second highest odds of adverse events and, despite cefdinir being rarely indicated by guideline-concordant treatment for aURIs, it was the fourth most prescribed antibiotic in this analysis. The analytic approach in this work adds further detail to the harms experienced from the practice of prescribing broad-spectrum antibiotics when they are not guideline-indicated treatments. We found that exposure to cefdinir increased the rate of combined adverse events in this analysis fourfold when compared to amoxicillin, a first-line treatment for many aURI diagnoses (cefdinir NNH = 327 vs. amoxicillin NNH = 1384).

In a meta-analysis reviewing 45 randomized placebo-controlled trials relying on patient-reported adverse events, amoxicillin/clavulanate has previously been reported to have aORs for diarrhea and candidiasis of 3.30 and 7.78, respectively [7]. Looking at clinically detectable

adverse events, we find that aORs following amoxicillin/clavulanate for diarrhea and candidiasis are 1.24 and 1.61. We also find that absolute harms are significantly lower when identifying adverse events requiring clinical attention as opposed to those reported by patients. Lastly, Gillies et al. were unable to identify a statistically significant correlation of amoxicillin—without clavulanate—with patient-reported diarrhea, finding an aOR of 1.14 (95% CI, 0.98–1.33). With the power of our analysis, we identified amoxicillin to have an aOR of 1.89 (95% CI, 1.85–1.93) for the adverse event of diarrhea requiring medical attention.

In our analysis, we expected a propensity for females to experience candidiasis following oral antibiotics due to vaginal candidiasis. However, we also identified that our analysis demonstrated higher ORs for all assessed adverse events in the combined age analysis, adult, and pediatric subgroups except for pediatric diarrhea and pediatric CDI. It had previously been reported, and was again confirmed in this analysis, that females were disproportionately likely to have an encounter coded for aURIs. Our analysis reasserts prior findings of females having higher odds of CDI [12].

Hospitalization was associated with increased ORs for adverse events in all assessed outcomes. Candidiasis had the smallest aOR of hospitalization association at an aOR of 2.64, whereas diarrhea had the highest association in our main analysis at an aOR of 4.93. Increasing age is a protective effect in all adverse events for our main model in pediatric populations, whereas it is a detrimental effect in all adverse events of the combined age model and adult model. In a secondary analysis, we found that for each additional Elixhauser comorbidity identified in the year prior to the index visit, there was an 18% increase (aOR 1.18, 95% CI, 1.17–1.18) in the probability for all combined adverse events.

Some antibiotics were found to be protective against CDI in this analysis. We suspect this finding to be a combination of individual antibiotic characteristics against the *C. difficile* organism and confounding by indication given that narrow-spectrum antibiotics are less likely to be prescribed to those who are at highest risk for CDI. Notably, doxycycline was found in our analysis to have a protective effect for CDI with an aOR of 0.94 (95% CI, 0.89–0.99, $p = 0.029$), in close agreement with previous literature [13, 14]. We are unable to identify previous evidence refuting the effect of individual antibiotics observed in this analysis to be protective for CDI.

This work attempts to define adverse event rates that are more clinically severe than prior analyses for patients, health systems, and policy makers. In doing so, we hope to assist decision makers in their attempt to focus resources on projects that optimize clinical care for their patient populations, such as antibiotic stewardship. Our work serves to underscore the iatrogenic harms that could be averted by successful antibiotic stewardship programs, such as those proposed and reported on by the Centers for Disease Control and Prevention and Institute for Healthcare Improvement.

Limitations

By limiting our assessment of adverse events to a higher severity, we report significantly lower odds of adverse event after receiving antibiotics for aURIs when compared to patient-reported outcomes alone. However, the poor sensitivity identified in ICD coding for aURIs, which our method relies upon, is likely to underestimate the absolute number of events, undercounting the true volume of adverse events severe enough to require medical evaluation. The methodology of identifying clinically diagnosed events by a provider may nevertheless overcount adverse events considered clinically significant if some diagnosed adverse events are considered minor by the provider and do not warrant additional treatment but are coded in their billing. Additionally, we were unable to determine the duration of antibiotic exposure, which—particularly in the diagnosis of candidiasis—will significantly correlate with the detected adverse event rate and warrants further investigation. Those that received antibiotics in aURI encounters may have been more severely ill, and this may indicate confounding by indication in our analysis. To address this issue, we included the Elixhauser comorbidity index, age, hospitalization, prior CDI diagnoses, and recent medical encounters in our reported results. Although we included the Elixhauser comorbidity index, we recognize that further investigation into specific disease states incorporated in this index—such as HIV or other immunocompromised states—may provide further detail into those risks for these specific patient populations. Lastly, future analyses may explore the extent of prior healthcare exposure in terms of numbers of prior hospitalizations, type and count of clinic exposures, and dialysis exposure separate

from that identified in the Elixhauser comorbidity index. Future analyses should also investigate whether repeated exposure may confer nonlinear added risk of adverse events such as CDI.

Our analysis was limited to the insured US population and thus may not represent a generalizable result to the entire US healthcare system. However, previous studies have found that the uninsured are more likely to receive antibiotics for aURIs—aOR 1.79 [15]. Thus we again find that our estimation would undercount the adverse events for the entire US population. We recognize that the overall outcomes of harm identified in this analysis may not be applicable to all US regions or those regions or countries outside the United States based on local antibiotic prescribing habits. Local utilization rates for specific antibiotics could either increase or decrease the overall odds of adverse events identified here and, to that end, we have published our observed event rates for specific antibiotics in both the adult and pediatric populations in our Tables S1–S3. Our administrative claims dataset does not allow for the validation of patient outcomes by electronic health record level data, including physician notes. However, previous assessments of adverse events following antibiotics in aURIs for the pediatric populations by EHR level data found a 10-fold discrepancy in patient-reported outcome and those observed in chart review [8]. The results from this analysis were not generalizable but are consistent with the gap described previously in patient-reported adverse events and the clinically detectable adverse events used in our analysis. Lastly, the extent by which these antibiotics contribute to antibiotic resistance is not well quantified in the literature. As we are unable to accurately estimate the contribution of antibiotic resistance for the patient or the US population, we are again underestimating the impact of these medications with the results identified in this analysis.

Conclusion

Our analysis identifies comparatively severe adverse events following antibiotic prescriptions for aURIs to be less common than those studies relying on patient-reported events. Although our findings observe a higher NNH following antibiotic prescriptions for aURIs, the volume of these prescriptions results in extensive iatrogenic harms within the US healthcare system. We conclude that there remains an unacceptable level of avoidable harm delivered to US patients via antibiotic prescribing practices, and outpatient antibiotic stewardship should be a priority for providers, healthcare organizations, insurers, and policy makers.

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Conflicts of interest

The authors of this work have no conflicts of interest to declare. All authors have participated in the work and approved it for submission.

Author contributions

Concept and design: Original concept and design attributed to Harris Carmichael, whereas all authors contributed to the final concept and design. *Acquisition of data; analysis of data; drafting of the manuscript*: Harris Carmichael. *Interpretation of data; critical revision of the manuscript for important intellectual content; obtained funding*: All authors.

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Correspondence: Harris Carmichael, Intermountain Healthcare Delivery Institute, Intermountain Healthcare, 5026 S. State Street, 3rd Floor, Murray, UT 84107-4825, USA.
Email: harris.carmichael@imail.org

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1: Regression results by antibiotic in combined age analysis.
Table S2: Pediatric model by antibiotic.
Table S3: Adult model by antibiotic.
Table S4: Number of antibiotics received.
Table S5: Staged model analysis in combined age groups.
Table S6: Main Analysis with Race and Income.
Table S7: Main analysis with other CDI methods.
Figure S1: Histogram of visit volume by year.
Figure S2: Percent of visits prescribed Antibiotics by year.

