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

A Cross-sectional Study

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

Objective: To examine trends in antibiotic prescribing in the 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 and primary and urgent care clinics in the Veterans Affairs health system.

Participants: All patient visits between 2005 and 2012 with primary diagnoses of ARIs that typically had low proportions of bacterial infection. Patients with infections or comorbid conditions that indicated antibiotic use were excluded.

Measurements: Overall antibiotic prescription; macrolide prescription; and patient, provider, and setting characteristics extracted from the electronic health record.

Results: The proportion of 1 million visits with ARI diagnoses that resulted in antibiotic prescriptions increased from 67.5% in 2005 to 69.2% in 2012 ($P < 0.001$). The proportion of macrolide antibiotics prescribed increased from 36.8% to 47.0% ($P < 0.001$). Antibiotic prescribing was highest for sinusitis (adjusted proportion, 86%) and bronchitis (85%) and varied little according to fever, age, setting, or comorbid conditions. Substantial variation was identified in prescribing at the provider level: The 10% of providers who prescribed the most antibiotics did so during at least 95% of their ARI visits, and the 10% who prescribed the least did so during 40% or fewer of their ARI visits.

Limitation: Some clinical data that may have influenced the prescribing decision were missing.

Conclusion: Veterans with ARIs commonly receive antibiotics, regardless of patient, provider, or setting characteristics. Macrolide use has increased, and substantial variation was identified in antibiotic prescribing at the provider level.

Primary Funding Source: U.S. Department of Veterans Affairs, Centers for Disease Control and Prevention.

Ann Intern Med. 2015;163:73-80. doi:10.7326/M14-1933 **www.annals.org**
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As the emergence of resistant pathogens outpaces our ability to develop new antibiotics, the problem of unnecessary antibiotic use—a primary cause of resistance—has become a major public health concern (1, 2). Despite limited benefits, most outpatient antibiotics are prescribed for acute respiratory infections (ARIs) (3, 4), a practice that is discouraged by guidelines (5, 6).

In response to this problem, efforts have been launched across the United States to improve prescribing behavior and develop criteria for using antibiotics to treat ARIs. Although overall antibiotic use for ARIs in children has significantly declined (7), use in adults remains high, and recent studies demonstrate a dramatic increase in the use of broad-spectrum antibiotics, particularly macrolides (8–10). 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 on patient and provider characteristics (12, 13). However, these associations are difficult to interpret without analytic techniques that consider the effects of different levels of health care delivery (provider, clinic, and health care system).

This study aimed to measure national trends in antibiotic prescribing for ARIs at outpatient facilities in the Veterans Affairs (VA) health care system during an 8-year period; investigate patient, provider, and setting factors associated with the prescription of any antibiotics, including macrolides; and measure variation at the provider, clinic, and medical center levels.

Methods

Setting

The VA network serves approximately 6.5 million of 8.5 million enrolled veterans each year at more than 1700 clinics and 152 hospitals, with approximately 13 million primary care visits per year (14). Where several hospital divisions operate as an integrated health care system under a single leadership team, these facilities are combined, resulting in 130 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 grounds of a VAMC and its local hospital or at a community-based outpatient

See also:

Web-Only
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EDITORS' NOTES

Context

The prescribing of antibiotics for acute respiratory infections that are unlikely to be of bacterial origin is a major contributor to overall antibiotic overuse.

Contribution

In a study of Veterans Affairs emergency departments and acute care settings, the clinical presentation, type of provider, and type of clinical setting did not influence prescribing for acute respiratory infections. Prescribing varied widely at the individual provider level. Overall prescription of antibiotics, including macrolides, increased.

Caution

Findings in a Veterans Affairs population may limit generalizability.

Implication

Research about variation in antibiotic prescribing at the individual provider level may be needed to curtail inappropriate antibiotic overuse.

clinic, which is a stand-alone facility that offers only outpatient services.

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

Participants

From 1 January 2005 to 31 December 2012, we identified all patient visits at EDs and primary and urgent care clinics with International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM), codes consistent with ARIs, including nasopharyngitis (460); pharyngitis (462); sinusitis (461.x); acute bronchitis (466.x); upper respiratory infection (465.8 and 465.9); and other infections, such as laryngitis (464) and tonsillitis (463). Visits that also had ICD-9-CM codes for skin or soft tissue infection, pneumonia, influenza, urinary tract infection, or other infections were excluded, as were patients who had had an ARI in the last 30 days. We also excluded visits with ICD-9-CM codes consistent with comorbid conditions that increase the risk for serious bacterial infections, including HIV; neoplasia; diabetes; chronic lung disease, including chronic obstructive pulmonary disease and asthma; end-stage renal failure; solid organ transplantations; or other immunocompromised states within 1 year of the visit. The Supplement (available at www.annals.org) lists the ICD-9-CM codes that were used.

Measurements

Patient, Provider, and Setting Factors

We extracted patient, provider, and setting characteristics (Table). Although patients with comorbid conditions that increased risk for serious bacterial infections were excluded, we estimated the burden of other comorbid conditions for included patients by extracting all ICD-9-CM codes given to each patient in the year before the ARI visit and applied the clinical classification system developed by the Agency for Healthcare Research and Quality (17). We grouped the conditions into categories relevant to the ARI diagnosis (such as 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 visit location.

We identified a single "primary provider" reported for the day of each visit. Although there could be several providers per visit, the primary provider is the single health professional who identifies himself or herself in the electronic health record as being responsible for the decision making, patient care, and documentation during that particular encounter. The primary provider for the encounter was not necessarily the primary care provider for the patient's general medical care; for example, if the patient presented to the ED, the primary provider for the visit would probably not be the primary care provider. In addition, the primary provider listed did not necessarily prescribe the medications because the electronic order entry of medications was not necessarily done by the same person who completed the documentation of the visit. However, this was the case for 90% of all listed physicians and midlevel providers.

We did not classify providers by level of training (residents or other trainees) because the attending physician was usually listed as the primary provider rather than the trainee. We did not measure specialty or years since licensure because of incomplete provider census information. 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 visits that contained missing values (less than 1%) were excluded from the analysis.

Antibiotic Prescriptions

We initially extracted all VA antibiotic prescriptions filled within 2 days before and 3 days after the visit. Because it was possible for patients to receive antibiotic prescriptions over the phone before a visit or to fill a prescription after the visit, we chose this date range to identify all filled prescriptions. Because some VA facilities lacked fill data due to the use of outside pharmacy services and variation in data collection, we then applied the Regular Expression Discovery, a natural language processing tool developed by the Veterans Informatics and Computing Infrastructure (18), to identify antibiotic prescriptions within unstructured clinical documents. The resulting Regular Expression Discovery algorithm demonstrated a positive predictive value

Table. Patient, Provider, and Setting Characteristics in ARI Visits for the Veteran Population*

Characteristic	All Visits (*n* = 1 044 523)	Antibiotics Prescribed (*n* = 714 552)	No Antibiotics Prescribed (*n* = 329 971)
Sex, %			
Male	85.8	85.5	86.6
Female	14.1	14.5	13.4
Median age (IQR), *y*	61 (49–69)	60 (49–68)	61 (49–70)
Median distance between residence and clinic (IQR), *mi*	12 (5–31)	12 (5–32)	12 (5–32)
Diagnosis, %			
Upper respiratory infection	51.5	42.5	70.9
Bronchitis	23.9	29.7	11.5
Sinusitis	18.5	23.4	8.0
Pharyngitis	10.7	10.5	11.3
Comorbid conditions, %			
>10 conditions	50.9	51.1	48.9
Cardiovascular disease	51.9	51.1	48.9
Psychiatric disease	42.4	42.6	42.1
Pulmonary disease	24.1	24.6	22.9
Infectious disease	19.3	20.0	17.8
Renal disease	3.7	3.6	3.7
Clinical features, %			
No fever (temperature <100.4 °F)	98.0	97.7	98.5
Fever (temperature of 100.4–101.9 °F)	1.6	1.8	1.2
High fever (temperature ≥102.0 °F)	0.4	0.4	0.3
Provider type, %			
Physician	62.4	62.3	62.7
Midlevel provider	24.5	25.1	23.3
Nurse	11.1	10.4	12.9
Other	1.9	2.3	1.1
Median provider age (IQR), *y*	50 (42–56)	50 (42–56)	49 (40–56)
Setting, %			
Primary care clinic	72.4	70.6	76.3
ED	22.9	24.2	20.0
Urgent care clinic	7.2	7.9	5.7
Community-based outpatient clinic, %	30.1	27.9	34.8
VAMC, %	69.9	72.1	65.2
Region of the United States, %			
West	19.6	17.7	23.6
Central	28.4	29.4	26.0
South	35.6	37.4	31.5
Northeast	16.5	15.4	18.8

ARI = acute respiratory infection; ED = emergency department; IQR = interquartile range; VAMC = Veterans Affairs medical center.
* Percentages may not sum to 100 due to rounding.

of 98% against a reference standard of physician review. After text classification, the proportion of visits that were identified to result in an antibiotic prescription increased from 60.7% to 68.4%.

Statistical Analysis

Relationship of Antibiotic Prescription With Patient, Provider, and Setting Characteristics

We used generalized estimating equations under multivariable linear logistic regression models to determine the probability of prescribing any antibiotic at a visit and prescribing a macrolide when an antibiotic was prescribed. Annual trends were tested for significance using the calendar year as the single linear predictor variable. The following predictors were used: patient sex, patient age, number of comorbid conditions, maximum temperature, diagnosis, distance to clinic, type of provider, provider age, daily number of ARI visits, 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 temperature, which had clinically defined cutoffs (high fever was defined as a temperature ≥102 °F and fever as a temperature between 100.4 °F and 101.9 °F), daily clinic load (1, 2, 3, and ≥4 ARI visits per day), and time of day (early morning was defined as 8:00 to 10:30

a.m., late morning as 10:30 a.m. to 12:30 p.m., early afternoon as 12:30 to 2:30 p.m., late afternoon as 2:30 to 5:00 p.m., and night as 5:00 to 8:00 p.m.).

Generalized estimating equations were used for this portion of the analysis to generate population-weighted average comparisons and provide statistical inferences that were more robust to potential misspecification of the model used to account for clustering by VAMC, clinic, and provider. The analyses were done with an independent working covariance model for encounters in the same VAMC to ensure that each encounter was weighted equally in each analysis. We used the marginal standardization approach to calculate the mean adjusted proportions, in which they were 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 provided 95% CIs and *P* values for the adjusted proportions. For a select group of variables, we also performed a separation of between- and within-cluster variables (**Appendix Table 1**, available at www.annals.org).

Variation in Antibiotic Prescribing Associated With Different Levels of Health Care Delivery

We fit a generalized linear mixed-effects model for antibiotic prescribing with provider, clinic or ED, and VAMC included as normally distributed, nested random effects on the logit scale and with fixed-effect terms representing the previously listed factors (20). Estimated variances for provider, clinic or ED, and VAMC were used to describe the variation in antibiotic prescribing specifically attributable to each level of the health care system after the fixed effects were controlled for.

To fit a nested model of providers, clinics, and VAMCs, we reassigned providers appearing in several clinics to the unique clinics in which they appeared most frequently. 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 providers with at least 100 patients in the study, representing 480 875 visits.

We used 3 approaches to visualize the different levels of variation in antibiotic prescribing. We first generated a histogram that displayed the observed, unadjusted distribution of proportions of antibiotic prescribing across providers. Second, we used the results of the generalized linear mixed-effects model to estimate density functions that described the total variation in prescribing attributable to each of the 3 random effects. We also displayed the density function with variance given by the sum of the estimated variance of the 3 random effects to describe the total variation in prescribing, incorporating variation from all 3 levels of health care delivery. Full details are described in the **Appendix** (available at www.annals.org). Third, we displayed conditional density curves to show the conditional distributions of antibiotic prescription across providers within clinics (with the prescribing proportion fixed at the 10th, 50th, and 90th percentiles of the distribution of antibiotic prescribing across clinics) and within VAMCs (with the prescribing proportion 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 (Salt Lake City, Utah) and the VA and with support from the Centers for Disease Control and Prevention. Statistical analyses were done using Stata, version 12.0 (StataCorp), and SAS, version 9.2 (SAS Institute). All analysis codes are shown in **Appendix Table 2** (available at www.annals.org).

Role of the Funding Source

This study was the result of work supported by the U.S. Department of Veterans Affairs through the Informatics Decision Enhancement and Analytic Sciences 2.0 Center of Innovation and the Centers for Disease Control and Prevention Get Smart Project. The Centers for Disease Control and Prevention participated in the study design and interpretation of the data.

RESULTS

Study Population

Of 2 481 520 patient visits with ARI diagnoses, 1 044 523 met our inclusion criteria (**Figure 1**). Patients were seen by 45 619 providers at 990 clinics or EDs in 130 VAMCs. Thirty percent of all visits occurred in community-based outpatient clinics, and the remainder occurred on VAMC campuses. Seventy percent occurred in primary care clinics, 23% in EDs, and 7% in urgent care clinics. A physician was listed as the provider for 62% of the visits, followed by midlevel provider (24%) and nurse (11%). The median age of the patient population was 61 years, 51.9% had a cardiovascular comorbid condition, and 24.1% had a pulmonary comorbid condition not included in the exclusion criteria. Twenty-five percent of the population lived more than 31 miles from their visit location.

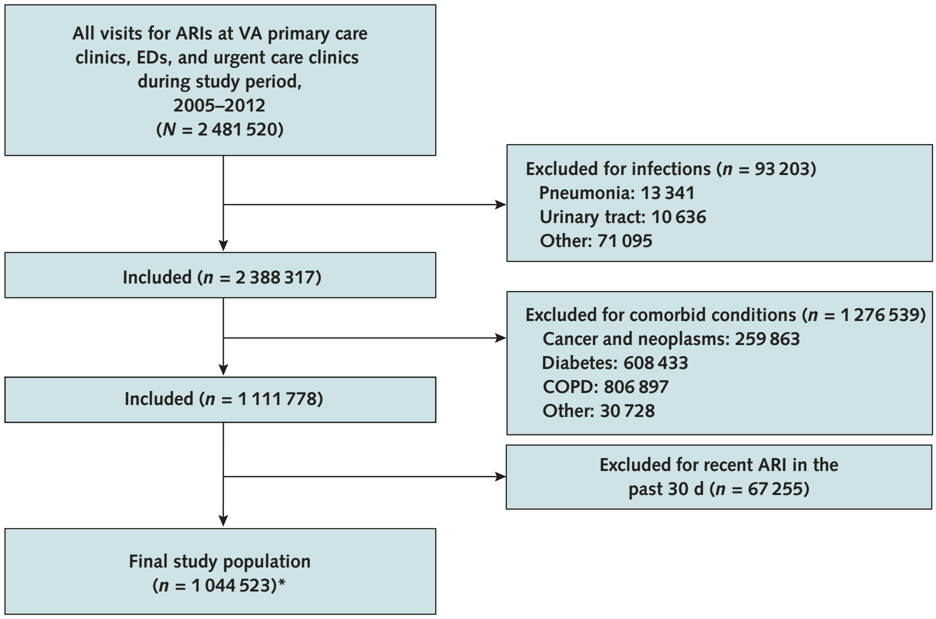
National Trends

We saw a small increase in the overall proportion of visits with antibiotic prescriptions during the study, from 67.5% in 2005 to 69.2% in 2012 ($P < 0.001$). Although we saw a seasonal trend in the number of ARI visits, there was no substantial seasonal variation in the proportion of visits at which antibiotics were prescribed (**Figure 2**). Of the visits in which an antibiotic was prescribed, macrolide prescriptions increased from 36.8% in 2005 to 47.0% in 2012 ($P < 0.001$) and prescriptions of penicillins (36.0% to 32.1%; $P < 0.001$) and fluoroquinolones (15.0% to 12.7%; $P < 0.001$) decreased over time (**Appendix Figure 1**, available at www.annals.org).

Predictors of Antibiotic Prescribing

Antibiotics were prescribed in 68.4% of all ARI visits (n = 714 552). **Appendix Figure 2** (available at www.annals.org) shows adjusted proportions of visits with antibiotic prescription for subgroups with selected factors. Subgroups associated with higher prevalence of antibiotic prescribing included a diagnosis of sinusitis (adjusted proportion, 86%) or bronchitis (85%); high fe-

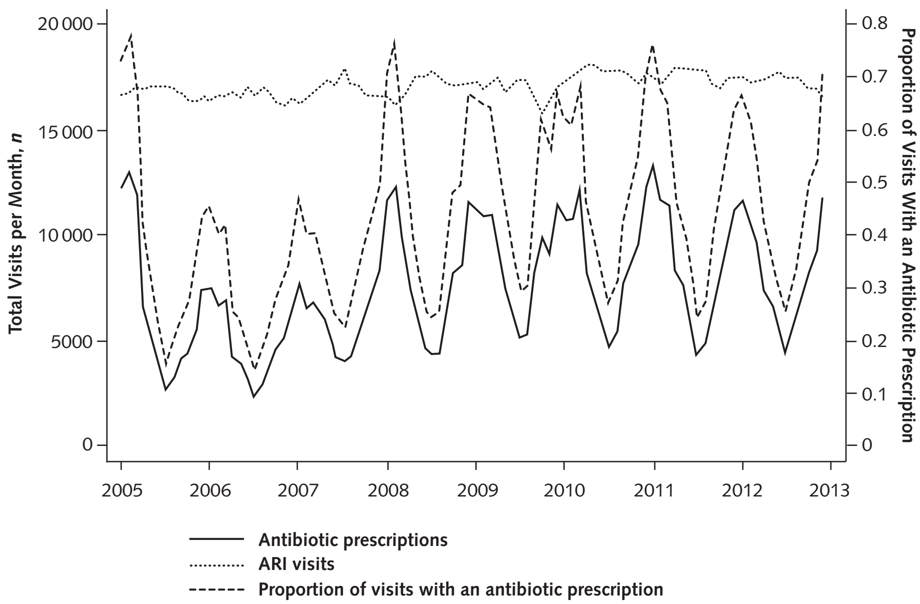
Figure 1. Study flow diagram.



Visits could meet several exclusion criteria; therefore, the sum of visits meeting each exclusion criterion exceeds the total number of excluded visits. ARI = acute respiratory infection; COPD = chronic obstructive pulmonary disease; ED = emergency department; VA = Veterans Affairs.
* There were 1 036 982 visits without missing values.

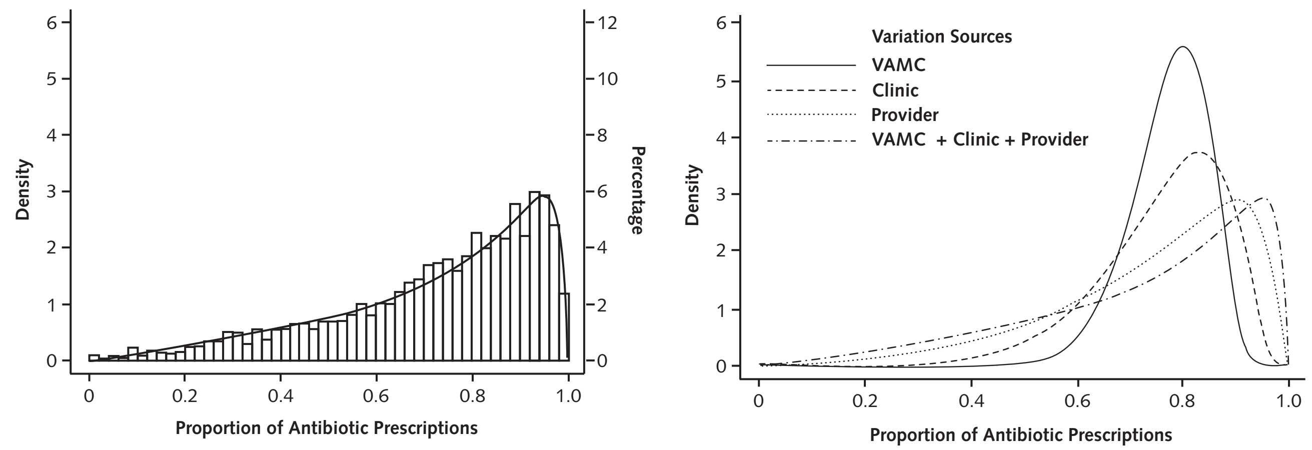
ver (78%); and visits that took place in an urgent care setting (75%), the southern region (71%), and the central region (71%). Midlevel providers also prescribed antibiotics slightly more frequently than physicians (70% vs. 68%). Visits with the primary provider designated as "other" (<2% of all visits) also had a greater prevalence of antibiotic prescribing (80%), probably due to the high proportion of pharmacists listed as primary providers during medication consultation. In addition, prescribing was slightly higher at VAMC-based clinics than at community-based outpatient clinics (70% vs. 64%). The number of patient comorbid conditions

Figure 2. Trends in overall antibiotic prescribing.



The number of ARI-related visits per month and monthly proportion of visits resulting in an antibiotic prescription are depicted. ARI = acute respiratory infection.

Figure 3. Variation in antibiotic prescribing.



ARI = acute respiratory infection; VAMC = Veterans Affairs medical center. **Left.** Variation among providers. The histogram shows the distribution of observed proportions of visits with an antibiotic prescription across 2594 providers with at least 100 ARI visits each (n = 480 875). The curve depicts the modeled distribution of antibiotic prescription across providers, after controls were set for the measured patient, provider, and setting characteristics listed in **Appendix Figures 2** and **3** (available at www.annals.org). **Right.** Sources of variation. The solid, dashed, and dotted lines depict modeled distributions describing variation in proportion of antibiotic prescriptions attributable specifically to VAMCs, clinics, and providers, respectively, after controls were set for the measured patient, provider, and setting variables listed in **Appendix Figures 2** and **3**. The dashed-and-dotted line corresponds to the curve in the left panel and depicts overall modeled variation in antibiotic prescription across providers, including differences between providers at different clinics and VAMCs.

that were not in the exclusion criteria had no association with antibiotic prescribing.

Of the antibiotics prescribed, 302 595 (43.4%) were macrolides. Subgroups with elevated adjusted prevalence of macrolide prescribing (**Appendix Figure 3**, available at www.annals.org) included a diagnosis of bronchitis (adjusted proportion, 51%) or upper respiratory infection (49%). A high fever was a negative predictor for macrolide use (36%). No clinically significant differences were seen in other patient characteristics, provider characteristics, or geographic regions.

Sources of Variation

The histogram in **Figure 3** (*left panel*) shows the variation in the proportions of visits with antibiotic prescriptions among providers who saw at least 100 patients with ARIs during the study period (480 875 visits with 2594 providers). When comparing providers on the basis of proportion of antibiotics they prescribed, the highest 10% prescribed antibiotics during at least 95% of their ARI visits, and the lowest 10% prescribed antibiotics during 40% or fewer visits. Among clinics, the highest 10% prescribed antibiotics during at least 89% of their visits, and the lowest 10% prescribed antibiotics for 41% or fewer. Among VAMCs, the highest 10% had a prescribing proportion of at least 86%, compared with 57% or fewer for the lowest 10%. The curve shows 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 that in the histogram suggests that these measured characteristics contributed only slightly to the overall variation in antibiotic prescribing across providers.

The solid, dashed, and dotted lines in **Figure 3** (*right panel*) show the model-generated estimates of variation specifically associated with each level of health care delivery (VAMC, clinic, and provider, respectively) with the same patient, provider, and setting fixed-effect factors acting as controls. After the fixed-effect factors were considered, variation attributable to providers, clinics, and VAMCs accounted for 59%, 28%, and 13%, respectively, of the total remaining variation in antibiotic prescription prevalence across the 3 levels of health care delivery. For comparison, the dashed-and-dotted line in the same figure (which is the same as the curve in the left panel) shows the model-based overall variation in prescribing among providers. **Appendix Figure 4** (available at www.annals.org) shows how the modeled distributions of prescribing across providers differ between clinics and VAMCs. Even within high- or low-prescribing VAMCs and clinics, we found considerable variation in provider prescribing.

DISCUSSION

Our 8-year study of 1 million patient visits found a persistently high prevalence of outpatient antibiotic prescriptions for ARIs in the national veteran population. During this period, macrolides have become the predominant class prescribed. Similar trends have been reported in studies using data from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey (3, 21–23). The lack of progress in reducing unnecessary antibiotic prescribing for ARIs is a major public health concern.

We aimed to better understand the factors driving this problem. Our granular data and large population of patients, providers, and clinics in the VA health system allowed us to explore relationships between antibiotic prescribing and several factors and characterize variation in antibiotic prescribing across different levels of health care delivery.

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

The greatest source of variability in management was the provider. Although 10% of the providers prescribed antibiotics during at least 95% of all of their ARI visits, another 10% prescribed antibiotics during 40% or fewer. After adjusting for 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 for ARIs have identified variation at the facility (11), health plan (24), and regional (25) levels. Cultural influences and context in both provider practices and patient expectations have been given as important reasons for environmental influences on antibiotic use (26). Indeed, much medical decision making is influenced by the system and social context. However, our findings suggest that providers have a strong tendency to choose the same treatment regardless of patient or clinic characteristics, indicating that individual provider preference or "style" heavily influences the antibiotic decision.

We found a substantial increase in macrolide prescribing in our system—a trend that was seen in other national studies (9, 10). The increased popularity of macrolides could be due to their short-course, convenient, once-daily dosing; their utility in community-acquired pneumonia; and marketing campaigns. Macrolides are not recommended as first-line therapy for either pharyngitis or sinusitis, and although we saw lower prescribing prevalence for these diagnoses, the proportion was still significant. This trend is concerning given the lack of additional benefit of macrolides over narrow-spectrum antibiotics for ARI treatment; the increase in macrolide-resistant pneumococcal disease (27); and potential cardiotoxicity (28), especially considering the large number of veterans in our study who had cardiovascular comorbid conditions.

Our study has several limitations. We used administrative data, defining our population with ICD-9-CM codes. We excluded many patients with comorbid conditions and diagnoses for infections in an attempt to identify cases with a low benefit from antibiotics, and our analysis of variation was limited to providers with at least 100 ARI visits during the 8-year period. Our graphical displays of modeled variation assumed that prescribing proportions were normally distributed on the logit scale for each level. Our study lacked additional clinical and provider data contributing to the antibiotic decision, such as symptom duration, physical examination findings, or provider specialty (29, 30). Different providers probably have different patient panels and thus different thresholds for antibiotic prescribing. For any individual patient, determining whether an antibiotic was appropriate is impossible. However, at the population level, we would expect a much lower overall proportion of antibiotic prescribing based on national treatment guidelines.

The provider-level variation remained after adjustment for patient characteristics, and providers differed widely among clinics, suggesting against a significant amount of variation based on measurable patient factors. Additional factors that might explain the degree of provider variation in antibiotic prescriptions, such as attitudes toward risks and benefits of antibiotics, interaction with local stewardship efforts, or patient preferences and expectations (and providers' understanding of them), could potentially be identified on a large scale in 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 many older male patients with a high burden of comorbid conditions. Despite this, we found that overall proportions and trends in macrolide use were similar to those in other studies. Ambulatory care and pharmacy services in the VA are more integrated and standardized than those in other settings. In other, more diverse systems, clinic- or system-based variations in infrastructure may play a larger role in antibiotic use. However, provider-level variation may be even greater in other systems.

Our findings have important implications for health systems and public health. Variation in ARI management seems to be strongly influenced by the prescribing patterns of individual providers. This is a ripe target for further research, quality improvement, and antibiotic stewardship interventions. Audit and feedback have shown promise as powerful tools to change behavior (31, 32). Creating provider-targeted decision-support tools that enable audit and feedback could help clinicians recognize and respond to their prescribing patterns.

Unnecessary antibiotic use for ARIs remains an important problem and requires new approaches. As our understanding of the relationship among providers, patients, settings, and treatment decisions improves, so will our ability to target future information and stewardship efforts.

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Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the U.S. Department of Veterans Affairs, Centers for Disease Control and Prevention, or U.S. government.

Acknowledgment: The authors thank Saundra Duffy-Hawkins for administrative support, Jenny Teng for data collection and management, and Qing Zeng-Treitler and Douglas Redd for natural language processing.

Disclosures: Authors have disclosed no conflicts of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M14-1933.

Grant Support: From the U.S. Department of Veterans Affairs through the Informatics Decision Enhancement and Analytic Sciences 2.0 Center of Innovation (IDEAS 2.0: CIN 14-267) and the Centers for Disease Control and Prevention Get Smart Project (14FED1412883).

Reproducible Research Statement: *Study protocol and statistical code:* Available from Dr. Jones (e-mail, barbara.jones@hsc.utah.edu). *Data set:* Not available.

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Appendix: Technical Details of Displays of Variation Under the Generalized Linear Mixed-Effects Model

The density curve in Figure 3 (*left panel*) was constructed in several steps. First, we used the results of the generalized linear mixed-effects model to construct a normal density with mean $\bar{x}^t\hat{\beta}$, in which $\bar{x}$ denotes the unweighted average of the fixed-effects factors across encounters and $\hat{\beta}$ denotes the maximum likelihood estimates of the coefficients of the fixed-effects factors obtained by the Gaussian quadrature. The variance of the normal density was obtained as the sum of the maximum likelihood estimates of the variances of the 3 nested random effects for VAMCs, clinics, and providers. Hence, the normal density reflects the overall variation across providers, without adjustment for differences in antibiotic prescription across VAMCs and clinics. We then applied the inverse logit transformation to this normal density to obtain the conditional density, which describes the variation in the prevalence of antibiotic prescription across providers, with the fixed effects set to their mean values.

A similar approach was applied to the results of the generalized linear mixed-effects model to estimate the density curves defining the variation in the prevalence of antibiotic prescription that is attributed specifically to VAMCs, clinics, and providers after adjustment for the fixed effects (Figure 3, *right*). In this case, the variances of the density curves were defined based on the individual variance components for VAMCs, clinics, and providers. Thus, the variation in the density for providers excludes provider variation resulting from differences in antibiotic prescription across VAMCs and clinics, and the variation in the density for clinics excludes clinic variation resulting from differences in antibiotic prescription across VAMCs.

The conditional density curves in Appendix Figure 4 were also constructed using the results of the generalized linear mixed-effects model. The figure displays modeled conditional densities of antibiotic prescription prevalence across providers conditioning on the random effect for clinics (with the clinic random effect set to its 10th, 50th, or 90th percentile), the random effect for VAMCs (with the VAMC random effect set to its 10th, 50th, or 90th percentile), and the mean values of the fixed effects. Comparison of the density curves corresponding to the different clinic and VAMC percentiles thus illustrates the variation in prevalence of antibiotic prescription due to the VAMCs and clinics, and the variation in the conditional density curves themselves illustrates differences due to the providers.

Appendix Table 1. Separation of Between- and Within-Cluster Variables

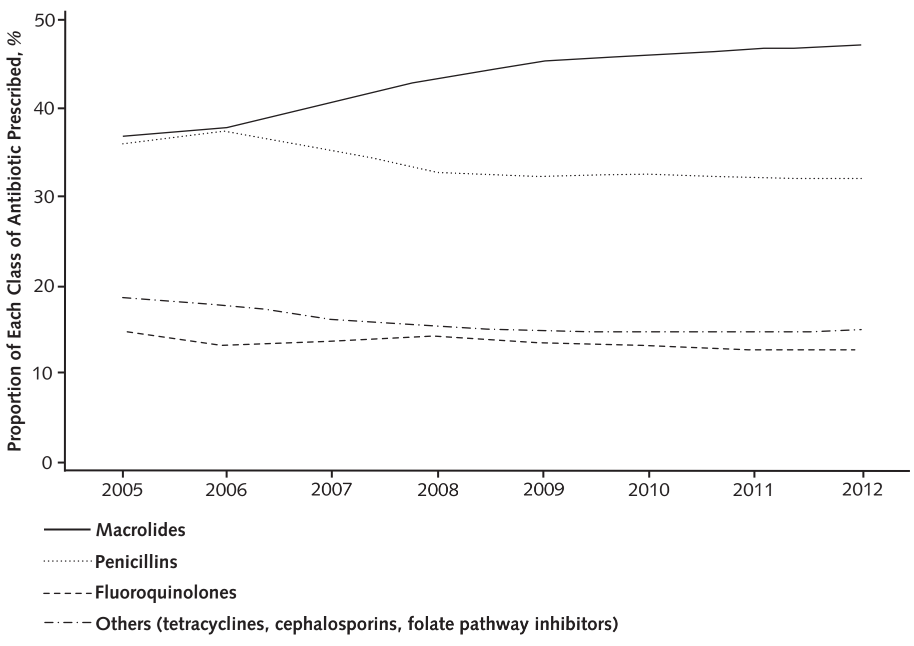
Parameter	Estimate	SE	Lower Confidence Limit	Upper Confidence Limit	*Z* Value	*P* Value
Between-cluster effect						
gender_F	−0.5187	1.703	−3.8565	2.8192	−0.3	0.7607
age_Grp_Q2	2.001	1.5109	−0.9604	4.9624	1.32	0.1854
age_Grp_Q3	0.3748	2.3599	−4.2505	5	0.16	0.8738
age_Grp_Q4	1.1494	1.2106	−1.2232	3.5221	0.95	0.3424
new_diagnosis_Bronch	1.1379	0.6865	−0.2077	2.4834	1.66	0.0974
new_diagnosis_Others	−4.6278	10.856	−25.905	16.6495	−0.43	0.6699
new_diagnosis_Pharyn	3.9372	2.1222	−0.2223	8.0966	1.86	0.0636
new_diagnosis_Sinusi	2.5533	0.8278	0.9308	4.1757	3.08	0.002
temp_cat_fever	2.8908	10.3451	−17.3851	23.1667	0.28	0.7799
temp_cat_high	−4.5976	26.803	−57.1306	47.9353	−0.17	0.8638
distance_cat_Q2	−0.0304	0.7503	−1.5009	1.4401	−0.04	0.9677
distance_cat_Q3	0.2217	0.5054	−0.7689	1.2123	0.44	0.6609
distance_cat_Q4	0.5989	0.6828	−0.7394	1.9373	0.88	0.3804
provider_experience_5-10	0.6312	0.6683	−0.6786	1.9409	0.94	0.3449
provider_experience_<5	−0.1142	0.5452	−1.1828	0.9544	−0.21	0.8341
ProviderTypeGrp_Mid_	−0.6589	0.3248	−1.2954	−0.0223	−2.03	0.0425
ProviderTypeGrp_Nurs	−1.0795	0.7126	−2.4763	0.3172	−1.51	0.1298
ProviderTypeGrp_Othe	1.2745	0.6094	0.0801	2.4689	2.09	0.0365
new_ccs9_count_grp_Q	3.2045	3.3289	−3.32	9.729	0.96	0.3357
new_ccs9_count_grp_Q	1.9928	1.959	−1.8468	5.8324	1.02	0.309
new_ccs9_count_grp_Q	0.489	2.0872	−3.6018	4.5799	0.23	0.8148
dailyvisit_ct_grp_Q2	2.1666	0.896	0.4105	3.9226	2.42	0.0156
dailyvisit_ct_grp_Q3	2.6899	0.4105	1.8852	3.4946	6.55	<0.0001
dailyvisit_ct_grp_Q4	1.0596	0.4151	0.2461	1.8731	2.55	0.0107
Within-cluster effect						
gender_F	0.0646	0.0158	0.0337	0.0956	4.1	<0.0001
age_Grp_Q2	−0.0002	0.0126	−0.0249	0.0245	−0.02	0.9878
age_Grp_Q3	0.0183	0.0129	−0.007	0.0435	1.42	0.1557
age_Grp_Q4	−0.0853	0.0156	−0.1159	−0.0547	−5.47	<0.0001
new_diagnosis_Bronch	1.589	0.0474	1.4961	1.6818	33.53	<0.0001
new_diagnosis_Others	0.4477	0.0455	0.3585	0.537	9.83	<0.0001
new_diagnosis_Pharyn	0.3559	0.037	0.2834	0.4283	9.63	<0.0001
new_diagnosis_Sinusi	1.6764	0.0636	1.5518	1.801	26.38	<0.0001
temp_cat_fever	0.4856	0.0339	0.4192	0.5521	14.33	<0.0001
temp_cat_high	0.6176	0.0693	0.4817	0.7534	8.91	<0.0001
distance_cat_Q2	0.0564	0.0169	0.0233	0.0896	3.34	0.0009
distance_cat_Q3	0.0562	0.0205	0.0161	0.0964	2.74	0.0061
distance_cat_Q4	0.0657	0.019	0.0285	0.1028	3.46	0.0005
provider_experience_5-10	−0.0694	0.0288	−0.1258	−0.0131	−2.41	0.0158
provider_experience_<5	−0.2284	0.039	−0.3048	−0.1519	−5.86	<0.0001
ProviderTypeGrp_Mid_	0.1656	0.0386	0.0899	0.2413	4.29	<0.0001
ProviderTypeGrp_Nurs	−0.157	0.0374	−0.2303	−0.0838	−4.2	<0.0001
ProviderTypeGrp_Othe	0.5606	0.1254	0.3148	0.8065	4.47	<0.0001
new_ccs9_count_grp_Q	−0.0022	0.0122	−0.0261	0.0217	−0.18	0.8581
new_ccs9_count_grp_Q	−0.0056	0.0139	−0.0328	0.0215	−0.41	0.6837
new_ccs9_count_grp_Q	−0.0308	0.0174	−0.065	0.0033	−1.77	0.0767
dailyvisit_ct_grp_Q2	0.0386	0.0229	−0.0063	0.0835	1.69	0.0919
dailyvisit_ct_grp_Q3	0.1261	0.0343	0.0589	0.1933	3.68	0.0002
dailyvisit_ct_grp_Q4	0.1527	0.076	0.0037	0.3016	2.01	0.0446

Appendix Table 2. Glossary of Analysis Codes

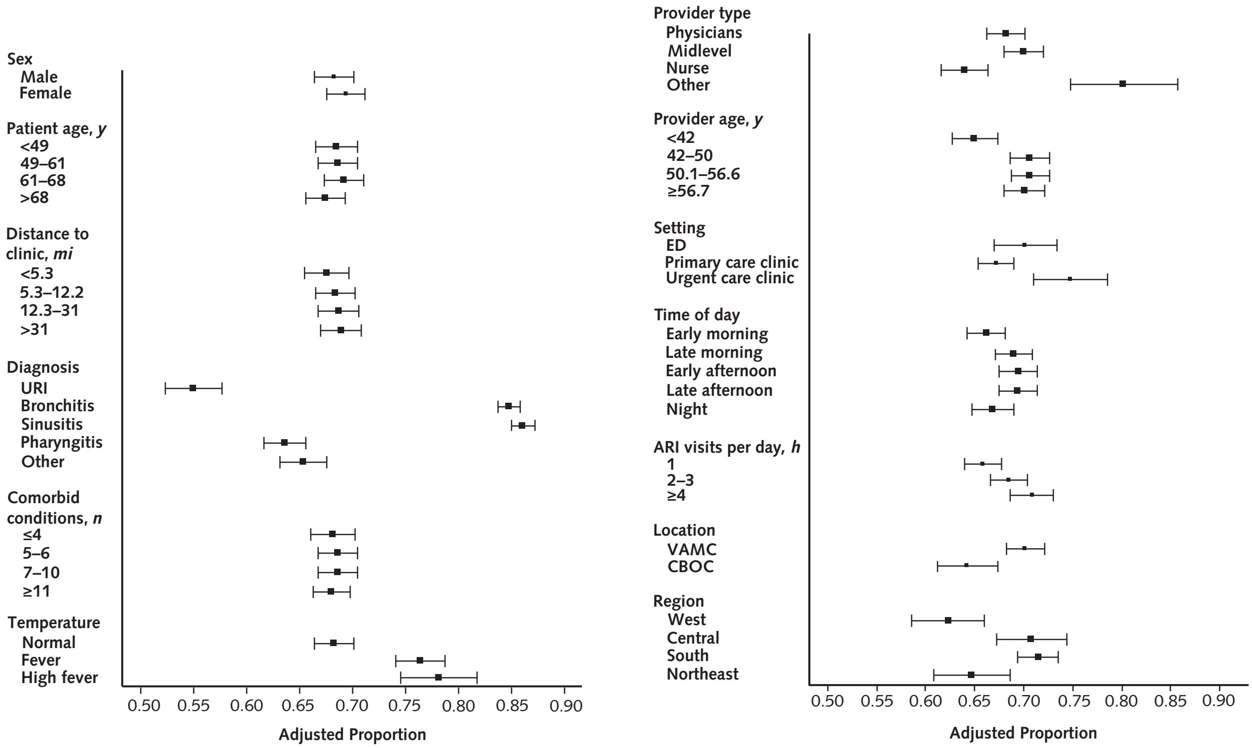
Code Name	Function	Input	Output	Product of Output
data manipulation.sas	Select records according to inclusion criteria, create variables	VINCI data set	Work data set	–
GEE.sas	Run GEE model for total antibiotics and macrolide	Work data set	Regression coefficient, *P* value	*P* values for Appendix Figures 1 and 2
bootstrapping 1.sas	Bootstrapping for total antibiotics	Work data set	output.mgn_mean1	summarize mgn mean.sas
bootstrapping macrolide1.sas	Bootstrapping for macrolide	Work data set	output.macro_mgn_mean1	summarize mgn mean.sas
summarize mgn mean.sas	Calculate means and SDs of the bootstrapping results	output.mgn_mean1 and output.macro_mgn_mean1	Summarization of bootstrapping	forest plot.sas
forest plot.sas	Create the forest plots	Summarization of bootstrapping	Appendix Figures 1 and 2	–
glimmix using only big providers.sas	Run GLMM to get variance at the 3 clustering levels	Work data set	Variance at the 3 clustering levels	density overlay histogram on p scale centered at mean X_beta.r, draw model based density function on p scale.r, draw model based panel density function on p scale.r
histograms.sas	To get proportion of antibiotics prescription of each provider, each clinic, or each VAMC	Work data set	Proportion of antibiotics prescription of each provider, each clinic, or each VAMC	density overlay histogram on p scale centered at mean X_beta.r, draw model based density function on p scale.r, draw model based panel density function on p scale.r
density overlay histogram on p scale centered at mean X_beta.r, draw model based density function on p scale.r, draw model based panel density function on p scale.r	Draw Figure 3 and Appendix Figure 4	Variance at the 3 clustering levels and proportion of antibiotics prescription of each provider, each clinic, or each VAMC	Figure 3 and Appendix Figure 4	–

GEE = generalized estimating equation; GLMM = generalized linear mixed model; VAMC = Veterans Affairs medical center; VINCI = Veterans Affairs Informatics and Computing Infrastructure.

Appendix Figure 1. Temporal trends in the proportion of all antibiotics prescribed for each antibiotic class.

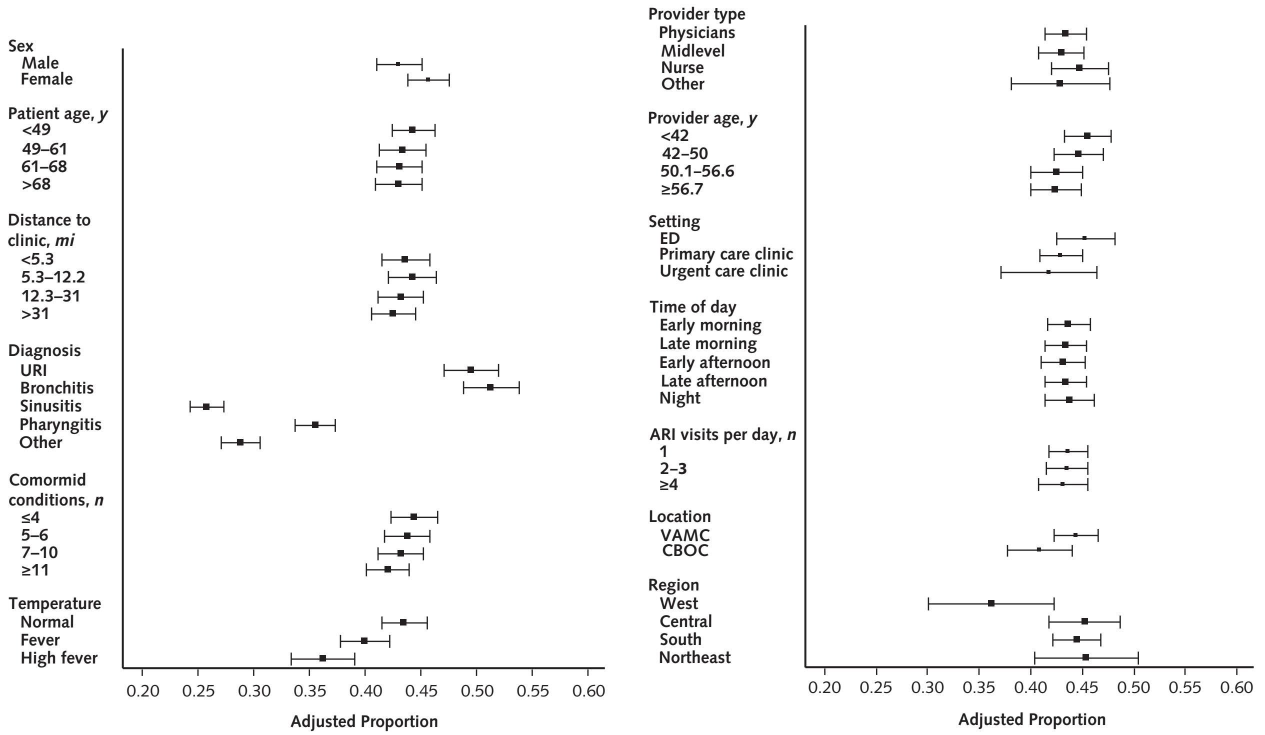


Appendix Figure 2. Predictors of antibiotic prescribing.



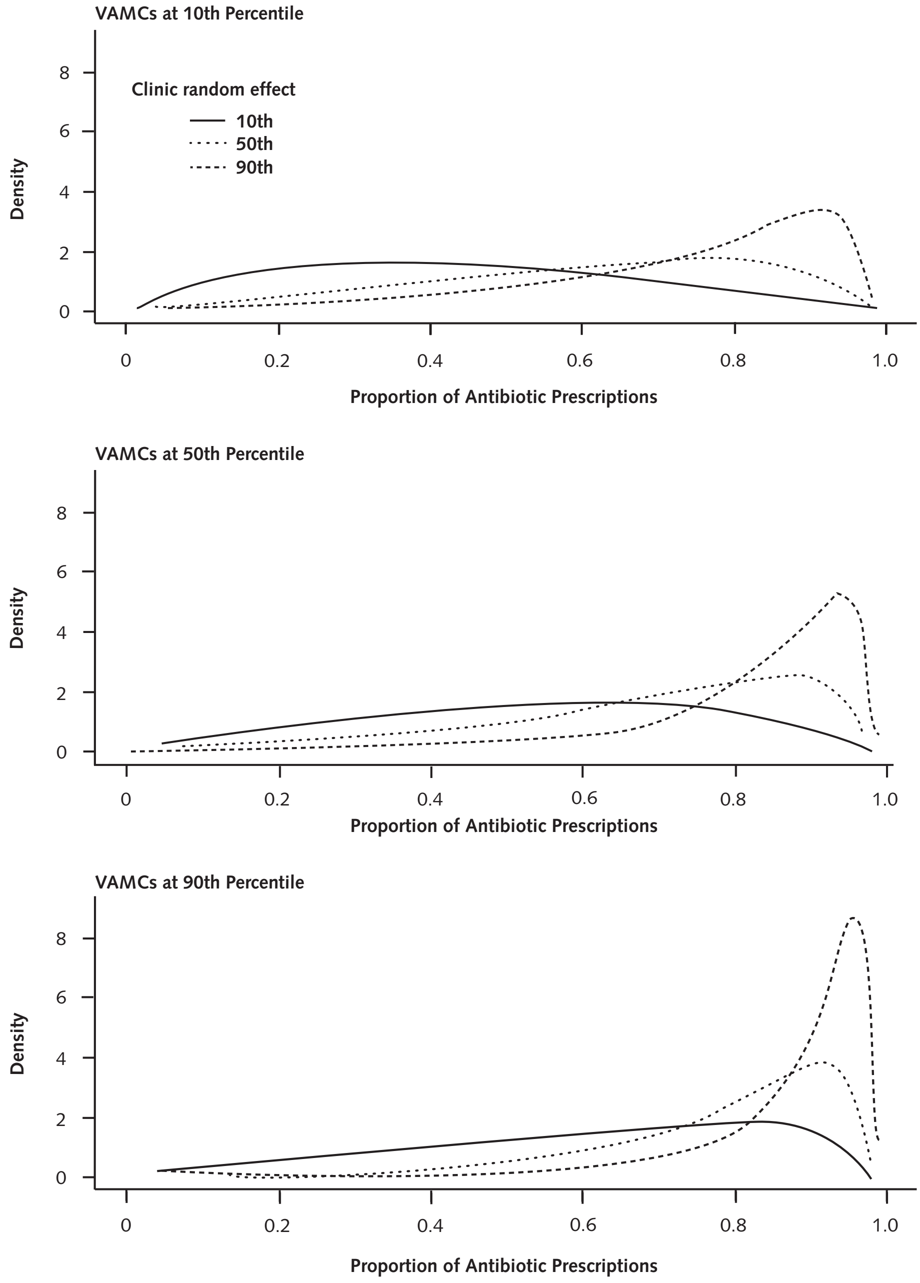
The adjusted proportion of visits with antibiotics prescribed based on the marginal standardization model is shown for each subgroup. There were 1 036 982 total visits. The model also included the calendar month and year. Statistically significant predictors ($P < 0.001$) included patient age, diagnosis, temperature, provider type, provider age, setting type, time of day, number of ARI visits per clinic per day, location type (CBOC vs. VAMC), and region, although the effect sizes were small. ARI = acute respiratory infection; CBOC = community-based outpatient clinic; ED = emergency department; URI = upper respiratory infection; VAMC = Veterans Affairs medical center.

Appendix Figure 3. Predictors of macrolide prescribing.



The adjusted proportion of antibiotic prescriptions that were macrolides is shown for each subgroup. There were 714 552 total visits. The model also included the calendar month and year. Statistically significant predictors ($P < 0.001$) included patient sex, diagnosis, temperature, and number of comorbid conditions, although the effect sizes were small. ARI = acute respiratory infection; CBOC = community-based outpatient clinic; ED = emergency department; URI = upper respiratory infection; VAMC = Veterans Affairs medical center.

Appendix Figure 4. 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 antibiotic prescribing across clinics) and within VAMCs (with prescribing prevalence fixed at the 10th, 50th, and 90th percentiles of the distribution of antibiotic prescribing across VAMCs) are shown. VAMC = Veterans Affairs medical center.