Title

Variation in Outpatient Antibiotic Prescribing for Acute Respiratory Infections in the Veteran Population: A Cross-sectional Study.

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"Variation in Outpatient Antibiotic Prescribing for Acute Respiratory Infections in the Veteran Population."

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ABSTRACT

BACKGROUND: Despite efforts to reduce antibiotic prescribing for acute respiratory infections (ARIs), information on factors driving prescribing is limited.

OBJECTIVE: To examine trends in antibiotic prescribing within the national Veterans Affairs population over an 8-year period and to identify patient, provider, and setting sources of variation.

DESIGN: Retrospective cross-sectional study.

SETTING: All emergency departments, primary care and urgent care clinics within the Veterans Affairs health system.

PARTICIPANTS: All visits between 2005 and 2012 with a primary diagnosis of acute respiratory tract infection that typically have low proportions of bacterial infection. Patients with infections or comorbidities indicating antibiotic use were excluded.

MEASUREMENTS: Overall antibiotic prescription, macrolide prescription, patient, provider, and setting characteristics extracted from the electronic medical record.

RESULTS: Of 1.0 million ARI patient visits, the proportion resulting in an antibiotic prescription increased from 67.5% in 2005 to 69.2% in 2012 ($P<0.001$). The proportion of antibiotic prescriptions that were macrolides increased from 36.8% to 47.0% ($P<0.001$). Antibiotic prescribing was highest for the diagnoses of sinusitis (adjusted proportion 86%) and bronchitis (85%), while prescribing varied little by fever, age, setting type, or comorbidities. The majority of variation in antibiotic use was attributable to providers: the highest 10% of providers prescribed antibiotics for ≥ 95% of their patients, while the lowest 10% prescribed antibiotics to ≤ 40%.

LIMITATIONS: Retrospective. Lacked some clinical data that may influence the antibiotic decision.

CONCLUSIONS: Patients with ARIs commonly receive antibiotics in the VA population, regardless of patient, provider, and setting features. The use of macrolides has increased. The majority of variation in antibiotic use was at the provider level.

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INTRODUCTION

As the emergence of resistant pathogens outpaces our ability to develop new antibiotics, the problem of unnecessary antibiotic use – a primary cause of the development of resistant organisms – has become a major public health concern.(1,2) Despite limited benefits, the majority of outpatient antibiotics are prescribed for acute respiratory infections (ARIs),(3,4) a practice that is discouraged by practice guidelines.(5,6)

In response to this problem, local and national efforts across the United States have been launched to improve prescribing behavior and develop criteria for using antibiotics to treat respiratory infections. While there has been a significant decline in overall antibiotic use for ARIs for children,(7) the use of antibiotics in adults remains high, and recent studies demonstrate a dramatic increase in the use of broad-spectrum antibiotics, particularly macrolides.(8,9,10) Tracking national practice patterns and identifying sources of variation in antibiotic use would improve our ability to target interventions more appropriately. Previous studies have identified facility-level variation in prescribing patterns(11) and differences based upon patient and provider characteristics;(12,13) however, these associations are difficult to interpret without analytic techniques that take into consideration the effects of different levels in healthcare delivery (provider, clinic and healthcare system).

The aims of this study were to: 1) measure national trends in antibiotic prescriptions for ARIs at outpatient facilities within the Veterans Affairs Health System during an eight-year period; 2) investigate patient, provider and setting factors associated with the prescription of any antibiotic as well as a macrolide; and 3) measure variation at the provider, clinic, and medical center levels.

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METHODS:

Setting

The Veterans Affairs network serves nearly 8.5 million Veterans each year at over 1700 clinics and 152 hospitals, with approximately 13 million primary care visits per year.(14) Where multiple hospital divisions operate as an integrated healthcare system under a single leadership team, these facilities are combined, resulting in 139 distinct VA Medical Centers (VAMCs). The primary care needs of Veterans are met in primary care, urgent care and emergency department (ED) settings across the VA system. These settings are either located on the physical grounds of a VA Medical Center and its local hospital (VAMC-based), or located at Community-Based Outpatient Clinics (CBOCs), which are stand-alone facilities that offer outpatient services only.

All healthcare settings within the VA share the same clinical electronic health record. All data for our study were accessed through the Veterans Health Information Systems and Technology Architecture (VistA), through the Veterans Informatics and Computing Infrastructure (VINCI), a computing environment that stores clinical data for research purposes.(15,16)

Participants

During the period of January 1, 2005, to December 31, 2012, we identified all patient visits at emergency departments, primary care, and urgent care clinics with *International Classification of Disease-Edition 9* (ICD-9) codes consistent with acute respiratory tract infections, including nasopharyngitis (460), pharyngitis (462), sinusitis (461.x), acute bronchitis (466.x), upper respiratory tract infection (465.8, 465.9), and other infections such as laryngitis (464) and tonsillitis (463). Visits with ICD-9 codes for skin or soft tissue infection, pneumonia, influenza, urinary tract infection, or other infections at the same visit were excluded, as were patients with a previous acute respiratory infection within the past 30 days. We also excluded patients with ICD-9 codes consistent with comorbidities that increase the risk of serious bacterial infections, including HIV, neoplasms, diabetes, chronic lung disease including COPD and asthma, end stage renal failure requiring hemodialysis, solid organ transplantations, or other immunocompromised states within one year of the visit. A complete list of ICD-9 codes used for inclusion and exclusion is listed in Appendix A.

Measurements: patient, provider, and setting factors

We extracted all patient, provider, and setting features listed in Table 1. Although patients with comorbidities that increase risk of serious bacterial infections were excluded, we estimated the burden of other comorbidities for each included patient by extracting all ICD-9 codes given to each patient within the year prior to the ARI visit, and applied the Clinical Classification System (CCS) developed by the Agency for Health care Research and Quality.(17) We further grouped the CCS into six categories relevant to the ARI diagnosis (infection, pulmonary, renal, cardiovascular, psychiatric, and immunodeficient disease). Patient distance to the facility was measured by calculating the travel distance between the patient's home address and the location of the visit.

We identified a single "primary provider" reported for the day of each visit. Although there could be multiple providers for multiple visits in one day, the primary provider is the single health professional who identifies him/herself in the electronic health record as the individual who is responsible for the decision-making, patient care, and documentation at that particular encounter. The primary provider for the encounter was not necessarily the *primary care provider* (PCP) for the patient's general medical care; for example, if the patient presented to the emergency department, the "primary provider" for the visit would likely be a provider other than the PCP. Additionally, the primary provider listed was not necessarily the prescriber of medications, as the electronic order entry of medications was not necessarily performed by the same individual who completed the documentation of the visit. However, this was the case for 90% of all listed physicians and mid-level providers.

We did not classify providers by level of training (residents or other trainees), as the attending physician rather than trainee was usually listed as the primary provider. Due to incomplete provider census information, we did not measure specialty or years since licensure. Patient visits that lacked documentation of a temperature (16%) were categorized as having no fever. Missing provider age (22%) was included in the model as a separate category. The remainder of the visits that contained missing values (totaling less than 1%) were excluded from the analysis.

Measurements: antibiotic prescriptions

We initially extracted all VA antibiotic prescription fills within 2 days prior and 3 days after the patient visit. As it was possible for patients to receive antibiotic prescriptions over the phone prior to a visit or to fill a prescription after the visit occurred, we chose this date range to identify all prescription fills. Because some VA facilities lacked fill data due to outside pharmacy services as well as variation in data collection, we then applied RED, a natural language processing tool developed by VINCI,(18) to identify antibiotic prescriptions within unstructured clinical documents. The resulting RED algorithm demonstrated a positive predictive value of 98% against a reference standard of physician review. After text classification, the proportion of patient visits that were identified to result in an antibiotic prescription increased from 60.7% to 68.4%.

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Statistical Analysis

Annual trends in overall antibiotic prescriptions as well as macrolide prescriptions were tested for significance using univariate logistic regression with the calendar year as the single linear predictor variable.

Relationship between antibiotic prescription and patient, provider and setting characteristics

We used generalized estimating equations (GEE) under multivariable linear logistic regression models to predict the probability of 1) prescribing any antibiotic at a patient visit, and 2) prescribing a macrolide when an antibiotic was prescribed. The following predictors were used: patient gender, patient age, number of comorbidities, maximum temperature, diagnosis, distance to clinic, type of listed provider, provider age, daily ARI visit load, time of day, calendar month, and calendar year. Calendar year was modeled as a linear predictor of antibiotic prescribing. All other continuous variables were categorized into quartiles as cutoff points except for temperature, which had clinically defined cutoffs ("high fever" = temperature ≥ 102F; "fever" = temperature 100.4F and < 102F), daily clinic load (1, 2, 3, and ≥4 ARI visits per day), and time of day (early morning 0800-10:30, late morning 10:30-12:30, early afternoon 12:30-14:30, late afternoon 14:30-17:00, and night 17:00-08:00). GEE was used for this portion of the analysis to generate population weighted average comparisons and to provider statistical inferences that were more robust to potential misspecification of the model used to account for clustering by VAMC, clinic and provider. The GEE analyses were performed with an independent working covariance model for encounters within the same VAMC to assure that each encounter was weighted equally in each analysis. We calculated the mean adjusted proportions using the marginal standardization approach, in which adjusted proportions are

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summed to a weighted average reflecting the distribution of the remaining predictor variables in the target population.(19) Bootstrapping with 400 independent samples drawn from the 130 VAMCs was utilized to provide 95% confidence intervals and p-values for the adjusted proportions.

Variation in antibiotic prescribing associated with different levels of healthcare delivery

We fit a generalized linear mixed effect models for antibiotic prescribing, with provider, clinic/ED, and VAMC included as normally distributed nested random effects on the logit scale, and with fixed effects terms representing the above listed patient, provider, and setting factors. The estimated variances for provider, clinic/ED, and VAMC were used to describe the variation in antibiotic prescribing specifically attributable to each of these levels of the healthcare system, after controlling for the fixed effects.

Because providers are not perfectly nested within clinic, providers who appeared in multiple clinics were reassigned to the unique clinics in which they appeared most frequently. In order to simplify computations and compare the modeled results with the observed variation in the prevalence of antibiotic prescription across providers, we restricted this analysis to those providers with at least 100 patients in the study, representing a total of 480,875 visits.

We used three approaches to visualize the different levels of variation in antibiotic prescribing. We first generated a histogram displaying the observed, unadjusted distribution of antibiotic prescribing proportions across providers. Second, we used the results of the generalized mixed model to estimate density functions describing the total variation in prescribing attributable to each of the three random effects. We also displayed the density function with variance given by the sum of the estimated variance of the three random effects to

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describing the total variation in prescribing, incorporating variation from all three levels of healthcare delivery.

Third, we displayed conditional density curves to display the conditional distributions of antibiotic prescription prevalence across providers within clinics with prescribing prevalence fixed at the 10th, 50th, and 90th percentiles of the distribution of antibiotic prescribing across clinics, and within VAMCs with prescription prevalence fixed at the 10th, 50th, and 90th percentiles of the distribution of antibiotic prescribing across VAMCs.(20)

The study was conducted with approval from the University of Utah Institutional Review Board (IRB#00058373) and the VA, and with support from the Centers for Disease Control and Prevention, who participated in study design and interpretation of the results. Statistical analyses were performed using STATA 12.0 and SAS 9.2. All analysis code is documented in Appendix C.

RESULTS

Study Population

Of 2,481,520 total patient visits with a diagnosis of ARI, we identified 1,044,523 that met our inclusion criteria (Figure 1). These were staffed by 45,619 providers at 990 clinics or emergency departments within 130 VAMCs. Thirty percent of all visits occurred in community-based outpatient clinics, while the remainder occurred in clinics/EDs on VAMC campuses. Seventy percent occurred in primary care clinics, 23% in emergency departments, and 7% in urgent care clinics. A physician was listed as the primary provider for 62% of visits, followed by mid-level provider (24%) and nurse (11%). The median age of the patient population was 61; 51.9% had documentation of a cardiovascular comorbidity, and 24.1% had documentation of a

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pulmonary comorbidity not included in the exclusion criteria. Twenty-five percent of the population lived >31 miles from their visit location.

National Trends

We observed a small, unadjusted absolute increase in overall proportion of visits with antibiotic prescriptions during the study period from 67.5% in 2005 to 69.2% in 2012 (P<0.001). Although we observed a seasonal trend in the number of ARI-related visits, there was no substantial seasonal variation in the proportion of these visits for which antibiotics were prescribed (Figure 2). Of the visits resulting in an antibiotic prescription, macrolide prescriptions increased from 36.8% in 2005 to 47.0% in 2012 (P<0.001), while penicillins (36% to 32.1%, P<0.001) and fluoroquinolones (15.0% to 12.7%, P<0.001) decreased over time (Figure 3).

Predictors of antibiotic prescribing

Antibiotics were prescribed in 68.4% of all ARI visits (N=714,552). Figure 4 displays adjusted proportions of visits with antibiotic prescription for subgroups defined by selected factors. Subgroups associated with higher prevalence of antibiotic prescribing included a diagnosis of sinusitis (adjusted percent 87%) or bronchitis (85%), presence of a high fever (78%), occurrence in an urgent care setting (77%), southern region (72%), and central region (72%). Mid-level providers also prescribed antibiotics slightly more frequently than physicians (71% versus 69%). "Other" providers also had a higher prescribing prevalence (80%), likely due to the high proportion of pharmacists in this small group (<2% of all visits). Additionally, prescribing was slightly higher at clinics based in VA medical centers than at community-based

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outpatient clinics (71% versus 63%). The number of patient comorbidities that were not in the exclusion criteria had no association with antibiotic prescribing.

Of the antibiotics prescribed, 43.6% (N=302,595) were macrolides. Subgroups with elevated adjusted prevalence estimates for macrolide prescribing (Figure 5) included a diagnosis of bronchitis (adjusted percent 52%) or URI (50%). Presence of a high fever was a negative predictor for macrolide use (36%). No clinically significant differences were seen in other patient features, provider features, or geographic region.

Sources of variation.

The histogram in Figure 6a displays the variation in the proportions of visits with antibiotic prescriptions among providers who saw more than 100 patients with ARIs during the study period (N=480,875 visits, seen by 2,594 providers). The highest 10% providers prescribed antibiotics for at least 95% of their patients, while the lowest 10% prescribed antibiotics to ≤ 40% of their patients. The smooth curve in the same figure displays the modeled variation in prescribing among providers after adjustment for the previously described measured patient, provider and setting characteristics. The similarity of the curve to the histogram suggests that these measured characteristics contributed only slightly to the overall variation in antibiotic prescribing across providers.

The dashed curves in Figure 6b display the model-generated estimates of variation specifically associated with each level of healthcare delivery (provider, clinic, and VAMC), while controlling for the measured patient, provider, and setting fixed effect factors. After accounting for the fixed effect factors, variation attributable to providers, clinics, and VAMCs respectively accounted for 59%, 28% and 13% of the total remaining variation in antibiotic prescription

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prevalence across the three levels of healthcare delivery. For comparison, the solid curve in the same figure (which matches the solid curve in Figure 6a) displays the model-based overall variation in prescribing among providers. The figure of Appendix B displays how the modeled distributions of prescribing across providers varies between clinics and VAMCs. Even within high or low prescribing VAMCs and clinics, there was considerable variation in provider prescribing.

DISCUSSION:

Our 8-year study of 1 million patient visits demonstrates a persistently high prevalence of outpatient antibiotic prescriptions for acute respiratory infections in the national Veteran population. During the same period, macrolides have become the predominant class prescribed. Similar trends have been reported in studies using data from the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS). (21, 22, 23, 24) The lack of progress in reducing unnecessary antibiotic prescribing for ARIs is a major public health concern.

We aimed to gain a better understanding of the factors driving this problem. Our exceptionally large population of patients, providers, and clinics within the VA health system gave us the unique opportunity to characterize variation in antibiotic prescribing across different levels of healthcare delivery. The granularity of our data further enabled us to explore relationships between antibiotic use and multiple factors, including patient characteristics, provider experience, and clinic features.

Antibiotic prescribing was associated with many of the factors we measured, including temperature, distance to clinic, setting type, and geographic region. These associations, however, were small, and even when taken together, they had limited explanatory power. Antibiotic prescribing was common regardless of the patient and setting features we studied.

The greatest source of variability in management we identified was the provider. While 10% of our providers prescribed antibiotics for at least 95% of all of their ARI visits, another 10% prescribed antibiotics for 40% or less. After adjustment of all of the factors studied, we discovered a magnitude of variation at the provider level that overshadowed the clinic or medical center.

Other studies of antibiotic use in ARIs have identified variation at the facility,(11) health plan,(25) and regional(26) levels, and cultural influences and context in both provider practices and patient expectations have been provided as important reasons for environmental influences on antibiotic use.(27) Indeed, much medical decision-making is influenced by the system and social context. While environment is important, our findings suggest that providers have a strong tendency to choose the same treatment decision regardless of patient or clinic features, indicating that individual provider preference, or "style," exerts a heavy influence on the antibiotic decision.

We found a substantial increase in macrolide prescribing in our system, a trend that has been observed in other national studies.(9),(10) The increase in popularity of macrolides could be due to its short course, convenient, once-daily dosing, the recommendation of macrolides as first-line empiric treatment for community-acquired pneumonia, and successful marketing campaigns. Macrolides are not recommended as first line therapy for either pharyngitis or sinusitis, and while we observed lower proportions of macrolide use for these diagnoses than bronchitis and URIs, the proportion was still significant. This trend is concerning given the lack of additional benefit of macrolides over narrow-spectrum antibiotics for the treatment of ARI's,

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the increase in macrolide-resistant pneumococcal disease,(28) and potential cardiotoxicity,(29) especially considering the high proportion of Veterans in our study that had cardiovascular comorbidities.

We recognize several limitations to our study. We used administrative data, relying upon ICD-9 codes to identify our population. Additionally, we excluded a large number of patients with comorbidities and diagnoses for infections with greater risk for bacterial infections in an attempt to identify cases with a low risk for bacterial infection (and hence a lower likelihood to benefit from antibiotics). For any individual patient, whether an antibiotic was appropriate is impossible to determine. However, at the population level, we would expect a much lower overall proportion of antibiotic prescribing for this group of patients based upon national treatment guidelines.

Due to the diversity of settings studied and variation in charting practices, our study lacked additional clinical data that have been previously shown to play a role the antibiotic decision, such as symptom duration or physical exam findings, or provider information such as specialty or training background.(30, 31) While we attempted to exclude patients who had comorbidities that would increase risk for serious bacterial infections, different providers have different patient panels, and thus different thresholds for antibiotic prescribing. However, the provider-level variation that we observed remained after adjusting for additional patient comorbidities and other clinical features, and providers varied widely within clinics, suggesting against a significant amount of tailoring based on measurable patient factors. Additional factors that might explain the degree of provider variation in antibiotic prescriptions, such as attitudes toward the risks and benefits of antibiotics, responsiveness to local surveillance data or stewardship efforts, or patient preferences and expectations (and providers' understanding of

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them), could potentially be identified on a large scale within the clinical record in the future. Further research that incorporates qualitative methods will also improve our ability to elucidate these mechanisms.

Our Veteran population includes a greater proportion of older, male patients with a higher comorbidity burden. Despite this, we found similar overall proportions, geographic differences, and trends in macrolide use to those in other studies. Ambulatory care and pharmacy services at the VA are more integrated and standardized than other ambulatory settings. In other more diverse practice settings, clinic- or system-based variations in infrastructure might play a larger role in driving differences in antibiotic use. However, the provider-level variation that we observed might also be even greater in other systems.

Our findings have important implications for health systems and public health. Variation in management of acute respiratory infection does not appear to be driven by tailoring of treatment to an individual patient's circumstances but rather by prescribing patterns of individual providers. As a prime example of unexplained variation, this is a ripe target for quality improvement and antibiotic stewardship interventions. Audit and feedback has shown promise as a powerful tool to change behavior,(32, 33) and new provider-targeted decision support tools could help clinicians recognize and respond to their prescribing patterns compared to similar provider and patient populations.

Unnecessary antibiotic use for acute respiratory infections remains an important problem. The persistence of this problem requires new approaches. As our understanding of the relationship between providers, patients, settings and treatment decisions improves, so will our ability to target future information and stewardship efforts.

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TABLE AND FIGURES

Table 1. Patient, provider and setting characteristics in ARI visits for the Veteran population.

Figure 1. Study population.
Visits could meet multiple exclusion criteria, and thus the sum of visits meeting each exclusion criteria exceeds the total number of excluded visits.

Figure 2. Trends in overall antibiotic prescribing.
Number of ARI-related visits per month and monthly proportion of visits resulting in an antibiotic prescription.

Figure 3. Temporal trends in the proportion of all antibiotics prescribed for each antibiotic class.

Figure 4. Predictors of antibiotic prescribing.
For each subgroup, the adjusted proportion of visits with antibiotics prescribed based on the marginal standardization model is shown. N = 1,036,982 visits. Model also included calendar month and year. Statistically significant predictors ($p<0.001$) included the diagnosis of sinusitis or bronchitis, fever or high fever, provider type of “other”, urgent care clinic, daily clinic ARI load > 4 visits, central region, and south region.

Figure 5. Predictors of macrolide prescribing.
For each subgroup, adjusted proportion of antibiotic prescriptions that were macrolides is shown. N = 714,552 visits. Model also included calendar month and year. Statistically significant predictors ($p<0.001$) included the diagnosis of URI, bronchitis, and normal temperature.

Figure 6. Variation in antibiotic prescribing.
Figure 6a. Variation in antibiotic prescribing among providers.
Histogram displays the distribution of observed proportions of visits with an antibiotic prescription across 2,594 providers with at least 100 ARI visits each (total N=480,875). Smooth curve depicts the modeled distribution of antibiotic prescription across providers, after controlling for measured patient, provider, and setting features listed in Figures 4 and 5.

Figure 6b. Sources of variation in antibiotic prescribing.
Dashed curves depict modeled distributions describing variation in antibiotic prescription proportions attributable specifically to providers, clinics and VAMCs after controlling for the measured patient, provider and setting parameters listed in Figures 4 and 5. Solid curve corresponds to the solid curve in Figure 6a, and depicts overall modeled variation in antibiotic prescription across providers, including differences between providers at different clinics and VAMCs.

APPENDIX A. Definitions of inclusion, exclusion criteria and diagnostic code groupings.

APPENDIX B. Figure. Conditional distribution of antibiotic prescribing.
Conditional density curves of antibiotic prescribing prevalence across providers within clinics with prescription prevalence fixed at the 10th, 50th, and 90th percentiles of the distribution of

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antibiotic prescribing across clinics, within VAMCs with prescribing prevalence fixed at the 10^{th}, 50^{th}, and 90^{th} percentiles of the distribution of antibiotic prescribing, across VAMCs.

APPENDIX C. Analysis code, statistical appendix, and separation of between-cluster and within-cluster variables.

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