Antibiotics and acute respiratory tract infections: a policy evaluation of the CDC's *Get Smart about Antibiotics* campaign.

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Abstract

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Acute respiratory tract infections (ARTIs) account for >20% of all outpatient visits in adults. Many of these patients are prescribed antibiotics that are inappropriate based on clinical practice guidelines (CPGs). Over the last 15+ years the Center for Disease Control (CDC) has conducted the Get Smart about Antibiotics (GSA) campaign to reduce over-prescribing to patients with self-limiting ARTIs that are non-indicated for antibiotics. I analyzed the impact of three nationally-focused GSA campaign activities (i.e., publishing CPGs, a national media campaign, and re-publishing material for Spanish-speaking populations) and two state-level GSA campaign activities (i.e., state-level funding and state-level participation in the GSA Week) on antibiotic prescribing in adult patients with office-diagnosed, non-indicated ARTIs (i.e., acute bronchitis, acute pharyngitis, acute rhino-sinusitis, and the common cold or acute non-specific upper respiratory tract infections). The analyses used two primary datasets: (1) Medical Expenditure

Panel Survey (MEPS), which is nationally representative, and (2) the MarketScan claims database, which includes patients enrolled in large employer-sponsored health insurance plans. The odds that any antibiotics were prescribed were reduced after the publication of CPGs (MEPS: OR=0.68, p-value=0.01) and after the national media campaign (MEPS: ORR=0.76, p-value=0.01), which was driven by lower antibiotic prescribing to patients diagnosed with the common cold or acute non-specific upper respiratory tract infections. I did not find evidence of code-shifting into antibiotic-indicated ARTIs (i.e., streptococcal pharyngitis and pneumonia) associated with these campaign events. I also found that the odds of antibiotics prescribing were reduced with each additional year of state-level funding (MEPS: ORR=0.96, p-value=0.03; MarketScan: ORR=0.97, p-value < 0.001), which was driven by lower prescribing to patients across all non-indicated ARTIs. In summary, I found that the multi-faceted approach of the GSA campaign lowered antibiotic prescribing to adult patients diagnosed with a non-indicated ARTI in an office-based setting through the publication of CPGs, a national media campaign targeting patients and clinicians, and state-level funding to develop local campaigns. However, the rates of antibiotic prescribing in the sub-group of patients with acute bronchitis remained high (50-60%). Future efforts to reduce antibiotic prescribing should include targeting patients diagnosed with acute bronchitis.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

Chapter 1. INTRODUCTION

In the United States antibiotics are over-prescribed to adults with acute respiratory tract infections (ARTIs) in the outpatient setting. Between the years 2000-2010, ARTIs accounted for >20% of all outpatient visits in adults 18-65 years old; 50-70% of these patients were prescribed antibiotics [1]. The majority of these were not in line with clinical practice guidelines (CPGs). Antibiotic use increases the risk of a secondary *C. difficile* infection [2-8] and allergic drug reactions [9, 10]. Overuse also contributes to antibiotic resistance [11], which renders antibiotics ineffective against bacterial pathogens and is associated with 23,000 deaths each year in the US and costs the healthcare system $20-55 billion annually [12]. Standard management of ARTIs focuses on ruling out serious illnesses that require antibiotics, such as bacterial pneumonia, and otherwise providing symptomatic relief [13]. Self-limiting ARTIs such as acute bronchitis, which we refer to as ‘non-indicated ARTIs’, should not be treated with antibiotics unless certain clinical symptoms are present [14-16].

In 1995, the Center for Disease Control (CDC) initiated a campaign to reduce over-prescribing of antibiotics to patients with non-indicated, non-complicated ARTIs diagnosed in the outpatient setting, which was initially called the Campaign for Appropriate Antibiotic Use in the Community and later rebranded as the campaign to Get Smart about Antibiotics (GSA) in 2003 [17-19]. The GSA campaign website went live in 2001 and accompanying action plan were put forward within a more comprehensive initiative to combat antibiotic resistance. The campaign intended to influence antibiotic prescribing through three major activities targeting patients and clinicians: (1) developing CPGs and educational & behavioral change material, (2) a national media campaign including public service announcements, and (3) funding state health departments to develop local campaigns.

The first major activity of the GSA campaign occurred in March of 2001 with the publication of 4 CPGs addressing the management of non-indicated ARTIs in adults (i.e., acute bronchitis, acute pharyngitis, acute rhino-sinusitis, and the common cold or acute non-specific upper respiratory tract infections) [19-31].

In September of 2003, the CDC conducted the first phase of a national media campaign (NMC) with public service announcements (PSAs). In 2005, the second phase of the NMC retargeted healthy adults and Spanish-speaking populations (the exact dates could not be determined). And in September of 2006, there was a major restructure and publication of the website into Spanish with additional educational & behavioral change material, which I refer to as the Spanish-speaking initiative (SI).

The GSA campaign also included state-focused activities. In 2001, the CDC began (and continues) funding state health departments to develop local campaigns and provide educational & behavioral change material. Beginning in 2008 and continuing to present day, the CDC conducts the annual Get Smart about Antibiotics Week (GSAW) with opt-in state-level participation, which continues to be the premier media event of the GSA campaign. Additional activities included: coordinating development of the Healthcare Effectiveness Data and Information Set (HEDIS) measures, which are self-reported measures by health plans on the quality care that cover 40% of the US population (e.g., acute bronchitis measure in adults, which was first measured in 2006) [32]; developing a medical school curriculum (full availability ~2010); and the Get Smart about Antibiotics - Pharmacy Initiative. (See Figure 1.1)

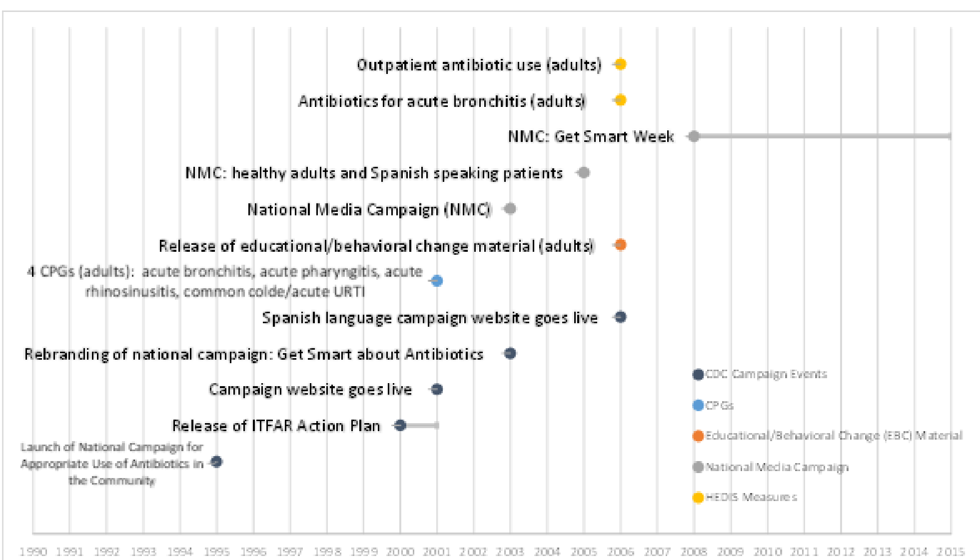


Figure 1.1. Timeline of major activities and events associated with the GSA campaign.

Antibiotic prescribing to adult patients with non-indicated ARTIs appears to have decreased during the GSA campaign. An analysis based on the National Ambulatory Medical Care Survey (NAMCS) showed rates of antibiotic prescribing decreased in these patients from 63% to 54% between the years of 1995-2006 [17]. And an analysis based on the Medical Expenditure Panel Survey (MEPS) showed rates decreased in similar patients from 73% to 53% between the years of 2000-2010 [1]. However, in adult patients with acute bronchitis, which accounts for 10 million office visits per year, overuse of antibiotics is consistently over 60% in the outpatient setting according to HEDIS measures [32, 33]. In recent years the rates have risen to >70%. National surveys (i.e., the NAMCS and MEPS) show comparable rates in patients with acute bronchitis [1, 34].

There has not been a comprehensive policy evaluation of the GSA campaign activities and antibiotic prescribing. A comprehensive evaluation of these activities and the effect on antibiotic prescribing could better inform future policies to reduce overuse of antibiotics. One previous national-level analysis focused on the impact of state-level funding on antibiotic prescribing in Medicaid patients. The analysis showed a significant 26% reduction in the odds of prescribing antibiotics to patients with ARTIs [35]. However, there were limitations to the analysis. The analysis was limited to Medicaid patients and to the impact of state-level funding between the years of 2002-2006. The research did not analyze the impact of CPGs, the national media campaign, or attempt to resolve how the campaign impacted antibiotic prescribing (e.g., clinician versus patient behavior). Most concerning, the analysis did not control for baseline rates of antibiotic prescribing prior to state-level funding. In my dissertation, I performed a comprehensive policy evaluation of the GSA campaign to address these limitations, which will help the CDC design and target future initiatives to reduce antibiotic prescribing in patients with ARTIs.

1.1 STRATEGIES AND INTERVENTIONS TO CONTROL OVERUSE OF ANTIBIOTICS

In 2014, the AHRQ initiated an evidence-based practice report to synthesize the literature on strategies and interventions to control overuse of antibiotics in outpatients with ARTIs [13]. I adapted their evaluation framework to contextualize and evaluate the strategies and activities of the GSA campaign, see Figure 2.

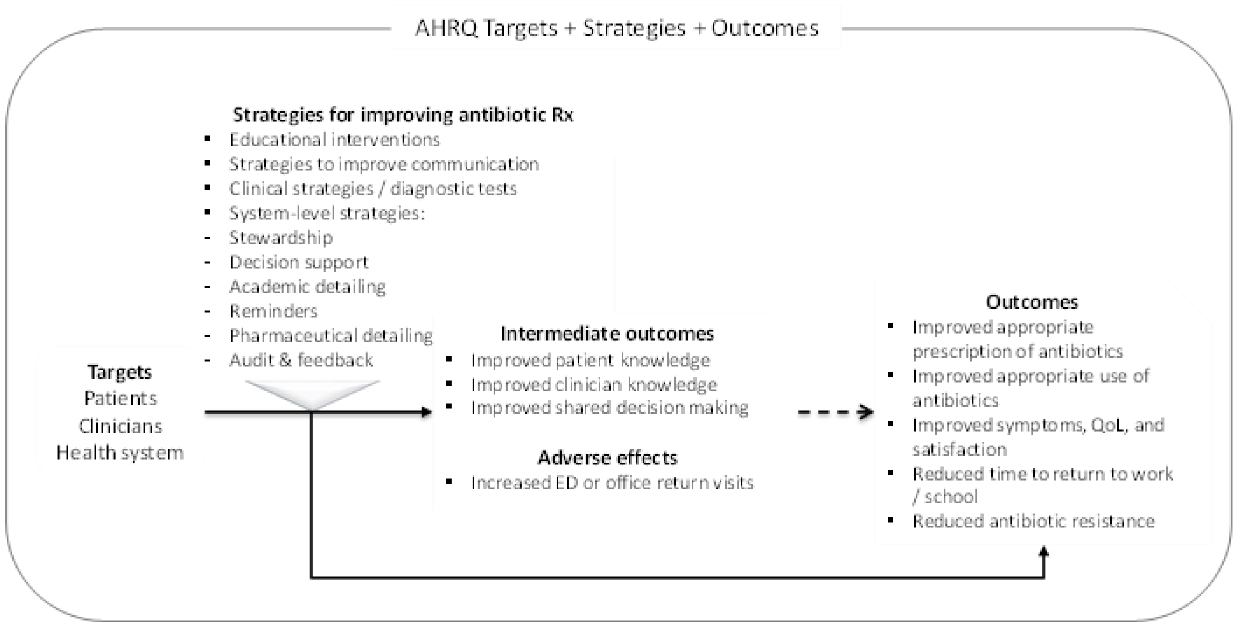


Figure 2: Strategies for controlling antibiotic prescribing.

Strategies include: clinical strategies such as delayed prescribing and diagnostic tests; educational interventions targeting clinicians or patients; strategies to improve communication and shared decision making between patients and clinicians; and system-level strategies such as clinician reminders and audit & feedback. Targets include: patients, clinicians, and health systems. Outcomes include: appropriate prescribing and use of antibiotics; control of antibiotic resistance and medical complications; and knowledge, shared decision making, and clinical skills. Two previous systematic reviews provide evidence of a modest effect for some of these strategies, but no singular strategy seems to dominate [36, 37]. Passive strategies such as printed educational material, didactic lectures, point-of-care reminders, and clinician audit & feedback tend to have minimal impact [37, 38]. Interactive educational strategies targeting clinicians or patients seem more effective [39, 40]. General strategies targeting multiple conditions, patients and clinicians, and multi-faceted interventions are most effective [41, 42]. The evidence-base to inform these reviews were incomplete, which motivated the more recent and on-going effort by AHRQ to evaluate these strategies. The GSA campaign targeted both patients and clinicians, and employed a multifaceted approach, including developing CPGs and educational & behavioral change material, a national media campaign, and funding state health departments to develop local campaigns. The existing evidence suggests the campaign was well conceived to reduce over-prescribing of antibiotics.

1.2 FACTORS THAT CONTRIBUTE TO OVERUSE AND PRESCRIBING OF ANTIBIOTICS

According to the academic literature, a combination of *factors* is associated with overuse and prescribing of antibiotics in outpatients with ARTIs. These *factors* tend to group into: (1) *observable states* of a *system* (i.e., system = patients, clinicians, or health system), such as the gender of a patient, training or age of a clinician, and office-based versus urgent care setting; and (2) the *processes* that operate between or within these *systems*, which are frequently classified as clinical/technical, behavioral & socio-cultural, and economic factors [43]. The *observable states* tend to provide some indication of who (or what) should be the target of an intervention. In contrast, the *processes* tend to be more informative, indicating the type of intervention that could reduce overuse and prescribing.

Based on the literature, *observable states* associated with overuse and prescribing of antibiotics include[1]:

<u>Patient-level factors:</u> age (older people > [1, 17, 44, 45], younger > [35, 46, 47], null [34, 48]), gender (female > [45, 48], male > [46], null [34, 44, 47]), race (Black < [35, 48], null [34, 46, 47]), income (null [47]), ethnicity (Hispanic<[35], null[44, 47, 48]), lifestyle (smoker > [44]), co-morbidities (chronic RTIs < [47]), and payment type (private > Medicare > Medicaid [46], null [44, 47, 48]).

<u>Clinician-level factors:</u> training (general/family medicine > general internal medicine [49] > ENT [47], null [48]) and experience (resident/intern < staff [44]).

<u>System-level factors:</u> practice setting (office-based > urgent care/ED[46], null[34]), geographical region (S > NE, E, and W [45, 46, 50], null [34, 44, 47, 48]), population density (rural > [35, 48], null [34, 46]).

Some of the conflicting findings could be explained by practice setting (e.g. Stone et al. [44] analysis was restricted to the NHAMCS); period (Barnett et al.-A & B [34, 46] were primarily from 2000s; Stone et al. [44] and Gonzales et al. [48] were from 1990s); diagnosis (Barnett et al.-

[1] I based these findings on systematic reviews and published analyses of large, national-level data, such as NAMCS, NHAMCS, and MEPS.

A [46] was in patients with sore throats, Barnett et al.-B [34] was in patients with acute bronchitis, Smith et al. [47] was in patients with rhino-sinusitis); patient population (Zhang et al. [50] was in Medicare patients, Li et al. [35] was in Medicaid patients); or adjusted versus unadjusted analyses or study design (Barnett et al.-B [34] and Rutschmann et al. [49] reported adjusted analyses; Barnett et al.-A [46] and Stone et al. [44] reported unadjusted analyses, and Smith et al. [47] and Gonzales et al. [48] reported both). The conflicting null findings could be attributed to underpowered studies. However, this is unlikely because I focused on analyses of large, nationally-representative data. Another explanation is that self-selection mechanisms could lead to systematic differences in the severity of symptoms during the clinical visit (e.g., sicker patients will get over-represented in the clinic if a patient-focused strategy reduces their propensity to visit the clinic, which could result in a lower incidence of clinically diagnosed ARTI cases, but may not change observable rates of antibiotic prescribing).

Clinical/technical processes are a frequent explanation for over-prescribing. The majority of ARTIs will resolve without antibiotic intervention. However, clinicians must rule out more serious infections of bacterial origin, such as community-acquired pneumonia (CAP), which requires immediate treatment with empiric antibiotics. CAP can be difficult to diagnose based on a physical exam alone [51]. Clinicians report that diagnostic complexity of ARTIs contributes to over-prescribing [52], and there is some research to support this explanation [53]. Decision tools that aid diagnosis reduce over-prescribing, which provide support to this explanation [54].

Another explanation is the evidence to support current guidelines is insufficient to satisfy some clinicians[2]. In a recent survey, clinicians report familiarity with clinical practice guidelines and concern about antibiotic resistance, but some treated against indication because they questioned the guidelines [55]. Historical evidence may have supported this view [56], but current research and meta-analyses consistently demonstrate negligible or no benefit of antibiotics in patients with ARTIs. A subset of clinical symptoms drives over-prescribing, primarily purulent sputum and

[2] There is overlap in my classification of explanatory factors. For example, doubts about clinical practice guidelines could be considered a clinical/technical source of variation or a behavioral source of variation.

altered breathing [57-61]. Antibiotics may have a very small (or negligible) benefit for patients with these symptoms, but they are known to have poor diagnostic properties [62].

A significant component of antibiotic prescribing is known to be uncorrelated with symptoms and attributable to non-clinical cues [63]. Behavioral and social processes, and economic factors are frequent explanations for over-prescribing. Surveys and observational studies support the theory that demand-induced supply due to patient expectations (or a clinician's perception thereof) contributes to over-prescribing [52, 55, 64-69]. And patients with more severe symptoms of longer duration or a "positive" past experience are more likely to want antibiotics [70]. Patients may overestimate the benefits and underestimate the downside risks, and pressure clinicians to prescribe antibiotics (against their judgment). However, the clinician must perceive and concede to these expectations to have an influence on antibiotic prescribing. Time constraints or other economic factors, such as practice-building incentives, might predispose a clinician to concede to these expectations. Clinicians report that time constraints contribute to over-prescribing [52, 55], and there is research to support this explanation [71, 72]. In time-constrained visits, clinicians may prescribe antibiotics against their clinical judgment rather than engage the patient in a discussion regarding the lack clinical benefit and the downside risks of antibiotics. I did not find research to support practice-building incentives as an explanation for over-prescribing antibiotics. More squarely on the clinician side, socializing forces (or norms of practice) are another explanation for over-prescribing. In high-prescribing settings, residents tend to prescribe at lower rates, but later adopt antibiotic prescribing patterns closer to that of staff clinicians [73]. However, during (or in tension with) this socializing process, clinicians seem to establish and then adhere to *idiosyncratic* norms of best practice [64, 74]. Another explanation, according to clinician surveys, are legal concerns and defensive medicine [55]. Reducing the use of antibiotics in non-indicated ARTIs has been associated with a small increase in follow-up visits, which could motivate a defensive approach [75-80]. It may be that clinicians continue to prescribe antibiotics to avoid a small chance of an infection that doesn't resolve without antibiotics and the potential legal consequences.

To add clarity, I provided a conceptual model of the clinical setting and factors associated with antibiotic prescribing, which I based on a model first proposed in a technical review by the AHRQ on antibiotic prescribing and quality improvement strategies [36], see Figure 3.

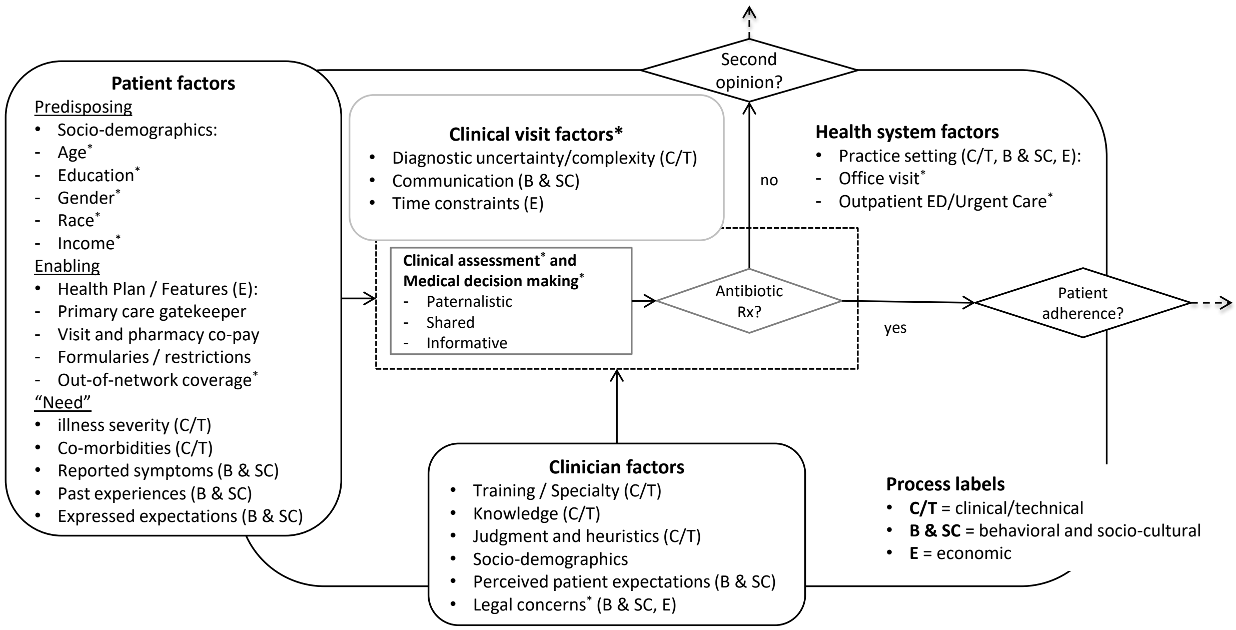


Figure 3: Conceptual model for antibiotic prescribing in the outpatient setting.

The original model was an adaptation of a socio-cultural model of the clinical setting proposed by Kleinman and colleagues [81]. Antibiotic prescribing is influenced by processes that initiate before the clinical visit, such as clinician *idiosyncratic* norms of best practice and patient expectations for antibiotics. However, the clinical visit is the focal point where these processes interact and coalesce to influence antibiotics prescribing. In my adaptation, I added detail on the clinical visit and an embedded framework of medical decision-making based on social science research [82-86]. The decision-making models are organized along a continuum that depends on the type of patient autonomy (or involvement in decision making) and the type of information exchange: the paternalistic model (patient concedes decision to the clinician; one-way information flow from patient to clinician), deliberative model (shared decision making; 2-way information exchange), and informative model (patient in control of medical care; one-way flow of technical expertise from clinician to patient). In addition, inspired by the Andersen behavioral model research [87], I grouped patient-level factors into predisposing, enabling, or "need" based factors.

Although my conceptual model provides a hierarchical organization to the factors associated with antibiotic prescribing and contextualizes these to the clinical setting, it is not a theoretical model with testable hypotheses. From the AHRQ Closing the Quality Gap series [88], paraphrasing

McDonald et al., conceptual models are a simplified abstraction within a hierarchy of knowledge, which are primarily used to clarify, describe, and organize ideas; theories are an organized, coherent, and systematic set of statements that are communicated in a meaningful whole, which not only describe, but also summarize the current evidence, propose explanations, and yield testable hypotheses. A theoretical model for this clinical setting that accurately represents the decision-making process would better support evaluations of strategies and interventions to reduce overuse and prescribing antibiotics in patients with ARTIs

1.3 SPECIFIC AIMS

In my dissertation, I conducted a comprehensive policy evaluation of the GSA campaign and the impact on antibiotic prescribing in adults with non-indicated ARTIs in the outpatient setting. Specifically, I addressed three specific aims:

SPECIFIC AIM 1: To evaluate the impact of three nationally-focused activities of the GSA campaign on antibiotic prescribing targeting patients and clinicians: (1) developing & publishing CPGs and (2) the national media campaign, and (3) the Spanish-speaking initiative.

SPECIFIC AIM 2: To evaluate the impact of two state-focused activities of the GSA campaign on antibiotic prescribing: (1) state-level funding and (2) state participation in the GSA Week.

SPECIFIC AIM 3: To develop and apply a latent-factor structural model of antibiotic prescribing behavior, including behavioral factors for (1) clinician idiosyncratic norms of best practice and (2) demand-induced supply (i.e., a patient desire for antibiotics influencing a clinician's prescribing behavior), and use it to explore patterns in prescribing behavior with respect to these channels.

Chapter 2. DATA SOURCES

I used two primary data sources to analyze antibiotic prescribing: The Medical Expenditure Panel Survey (MEPS) and the MarketScan employer claims database. MEPS is a nationally representative set of surveys of individuals, families, and their medical providers and employers, which can be used to estimate healthcare use, expenditures, and health insurance coverage [89]. Approximately 15,000 families and 35,000 peoples are sub-sampled each year from the parent survey, the National Health Interview Survey, and followed for two years using an overlapping, five-panel design. MEPS has three main components: the household component, the insurance component, and the medical provider component. Combined, these components have information on families and their demographic makeup (e.g. race, education), health conditions and treatments (e.g. ICD9 codes for recorded conditions and NDC numbers for drug treatments), health insurance and plan type, sources of healthcare, and healthcare expenditures. The MEPS is available online through the Agency for Healthcare Research and Quality (AHRQ). Through a restricted data use agreement, the AHRQ supports state-level identification for a subset of 29 sufficiently populated states.

MarketScan is a claims database of enrollees in participating employer-based plans that has national scope [90]. The database includes all inpatient, outpatient, and pharmacy claims during enrollment, which includes information on enrollee demographics (i.e., age, gender, and MSA region), health conditions (e.g., ICD9 codes), health plan type (e.g., HMO, PPO) and features (e.g., out-of-network coverage, primary-care gatekeeper plan), and place of healthcare service (e.g., outpatient hospital, office visit) and provider type (e.g., physician, RN). I had access to the MarketScan database from 2007-2012.

The CDC published guidelines for adults with non-complicated ARTIs: acute bronchitis, acute pharyngitis, acute rhino-sinusitis, and the common cold or acute URTI. Therefore, I restricted the analyses to patients between the ages of 18-64 years that were diagnosed with a non-indicated ARTI in an office-based setting. I identified non-indicated ARTIs using ICD9 diagnostic codes from the index visit: acute bronchitis = 466, 490; acute pharyngitis = 462; acute sinusitis = 461; common cold or acute URTI (NOS-not otherwise specified) = 460, 465.

Most of these patients would not be indicated for antibiotics. However, I would not expect a baseline rate of 0% under ideal prescribing behavior because patients with more severe or longer-duration conditions could be indicated for antibiotics. For example, the current guideline for acute sinusitis[3] indicate antibiotics if the symptoms are: severe (>3-4 days of fever with purulent nasal discharge or facial pain), persistent symptoms (>10 days) without improvement, or worsening symptoms (3-4 days). Therefore, I defined an index visit as a patient without a previous ATRI diagnosis within the 2 months prior, which included indicated and non-indicated ATRIs. Indicated ARTIs included: otitis media, pertussis, pneumonia (bacterial), and streptococcal pharyngitis (see Table 1). I excluded potentially complicated cases if there was an antibiotic appropriate diagnosis (soft tissue infection, urinary tract infection, or infectious disease) within 2 months prior to the index visit, or a chronic RTI (rhinitis, sinusitis, tonsillitis, and COPD) or an immuno-compromising condition (cancer, HIV, organ transplant, asplenia, or a disorder of the immune system) diagnosed within the 6 months prior. For a complete set of inclusion and exclusion criteria, see Appendix, Table 20 (page 76).

Table 1: ARTIs and antibiotic indications[4].

<u>Non-indicated ARTIs</u>
Acute bronchitis
Acute pharyngitis (non-strep)
Acute sinusitis/rhino-sinusitis (uncomplicated)
Common cold or Acute upper RTIs (NOS)
<u>Antibiotic appropriate ARTIs</u>
Otitis media
Pertussis
Pneumonia (bacterial)
Streptococcal pharyngitis
Sinusitis (complicated)

[3] There are no ICD9 codes for acute rhino-sinusitis, only acute sinusitis. Based on my review and consulting committee experts, the CPG for acute rhino-sinusitis aligns with current guidelines and coding for acute sinusitis.

[4] I planned to analyze antibiotic prescribing in patients with acute sinusitis. However, in MEPS, a diagnosis of acute sinusitis was not commonly recorded (< 0.1% of all cases of non-indicated ARTIs), so I dropped these cases from the MEPS analysis because they destabilized our regression model; I retained these patients in the analysis of MarketScan data.

MEPS provides a linkage between the diagnosis and the prescribed medications. For the MarketScan database, I linked an antibiotic prescription if it occurred within a 7-day window after the diagnostic visit and there was no interim indication for antibiotics.

Chapter 3. SPECIFIC AIM 1: ANALYSIS OF NATIONAL ACTIVITIES

3.1 Specific Aim

In my first specific aim, I evaluated nationally-focused GSA campaign activities targeting patients and clinicians and their impact on the rate of antibiotic prescribing to adult patients with non-indicated ARTIs, including: the publication of CPGs, the national media campaign, and the Spanish-speaking initiative.

3.2 Methods

I used an internet archive of the CDC's website of the GSA campaign to identify major, nationally-focused activities and events, which included: the publication of CPGs (in March, 2001), the national media campaign (initiated in November, 2003), and the Spanish-speaking initiative (in September, 2006) [91]. I used an interrupted time series study design and regression methods to analyze the impact of the campaign events on antibiotic prescribing in the Medical Expenditure Panel Survey (MEPS) from 1999-2008.

3.2.1 Antibiotic prescribing rates in non-indicated ARTIs

I used logistic regression to analyze impact of the 3 campaign events on antibiotic prescribing rates. MEPS has a complex survey design with probability sampling of underrepresented populations and cluster-based sampling within strata. There are 100+ strata and 400+ cluster-based sampling units. MEPS includes identifiers for strata and clusters, and weights to adjust for non-response [92, 93]. I used the method of Taylor Series Linearization to estimate standard errors and accommodate for the complex sampling design [94]. In addition, I adjusted descriptive summary statistics for the population weights (e.g., the incidence of ARTIs and antibiotic prescribing rates). (See Equation 1)

For each campaign event, I fit a regression model to a 5-year window centered around the campaign event. The regression model included a term for the month of the visit and a term for the elapsed time (i.e., from the beginning of the window), additional covariates (see below), and 2 terms that capture the effect of the campaign event: an exposure variable indicating if the index visit occurred after the campaign event, which captures the immediate effect on antibiotic prescribing rates, and an interaction term with elapsed time from the event-exposure until the index visit, which captures the change in the time trend. There is no control group in this analysis because these were nationally-focused campaign activities. I chose a 5-year window to estimate a stable trend in antibiotic prescribing rates in the 2.5 years prior to each event and then a change in the trend in 2.5 years following each event. I limited the length of the observation window because I expected the effect to stabilize in time (i.e., reach a new steady state in antibiotic prescribing rates in response to the campaign event); an extended window would diminish the trend effect. If the event windows overlapped with another campaign event, I truncated the window to less than 5 years to isolate the analyses (i.e., 2 years after the Spanish initiative the first GSA Week occurred, so I truncated the analysis window). For statistical inference, I also included a joint Wald test of the 2 terms that capture the effect of each campaign event (i.e., the immediate effect and the time trend effect). If I found a significant overall campaign effect, I performed a sub-group analysis within each ARTI to explore if there was a diagnostic sub-group driving the overall effect.

I adjusted all analyses for additional covariates: diagnosis (acute bronchitis, acute pharyngitis, common cold or acute non-specific upper respiratory tract infection (acute URTI (NOS)), sex, age (18-24, 25-44, 45-64), race (White, Black, Other), predominant language (Spanish vs. English/non-Spanish), census region (Northeast, Midwest, South, West), metropolitan service area (yes vs. no), education (no degree, GED or HS diploma, bachelor’s, master’s or doctorate, other), employment (full vs. less than full), prescription medical insurance (yes vs. no), and general health (excellent/very good/good vs. fair/poor).

Equation 1: Regression models for antibiotics.
variable indices: s = MEPS sampling strata, p = panel, r = round, i = person id, and c = case

$$\mathrm{P}(\text{antibiotic Rx} \mid X_{CPGs}, \mathrm{Z}) = \mathrm{g}_{\text{inv-logit}}\left(\begin{array}{c} \overrightarrow{\beta_S} \\ + \\ \mathrm{I}_{\mathrm{CPG}}(\mathrm{t}_{\mathrm{spric}} > \text{March 30, 2001}) * \beta_{\mathrm{CPG}} \\ + \\ \mathrm{I}_{\mathrm{CPG}}(\mathrm{t}_{\mathrm{spric}} > \text{March 30, 2001}) * (\mathrm{t}_{\mathrm{spric}} - \text{March 20, 2001}) * \beta_{\text{CPG trend}} \\ + \\ Z \end{array}\right) \tag{1.1}$$

$$\mathrm{P}(\text{antibiotic Rx} \mid X_{NMC}, \mathrm{Z}) = \mathrm{g}_{\text{inv-logit}}\left(\begin{array}{c} \overrightarrow{\beta_S} \\ + \\ \mathrm{I}_{\mathrm{NMC}}(\mathrm{t}_{\mathrm{spric}} > \text{Sept 17, 2003}) * \beta_{\mathrm{NMC}} \\ + \\ \mathrm{I}_{\mathrm{NMC}}(\mathrm{t}_{\mathrm{spric}} > \text{Sept 17, 2003}) * (\mathrm{t}_{\mathrm{spric}} - \text{Sept 17, 2003}) * \beta_{\text{NMC trend}} \\ + \\ Z \end{array}\right) \tag{1.2}$$

$$\mathrm{P}(\text{antibiotic Rx} \mid X_{SI}, \mathrm{Z}) = \mathrm{g}_{\text{inv-logit}}\left(\begin{array}{c} \overrightarrow{\beta_S} \\ + \\ \mathrm{I}_{\mathrm{SI}}(\mathrm{t}_{\mathrm{spric}} > \text{Sept 20, 2006}) * \beta_{\mathrm{SI}} \\ + \\ \mathrm{I}_{\mathrm{SI}}(\mathrm{t}_{\mathrm{spric}} > \text{Sept 20, 2006}) * (\mathrm{t}_{\mathrm{spric}} - \text{Sept 20, 2006}) * \beta_{\text{SI trend}} \\ + \\ \mathrm{I}(\text{Spanish speaker}) * \mathrm{I}_{\mathrm{SI}}(\mathrm{t}_{\mathrm{spric}} > \text{Sept 20, 2006}) * \beta_{\mathrm{SI}} \\ + \\ \mathrm{I}(\text{Spanish speaker}) * \mathrm{I}_{\mathrm{SI}}(\mathrm{t}_{\mathrm{spric}} > \text{Sept 20, 2006}) * (\mathrm{t}_{\mathrm{spric}} - \text{Sept 20, 2006}) * \beta_{\text{SI trend}} \\ + \\ Z \end{array}\right) \tag{1.3}$$

Analyses were performed in SAS 9.3 using Proc Surveylogistic.

3.2.2 Incidence of antibiotic-indicated ARTIs

I would not expect a change in the underlying incidence of ARTIs in response to the GSA campaign. However, if a clinician preferred to prescribe antibiotics they could code-shift into an antibiotic-indicated ARTI diagnosis to appear in accord with guidelines. Therefore, I analyzed the impact of the campaign events on the incidence of antibiotic-indicated ARTIs. I used generalized estimating equations (GEE) to analyze person-level counts of office-diagnosed disease during each panel-round of observation [95]. I used a log-link function and an offset for the person-level (log) calendar days of observation. I included the same covariates as in my analysis of antibiotic prescribing rates, and additionally adjusted for health insurance (in addition to prescription medical insurance). For subjects with a panel-round that overlapped a campaign event, I split the observation window into counts pre-and-post the event exposure. I focused on antibiotic-indicated

ARTIs that are more common in adults: streptococcal pharyngitis and pneumonia (bacterial). I did not evaluate for code shifting into otitis media or pertussis, which are primarily diagnosed in children. I used delete-1 jackknife variance estimates for complex surveys to estimate standard errors [96]. (See Equation 2)

Equation 2: Regression models for the incidence of ARTIs.
variable indices: s = MEPS sampling strata, p = panel, r = round, i = person id, and c = case

$$\mathrm{E}(\#\text{ of antibiotic ARTI visits} \mid X_{CPGs}, \mathrm{Z}) = exp\begin{pmatrix} \log(\text{length of observation window}) + \overrightarrow{\beta_S} \\ + \\ \mathrm{I_{CPG}}(\mathrm{t_{spric}} > \text{March 30, 2001}) * \beta_{\mathrm{CPG}} \\ + \\ \mathrm{I_{CPG}}(\mathrm{t_{spric}} > \text{March 30, 2001}) * (\mathrm{t_{spric}} - \text{March 20, 2001}) * \beta_{\mathrm{CPG\ trend}} \\ + \\ Z \end{pmatrix} \quad (2.1)$$

$$\mathrm{E}(\#\text{ of antibiotic ARTI visits} \mid X_{NMC}, \mathrm{Z}) = exp\begin{pmatrix} \log(\text{length of observation window}) + \overrightarrow{\beta_S} \\ + \\ \mathrm{I_{NMC}}(\mathrm{t_{spric}} > \text{Sept 17, 2003}) * \beta_{\mathrm{NMC}} \\ + \\ \mathrm{I_{NMC}}(\mathrm{t_{spric}} > \text{Sept 17, 2003}) * (\mathrm{t_{spric}} - \text{Sept 17, 2003}) * \beta_{\mathrm{NMC\ trend}} \\ + \\ Z \end{pmatrix} \quad (2.2)$$

$$\mathrm{E}(\#\text{ of ARTI visits} \mid X_{NMC}, \mathrm{Z}) = \exp\begin{pmatrix} \log(\text{length of observation window}) + \overrightarrow{\beta_S} \\ + \\ \mathrm{I_{SI}}(\mathrm{t_{spric}} > \text{Sept 20, 2006}) * \beta_{\mathrm{SI}} \\ + \\ \mathrm{I_{SI}}(\mathrm{t_{spric}} > \text{Sept 20, 2006}) * (\mathrm{t_{spric}} - \text{Sept 20, 2006}) * \beta_{\mathrm{SI\ trend}} \\ + \\ \mathrm{I}(\text{Spanish speaker}) * \mathrm{I_{SI}}(\mathrm{t_{spric}} > \text{Sept 20, 2006}) * \beta_{\mathrm{SI}} \\ + \\ \mathrm{I}(\text{Spanish speaker}) * \mathrm{I_{SI}}(\mathrm{t_{spric}} > \text{Sept 20, 2006}) * (\mathrm{t_{spric}} - \text{Sept 20, 2006}) * \beta_{\mathrm{SI\ trend}} \\ + \\ Z \end{pmatrix} \quad (2.3)$$

Analyses were performed in SAS 9.3 using Proc Genmod.

3.3 RESULTS

The self-reported incidence of ARTIs varied between 4-17% per person-year and the office-diagnosed incidence varied between 1-2%, with common cold or acute URTIs (NOS) having the highest incidence across ARTIs (see Table 2). In patients with office-diagnosed ARTIs, clinicians prescribed antibiotics to 40-57% of patients, with the highest rates in patients with acute bronchitis (see Table 3).

Table 2: Incidence of non-indicated ARTIs.

Condition	Incidence (per person-year)			
	All*	Office	Outpatient	ER
Acute Bronchitis	0.04	0.015	<.001	0.002
Acute Pharyngitis	0.02	0.007	<.001	<.001
Common cold or URTI (NOS)	0.17	0.024	<.001	<.001

* Includes both patient-reported and visit diagnosed conditions.

Table 3: ARTI cases and Antibiotic Rx rates.

Diagnosis	N	%	Rx rates
Acute Bronchitis	2789	34	0.57
Acute Pharyngitis	1306	16	0.41
Common cold or URTI (NOS)	4011	49	0.40

Based on the joint Wald test, I found a significant effect of the CPGs and the NMC on reducing antibiotic prescribing rates (p-value=0.03 and 0.01, respectively) (see Table 4). The odds that any antibiotics were prescribed were 34% lower after the publication of CPGs in March 2001 (OR=0.68, p-value = 0.01) and 24% lower each additional year after the national media campaign in September 2007 (ORR=0.76, p-value=0.01) (see Table 4). As visual evidence, I provided a plot of the recycled prediction-based antibiotic prescription rates over the 5-year window and the counter-factual (i.e., if there were no campaign event), see Figure 4. The effect was driven by lower prescribing to patients with the common cold or acute URTIs (NOS), see Table 4. I did not find a significant change in the odds of antibiotic prescribing in the Spanish-speaking population after the Spanish-speaking initiative in September 2006 (p-value = 0.58; see Table 4).

Table 4: Regression analysis of non-indicated ARTI antibiotic Rx rates.

	Combined		Acute Bronchitis		Acute Pharyngitis		Common Cold	
	OR	P-value	OR	P-value	OR	P-value	OR	P-value
Clinical Practice Guidelines								
post-CPGs	0.68	0.01**	0.78	0.31	0.74	0.44	0.57	0.02*
post-CPGs X years	0.93	0.58	0.89	0.61	1.22	0.57	0.93	0.74
joint test		0.03*		0.52		0.59		0.05*
National Media Campaign								
post-NMC	1.18	0.30	1.37	0.26	0.68	0.26	1.21	0.42
post-NMC X years	0.76	0.01**	0.78	0.12	0.95	0.82	0.67	0.01**
joint test		0.01**		0.09		0.53		0.02**
Spanish Initiative (SI)								
Spanish-speaking X post-SI	0.59	0.37						
Spanish-speaking X post-SI X years	1.19	0.61						
joint test		0.58						

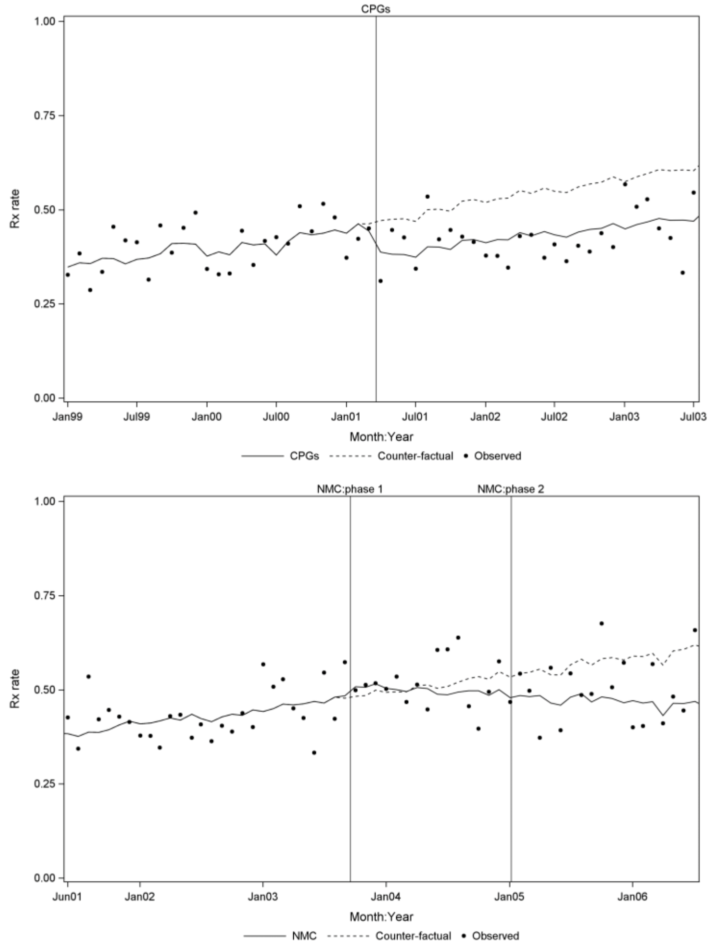


Figure 4: Recycled predictions of antibiotic Rx rates.

* The month and diagnosis effects have been averaged out.

The self-reported incidence of antibiotic-indicated ARTIs was ~1.5% per person-year for both streptococcal pharyngitis and pneumonia, and the office-diagnosed incidence was between 0.5-1.0% (see Table 5). The incidence of streptococcal pharyngitis and pneumonia were not significantly higher after the publication of CPGs in March 2001 or after the national media campaign in September 2007 (p-values=0.80 and 0.19, respectively; see Table 6).

Table 5: Incidence of antibiotic-indicated ARTIs.

Condition	Incidence (per person-year)			
	All*	Office	Outpatient	ER
Streptrococcal Pharyngitis	0.014	0.007	<.001	<.001
Pneumonia	0.013	0.005	<.001	0.001

* Includes both patient-reported and visit diagnosed conditions.

Table 6: Regression analysis of antibiotic-indicated ARTI incidence rates.

	Streptococcal Pharyngitis		Pneumonia	
	RR	P-value	RR	P-value
Clinical Practice Guidelines				
post-CPGs	1.06	0.82	0.61	0.12
post-CPGs X years	1.12	0.61	1.12	0.64
joint test		0.80		0.26
National Media Campaign				
post-NMC	0.80	0.30	0.62	0.06
post-NMC X years	1.27	0.13	0.84	0.30
joint test		0.19		0.10

3.4 DISCUSSION

My analysis of nationally-focused GSA campaign events found that the publication of CPGs and the first phase of the NMC (with PSAs that targeted patients and clinicians) significantly reduced antibiotic prescribing, primarily in patients with the common cold or acute URTIs (NOS). Clinical practice guidelines had an immediate impact, whereas the NMC had a lagged impact (i.e., in the trend over time). I did not find evidence of untended consequences associated with the campaign. Specifically, I did not find an increase in antibiotic-indicated ARTIs, which suggests the clinicians did not respond by code shifting to appear in compliance with guidelines.

I did not find an impact of re-publishing the GSA campaign website in Spanish (in October of 2006) along with additional educational & behavioral change material, which I labelled the "Spanish-speaking initiative", on antibiotic prescribing in Spanish-speaking populations. The analysis may have been under-powered because the number of office-diagnosed ARTI cases where the patient indicated that Spanish was their 'primary language spoken at home' was relatively small (N = 626, ~8%). Phase 2 of the NMC launched in 2005, which included PSAs targeting healthy adults and Spanish-speaking populations. However, I was not able to recover the start date of phase 2 from the internet archive of the GSA campaign website. It may be that phase 2 of the NMC had an earlier impact on these populations. Alternatively, among patients with ARTI cases, the Spanish-speaking population had lower rates of health insurance and prescription medical insurance and lower baseline rates of antibiotic prescriptions (data not shown). It may be that the

Spanish-speaking population had less access to health care resources and, therefore, were less likely to be treated for the common cold or acute URTIs (NOS).

The effect of the GSA campaign through CPGs and the NMC was driven by reduced antibiotic prescribing to patients with the common cold or acute URTIs (NOS), which accounted for approximately 2.4 office-diagnosed cases per 100 person-years. However, there was not an impact on patients with acute bronchitis (or acute pharyngitis), which accounted for 1.5 office-diagnosed cases per 100 persons-years. Although acute bronchitis had a lower incidence of office-diagnosed disease compared to the common cold, the antibiotic prescribing rates were 17% higher (on an absolute scale). Future efforts to reduce antibiotic prescribing should include targeting these patients.

Chapter 4. SPECIFIC AIM 2: ANALYSIS OF STATE-FOCUSED ACTIVITIES

4.1 SPECIFIC AIM

In my second specific aim, I evaluated the impact of two state-focused activities of the GSA campaign on antibiotic prescribing: (1) state-level funding and (2) state participation in the GSA Week (GSAW).

4.2 METHODS

I used an internet archive of the CDC's website of the GSA campaign to identify funding of state health departments for each year (see Figure 5), which occurred from 2001 to present day, and state-level participation in the annual GSAW for each year (see Figure 6), which occurred from 2008 to present day [91].

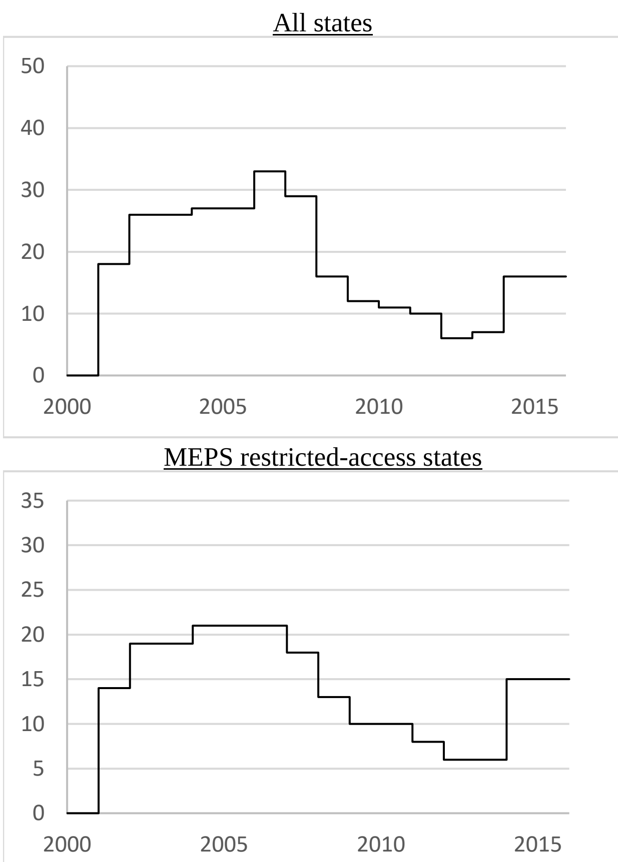


Figure 5: GSA-funded states.

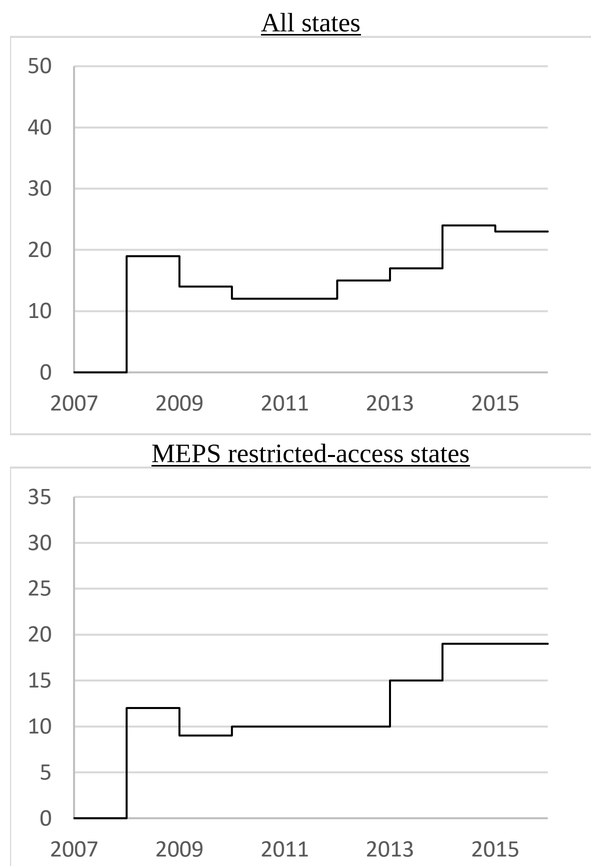


Figure 6: States participating in GSAW.

4.2.1 State-level funding to develop local GSA campaigns

I analyzed the impact of state-level funding on antibiotic prescribing rates in MEPS (on the sufficiently populated 29 states with state-level indices) from the years 1999-2012, and in MarketScan data from the years 2007-2012. I used an interrupted time series study design with a control group, which I achieved by exploiting variation in state-level funding, and regression methods to analyze antibiotic prescribing rates. Not all states received funding. Among the states that received funding there was variability in both the year of initiation and the duration of funding. After funding started it was typically extended for multiple years and then terminated, and very few states restarted funding (See Figure 5). The GSA campaign promoted a variety of activities for funded states, including participation in the GSAW (see Table 7 for the currently promoted activities).

Table 7: State-level activities promoted for funded states.

- Highlight Get Smart Week on your website
- Use Get Smart Week as a kickoff to begin a stewardship program
- Collaborate with CDC and local-level programs on projects
- Exchange in-kind services with CDC and local-level programs
- Provide assistance to local-level programs in producing educational materials or sponsoring events
- Issue a press release
- Distribute educational materials to the general public
- Distribute tools and guidelines to healthcare professionals and facilities
- Host local-level events
- Deliver presentations to interested parties
- Post social media messages and participate in the annual Twitter chat
- Share information with your organization's membership through e-mail or newsletters
- Include print materials or information in Explanation of Benefits statements
- Promote placement of matte articles in local media
- Place ads in local or national media (free standing inserts, print ads, television or radio ads, etc.)
- Include content in employee education materials
- Distribute materials at medical conferences and exhibits
- Develop a local government proclamation

MEPS

I used logistic regression to analyze the impact of funding on antibiotic prescribing rates. My primary regression variable is the number of cumulative years of funding (received by the patient's state of residence), which I parameterized for differential effects between the first year of funding versus each additional year of funding. State-level programs could have been funded for reasons correlated with baseline antibiotic prescribing rates. The state health department may be proactive and pursued funding or, alternatively, the state could have above average antibiotic prescribing rates and, therefore, the CDC encouraged participation. Similar institutional dynamics could explain termination of funding. However, I could not recover the reasons for awarding or terminating funding. Therefore, to address potential endogeneity, I included state-level fixed effects to allow each state to have a unique rate of baseline antibiotic prescribing. In addition, I included a variable for the number of cumulative years since state-level funding had terminated (for states that had received funding), which I parameterized for differential effects between the first year of defunding versus each additional year of defunding. (See Equation 3)

MEPS has a complex survey design with probability sampling of underrepresented populations and cluster-based sampling within strata. There are 100+ strata and 400+ cluster-based sampling units. MEPS includes identifiers for strata and clusters, and weights to adjust for non-response [92, 93]. I used the method of Taylor Series Linearization to estimate standard errors and accommodate for the complex sampling design [94]. For statistical inference, I included a joint Wald test of the 2 terms that capture the funding effect (i.e., the immediate effect and the time trend effect). If I found a significant effect, I performed a sub-group analysis within each ARTI to explore if there was a diagnostic group driving the overall effect. In addition, I adjusted descriptive summary statistics for the population weights (e.g., the antibiotic prescribing rates).

I adjusted the MEPS analyses for additional covariates: patient's state of residence, the month of the visit and the elapsed time (from the January, 1, 1999), exposure to the significant nationally-focused campaign events, diagnosis (acute bronchitis, acute pharyngitis, common cold or acute URTI (NOS)), sex, age (18-24, 25-44, 45-64), race (White, Black, Other), predominant language (Spanish vs. English/non-Spanish), census region (Northeast, Midwest, South, West), metropolitan service area (yes vs. no), education (no degree, GED or HS diploma, bachelor's, master's or doctorate, other), employment (full vs. less than full), prescription medical insurance (yes vs. no), and general health (excellent/very good/good vs. fair/poor). I also adjusted for the number of GSAWs participated at the state level.

Equation 3: Regression model for antibiotics and state-level funding.

$$P(I\{Antibiotic\ Rx\} = 1 \mid X, Z) = g_{inv-logit}\left(\begin{array}{c} \vec{C}\{\text{state}\} * \vec{\beta}_{state} \\ + \\ years\ (continuous) * \vec{\beta}_{year} \\ + \\ \vec{C}\{\text{month}\} * \vec{\beta}_{month} \\ + \\ I\{\text{funded}\} * \beta_{1A} + X\{\text{years of funding} > 1\} * \beta_{1B} \\ + \\ I\{\text{defunded}\} * \beta_{2A} + X\{\text{years post-funding} > 1\} * \beta_{2B} \\ + \\ \vec{Z} * \vec{\beta} \end{array}\right) \tag{3.1}$$

where, for readability, I omitted indices on variables: p=panel, r=round, i=person id, and c=case
$and\ \vec{C}\{\cdot\}\ are\ categorical\ variables\ and\ I\{\cdot\}\ are\ indicator\ functions$

MarketScan

MarketScan is a convenience sample of employer-based plans, so I used Generalized Estimating Equations (GEEs) with a logit-link function and a state-level exchangeable correlation structure to analyze antibiotic prescribing rates [97]. The MarketScan database is too large for a complete-case regression analysis (i.e., on the order of 3M-5M ARTI cases per year, and 25M ARTI cases across 2007-2012). Therefore, I split the analysis dataset into 1% random, non-overlapping sub-samples, which I fit to GEE regression models. I then averaged parameter estimates (of the log-odds ratios) across regressions to arrive at final point estimates. I used the delta method to estimate variances of the odds ratios [98]. (See Equation 3 and Equation 4)

Equation 4: Variance model for MarketScan analysis.

Aggregated parameter estimator and variance:

$$\begin{aligned} &\hat{\beta}_{overall} := \left(\frac{1}{100}\right)\sum_{i=1}^{100}\hat{\beta}_{i\,(1\%)} \\ &V\left(\hat{\beta}_{overall}\right) = \left(\frac{1}{100}\right)^2 \sum_{i=1}^{100} V\left\{\hat{\beta}_{i\,(1\%)}\right\} \text{ assuming } i.i.d. \\ &\text{where } \hat{V}\left\{\hat{\beta}_{i\,(1\%)}\right\} \text{ are obtained from the regression analysis} \end{aligned} \tag{4.1}$$

Transformed parameter estimator and delta method-based variance:

$$\begin{aligned} &\hat{g}_{inv-link}(\beta) := \hat{f}(\beta) := f\left(\hat{\beta}_{overall}\right) \\ &V\left\{f\left(\hat{\beta}_{overall}\right)\right\} \approx f^2\left(\hat{\beta}_{overall}\right) * V\left(\hat{\beta}_{overall}\right) \end{aligned} \tag{4.2}$$

Wald-based confidence intervals:

$$\left[f\left(\hat{\beta}_{overall}\right) \pm z_{0.975} * f\left(\hat{\beta}_{overall}\right) * \frac{1}{100}\left\{\sum_{i=1}^{100}\hat{V}\left(\hat{\beta}_{i\,(1\%)}\right)\right\}^{-2}\right] \tag{4.3}$$

I adjusted the MarketScan analysis for additional covariates: patient's state of residence, the month of the visit and the elapsed time (from the January, 1, 1999), diagnosis (acute bronchitis, acute pharyngitis, acute sinusitis, common cold or acute URTI (NOS)), sex, age (18-34, 35-44, 45-54, 55-64), plan type (comprehensive, EPO, HMO, POS, PPO, POS with capitation, CDHP, HDHP), and occupational industry (oil/gas/mining, manufacturing, transportation/communication/utilities, retail trade, finance/insurance/real estate, services). I also adjusted for the number of GSAWs participated at the state level.

4.2.2 State-level participation in GSA Week

I applied similar regression models to analyze the impact of state-level participation in the GSAWs and antibiotic prescribing in both MEPS and MarketScan for the years 2007-2012, with some modifications. I limited the analysis to visits occurring in a 4-month window centered around the GSAW for each calendar year and I adjusted for year and month as categorical variables. I included a variable indicating state-level participation in the GSAW (in the same calendar year), a variable indicating exposure to GSAW (i.e., pre-vs-post GSAW in the same calendar year), and the interaction between these indicator variables to capture the effect of the GSAW. I also adjusted for state-level funding and defunding (with the same coding as in the state-level funding analysis). I included 2007 as a non-GSAW event year to improve control of baseline state-of-residence effects and month-of-year effects. In study design terminology, I consider this an extension of an interrupted time-series design with a control group, because there are repeated GSAWs with variability in state-level participation across years. (See Figure 6 and Equation 5)

Equation 5: Regression model for antibiotics and GSAW.

$$P(I\{Antibiotic\ Rx\} = 1 \mid X, Z) = g_{inv-logit}\left(\begin{array}{c} \vec{C}\{\text{state}\} * \vec{\beta}_{state} \\ + \\ \vec{C}\{\text{year}\} * \vec{\beta}_{year} \\ + \\ \vec{C}\{\text{month}\} * \vec{\beta}_{month} \\ + \\ I\{\text{state participated in GSAW}\} * \beta_1 \\ + \\ I\left\{t > \text{date of GSW}_{\text{year(t)}}\right\} * \beta_2 \\ + \\ I\{\text{state participated in GSAW}\} * I\left\{t > \text{date of GSAW}_{\text{year(t)}}\right\} * \beta_3 \\ + \\ \vec{Z} * \vec{\beta} \end{array}\right) \quad (3)$$

where, for readability, I omitted indices on variables: p=panel, r=round, i=person id, and c=case
and t is the date of the visit
$and\ \vec{C}\{\cdot\}\ are\ categorical\ variables\ and\ I\{\cdot\}\ are\ indicator\ functions$

Analyses were performed in SAS 9.3.

4.3 RESULTS

The self-reported incidence of ARTIs varied between 4-16% per person-year and the office-diagnosed incidence varied between 1-2%, with the common cold or acute URTIs (NOS) having the highest incidence across ARTIs. (see Table 8). In the employer-sponsored health insurance (ESHI) population (i.e., MarketScan data), the office-diagnosed incidence was slightly higher (2-4%).

In patients with office-diagnosed ARTIs, clinicians prescribed antibiotics to 41-59% of patients, with the highest rates in patients with acute bronchitis, which was comparable to the rates in the states with restricted-access de-identification (see Table 9). Clinicians prescribed antibiotics at a comparable rate in the EHSI population (i.e., 41-60%) (see Table 10).

Table 8: Incidence of ARTIs.
(MEPS, all states: 1999-2012; MarketScan: 2007-2012)

Condition	**Incidence (per percson-year)**		
	MEPS		**Marketscan**
	All*	Office	Office
Acute Bronchitis	0.04	0.01	0.02
Acute Pharyngitis	0.02	0.01	0.02
Acute Sinusitis			0.04
Common cold or URTI(NOS)	0.16	0.02	0.03

* Includes patient-reported, office, outpatient, and ER-diagnosed conditions.

Table 9: ARTI cases and antibiotic Rx rates (MEPS: 1999-2012).

Diagnosis	N	%	Rx rates	N	%	Rx rates	N	%	Rx rates	N	%	Rx rates	N	%	Rx rates
MEPS-encyrpted state:	All			Yes			No			Missing					
Acute Bronchitis	3346	34	0.59	455	37	0.65	2738	34	0.58	153	33	0.53			
Acute Pharyngitis	1564	16	0.42	195	16	0.42	1281	16	0.42	88	19	0.41			
Common cold or URTI(NOS)	4913	50	0.41	575	47	0.43	4111	51	0.41	227	49	0.43			
Funding status:*	All			Pre-funding			Funding			Defunded					
Acute Bronchitis	2738	34	0.58	1023	34	0.53	1198	34	0.59	517	33	0.65			
Acute Pharyngitis	1281	16	0.42	486	16	0.46	558	16	0.41	237	15	0.33			
Common cold or URTI(NOS)	4111	51	0.41	1497	50	0.37	1789	50	0.40	825	52	0.49			
GSAW Participant:	All			No						Yes					
Post-GSAW:**				No			Yes			No			Yes		
Acute Bronchitis	487	34	0.68	220	33	0.68	100	37	0.66	92	29	0.63	75	36	0.76
Acute Pharyngitis	189	13	0.45	91	14	0.32	27	9.9	0.50	44	14	0.49	27	13	0.73
Common cold or URTI(NOS)	776	53	0.45	348	53	0.48	145	53	0.46	177	57	0.40	106	51	0.40

* All months.
** 4-month window centered around GSAWs.

Table 10: ARTI cases and antibiotic Rx rates (MarketScan: 2007-2012).

Diagnosis	N	%	Rx rates	N	%	Rx rates	N	%	Rx rates	N	%	Rx rates	N	%	Rx rates
Funding status:*	All			Pre-funding			Funding			Post-funding					
Acute Bronchitis	5932487	22	0.60	1432556	22	0.58	1844694	23	0.59	2655237	22	0.62			
Acute Pharyngitis	4777372	18	0.47	1163062	18	0.44	1395279	18	0.46	2219031	18	0.49			
Acute Rhino-sinusitis	8607843	32	0.64	2138078	33	0.62	2535273	32	0.62	3934492	32	0.66			
Common cold or URTI(NOS)	7296698	27	0.41	1692120	26	0.39	2145557	27	0.36	3459021	28	0.45			
GSAW Participant:	All			No						Yes					
Post-GSAW:**				No			Yes			No			Yes		
Acute Bronchitis	2529022	23	0.59	1297285	22	0.56	640153	23	0.62	249531	22	0.61	342053	23	0.62
Acute Pharyngitis	1901656	17	0.46	1024959	18	0.45	443918	16	0.49	200162	18	0.45	232617	16	0.47
Acute Rhino-sinusitis	3623202	32	0.62	1871882	32	0.58	910068	32	0.67	363592	33	0.65	477660	32	0.66
Common cold or URTI(NOS)	3160347	28	0.40	1593226	28	0.39	846926	30	0.44	300171	27	0.37	420024	29	0.38

* All months
** 4-month window centered around GSAWs

4.3.1 Analyses of state-level funding and antibiotic Rx rates.

In the MEPS population, the odds of antibiotics were 4% lower for each additional year of state-level funding compared to non-funded states between the years of 2001-2012 (ORR=0.96, p-value = 0.03), which was driven by lower prescribing to patients with the common cold or acute URTI (NOS) (see Table 11). In the ESHI population, the odds of antibiotics were 3% lower for each additional year of state-level funding between the years 2007-2012 (ORR=0.97, p-value < 0.001), which was driven by lower prescribing to patients with acute bronchitis and acute sinusitis (see Table 12).

4.3.2 Analyses of state-level participation in the GSAW and antibiotic Rx rates

In the MEPS population, the pre-versus-post-GSAW odds ratio trended higher in participating states compared to non-participating states, but the result was not significant (ORR=1.41, p-value=0.22) (see Table 11). In the ESHI population, the pre-versus-post-GSAW odds ratio was the same in participating states compared to non-participating states (ORR=1.00) (see Table 12).

Table 11: Regression analysis of GSA state funding and GSA Week.
(MEPS, restricted-access states: 1999-2012)

	Combined		Acute Bronchitis		Acute Pharyngitis		Common Cold	
	OR	P-value	OR	P-value	OR	P-value	OR	P-value
Funding terms								
Funded	1.22	0.07	1.14	0.48	1.37	0.23	1.22	0.17
Funded X years	0.96	0.03*	0.96	0.21	0.95	0.25	0.94	0.05*
joint test		0.01*		0.35		0.29		0.06
GSAW terms								
GSAW participant	0.70	0.11						
Post-GSAW	1.10	0.75						
GSAW participant X Post-GSAW	1.42	0.22						

Table 12: Regression analysis of GSA state funding and GSA Week.
(Marketscan: 2007-2012)

	Combined		Acute Bronchitis		Acute Pharyngitis		Actue Sinusitis		Common Cold	
	OR	P-value	OR	P-value	OR	P-value	OR	P-value	OR	P-value
Funding terms										
Funded	0.98	0.30	0.97	0.23	1.00	0.49	0.91	0.004	1.04	0.09
Funded X years	0.97	< 0.001	0.95	< 0.001	0.99	0.01	0.95	< 0.001	1.00	0.27
GSAW terms										
GSAW participant	1.02	0.02								
Post-GSAW	0.99	< 0.001								
GSAW participant X Post-GSAW	1.00	0.29								

4.4 DISCUSSION

My analysis of state-focused GSA campaign activities found that funding to develop local campaigns reduced antibiotic prescribing in both the general population (i.e., MEPS-based analysis) and in the ESHI population (i.e., MarketScan-based analysis). The trend manifested after the first year of funding, with a 3%-4% drop in the odds of antibiotic prescribing for each additional year. On average, states received 5 years of continuous funding, which would have led to a sizable reduction in antibiotic prescriptions.

In the general population, the funding effect was driven by lower antibiotic prescribing to patients with the common cold or acute URTIs (NOS). In the ESHI population, by contrast, the effect was driven by antibiotic prescribing to patients with acute bronchitis and acute sinusitis. However, upon inspection, there was a similar but non-significant trend of lower antibiotic prescribing to these patients in the general population (i.e., MEPS population). Acute bronchitis and acute sinusitis have a lower incidence compared to the common cold, so the null sub-group findings may have been from insufficient power. Alternatively, the difference may reflect true differences between the general population versus the EHSI population.

We were not able to determine the amount of funding received by individual states and type of activities engaged in by these states. It seems likely that the level of funding and the type of activities impacted the size of the reduction in antibiotic prescribing, which should be a focus of future analyses.

I did not find an impact of the GSA Week (GSAW) on antibiotic prescribing. However, residual confounding from endogenous processes may explain the null finding. In my analysis, I fit a model that assumes an (equivalent) impact of the GSAW for each year of participation, irrespective of past participation. Initially, I attempted to use conditional logistic regression (CLR) and condition on year to focus on within-year variation (intuitively, comparing antibiotic prescribing rates for the 2 months pre-GSAW versus the 2 months post-GSAW, in the participating versus non-participating states, for each year and then averaging across years) to control for potential confounding by endogeneity. However, the algorithm would not converge. As an alternative, I adjusted for ‘year’ as a categorical covariate in the regression model. However, this would not necessarily adjust away all confounding by endogenous processes, such as a state reducing future participation in response to a drop in antibiotic prescribing. I would have to adjust for the state’s past year’s prescribing rate or include a new state-by-year interaction term (see Figure 7). Or I could have used a similar approach to the analysis of state-level funding by including a term for stopping state-level participation in the GSAW. However, state participation in the GSAW varied more than funding (i.e., states participated on-and-off multiple times). My preliminary analyses suggest endogeneity confounded my analyses of the GSAW effect (data not shown). Future work will explore and adjust for confounding by endogeneity.

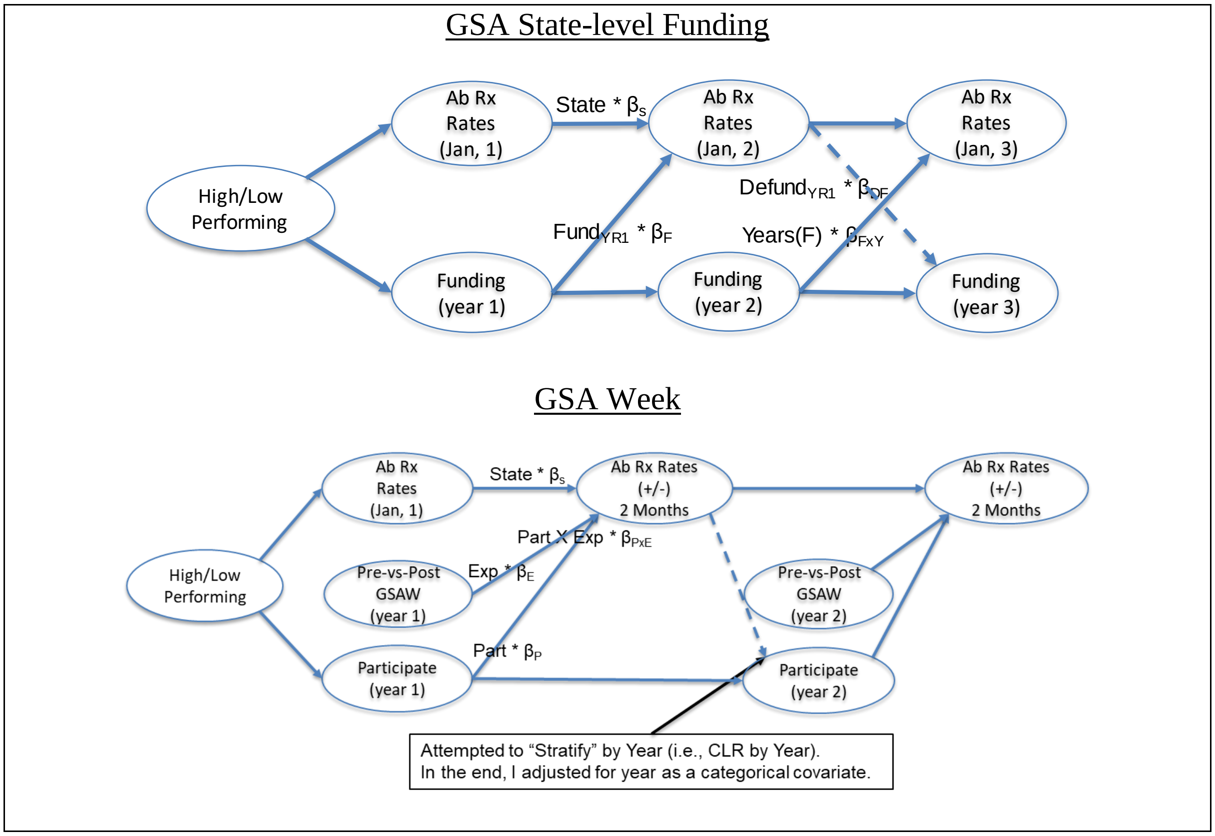


Figure 7: Simplified causal diagrams for GSA campaign state-level activities.

Chapter 5. SPECIFIC AIM 3: LATENT-FACTOR STRUCTURAL MODEL

5.1 SPECIFIC AIM

In my third specific aim, I developed and applied a latent-factor structural model of antibiotic prescribing behavior, including behavioral factors for (1) clinician idiosyncratic norms of best practice and (2) demand-induced supply (i.e., a patient desire for antibiotics influencing a clinician's prescribing behavior), which I then used to explore patterns in prescribing behavior with respect to these channels.

5.2 OVERVIEW

My objective was to model and explore changes in clinician idiosyncratic norms of best practice or in demand-induced supply. I think of these as durable, individual-level patterns (or habits) that arise through past education, training, experience, socializing forces, and other sources of (mis)information that give rise to a perceived benefit of antibiotics by patients and clinicians. I will use the terminology "subject-level latent behavioral factors" or more concisely "channels" to refer to these unobserved constructs. I took an exploratory approach to see if there were changes in these channels across time (i.e., years) or with respect to other covariates in the data.

A brief overview of my approach helps frame the methods section that follows. My modeling objective was to specify a model that accurately represents and parameterizes the latent behavioral factors (i.e., clinician idiosyncratic norms of best practice and demand-induced supply associated with the clinician-patient interaction). I wanted to specify a model such that parameters were identifiable in my data, which would then allow me to estimate and explore changes in these parameters. I drew on utility theory to specify a structural model for the decision to prescribe antibiotics (i.e., my structural model is a micro-economic model for decision making). Following this approach, my model includes two sets of high-dimensional utility terms, one is indexed by clinician $\{\theta_j\}$ and the other by patient nested within clinician $\{\lambda_{i(j)}\}$. These are intended to capture the subject-level latent behavioral factors (or channels) of interest. The patient is nested within clinician in my original model because demand-induced supply depends on the patient exerting influence on a clinician. The model also includes a utility term for the severity of disease (and an error term[5]) because antibiotics may be appropriate for more severe disease.

However, I have incomplete information due to limited knowledge and incomplete measurement, which I should model if I am to infer from patterns in the data. That is, I would like a model that accurately represents the data generating & measurement processes (DGPs). I proposed a measurement model that overlays my structural model and represents these behavioral factors as unobserved random variables, which I refer to as latent behavioral factors.

After specifying the structural + measurement model, I proposed two algorithms for estimating features[6] in my model: (1) a conditional logistic regression (CLR) algorithm, which failed to converge on my dataset, and (2) a mixed-effects logistic regression (MELR) algorithm based on a more parsimonious re-parameterization of my structural model (i.e., patient terms that were not nested within clinician $\{\lambda_i\}$, which assumes the patient's demand-induced supply is the same across all their clinicians). In contrast to CLR, MELR leveraged between-clinician variability to estimate patient-level effects. I provide a complete description in the methods sections that follow.

5.3 METHOD

5.3.1 Data Source

I used the MarketScan claims database from 2007-2012. I first used data from 2007, pre-GSAWs, to build a disease-severity model, which I then validated on a hold-out subset of the data (see Section 5.3.6). I used data from 2008-2012 to fit my latent-factor structural model, leveraging my disease-severity model to estimate and adjust for disease severity.

[5] The error term captures the remaining accumulation of variables that contribute to utility, which I choose not to separate out or don't know to separate out in the utility model - "known unknowns" and "unknown unknowns".
[6] I'll use the term features as an all-inclusive term that includes parameters, random effects, distributions, etc.

5.3.2 Discrete-choice latent-factor structural model

I used utility theory to develop a discrete-choice latent-factor structural model for antibiotic prescribing. My utility model has four terms: a baseline term for disease severity, terms (or behavioral factors) for clinician idiosyncratic norms of best practice and a patient's demand-induced supply, and an unobserved (to the econometrician) error term. The model is a discrete-choice structural model for antibiotic prescribing because the decision to prescribe antibiotics occurs at a utility threshold (without loss of generality set at ≥0 versus <0), which we observe according to the Survival distribution of the error term [99]. For analytic tractability, I modelled the error as a logistic distribution, which gives rise to a logit-link function. The model is a latent-factor structural model because the behavioral factors are unobserved (or latent) constructs, which I modelled as Gaussian random variables and will refer to as random effects when my focus is on the statistical model[7]. (see Equation 6)

In my MELR analysis, I treated clinician-level and patient-level factors as independent. However, an extension of my model would allow clinician-level and patient-level random effects to be correlated within a visit to better accommodate and study self-selection mechanisms (e.g., by high-demand patients into high-prescribing clinicians) (see Section 5.3.8).

[7] Throughout, I will tend to use the term "random effect" when my focus is on the statistical model, and "latent behavioral factor" when my focus is on their structural interpretation.

Equation 6: Discrete-choice latent-factor structural model for antibiotic prescribing.

Structural model of antibiotic prescribing

(i) Structural model:

$$U_{ijkt} = \beta_1 \cdot X_{ikt}^{ds} + \theta_{jk} + \lambda_{i(j)k} + \epsilon_{ijpt}^{*}$$

Indices:

i, j, k, t: patient i, seen by clinician j, in period $k \in \{\text{pre-GSAW}, \text{post-GSAW}\}$, at time t

Terms

X_{ikt}^{ds} : disease severity
θ_{jk} : clinician's idiosyncratic norm of best practice term
$\lambda_{i(j)k}$: patient's demand-induced supply term within a clinician
ϵ_{ijkt}^{*} : unobserved (to the econometrician) error term

(ii) Model features:

$$A_{ijkt} = I(U_{ijkt} \geq 0) = 1 \Rightarrow \text{patient is prescribed antibiotics}$$
$$\lambda_{i(j)k} = 0 \Rightarrow \text{patient has no influence}$$
$$\lambda_{i(j)k} > 0 \Rightarrow \text{patient has preferences that increase propensity to receive antibiotics}$$

Discrete-choice model (econometrician perspective)

$$\begin{aligned} P(A_{ijpt} = 1 | \theta, \lambda) = E(A_{ijkt}) &= S_{\epsilon}\{\mu + \beta_1 \cdot X_{ipt}^{ds} + \theta_{jk} + \lambda_{i(j)k}\} \\ &= g_{inv-logit}\{\mu + \beta_1 \cdot X_{ikt}^{ds} + \theta_{jk} + \lambda_{i(j)k}\} \end{aligned}$$

where:

$$\epsilon_{ijkt}^{*} = \mu - \epsilon_{ijkt}$$
$$\epsilon_{ijkt} \sim \text{Logistic}(location = 0, scale = 1)$$
S_{ϵ} is the survival function of ϵ_{ijkt}

Latent-factor distributions

$$\begin{pmatrix} \theta_{jk} \\ \lambda_{i(j)k} \end{pmatrix} \sim \text{Normal}\left(\begin{pmatrix} \mu_k^C \\ \mu_k^P \end{pmatrix}, \begin{pmatrix} \sigma_C(k) & \rho_k \\ \rho_k & \sigma_P(k) \end{pmatrix} \right)$$

On this first-pass Mixed-Effects Logistic Regression analysis, I constrain the latent-factor correlation: $\rho^k := 0$

5.3.3 Causal model

I extended my conceptual model (see Figure 3) into a causal model for antibiotic prescribing as a function of perceived utility (see Figure 8 for a pared down version, and Figure 29 for an extended version). I then used the causal model to motivate a surrogate for disease severity (see Section 5.3.6) and to motivate covariates for exploratory analyses (e.g., as potential explanatory variables of the latent factors).

Validating causal models is a deep endeavor, which I did not attempt to do in this exploratory work. And I do not believe my model captures (or correctly represents) all the processes shaping the decision to prescribe antibiotics. However, I consider it a reasonable first-pass attempt for exploratory work. I think of the latent behavioral factors as durable, individual-level patterns (or habits) that arise through past education, training, experience, socializing forces, and other sources of (mis)information that give rise to a perceived benefit of antibiotics by patients and clinicians, which is the frame of reference I used for constructing the causal model.

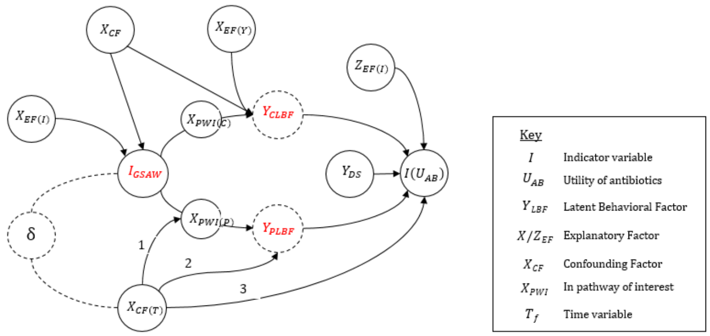


Figure 8: Causal directed acyclic graph (DAG) for the utility of antibiotics.

I also intend to leverage my causal model for future analyses. For example, I might consider a change in latent factors (Y_{CLBF}, Y_{PLBF}) in response to GSAW activities ($I_{GSAW\text{-}activities}$). I would want to adjust for components of the error that are correlated with both exposure to GSAW activities and latent behavioral factors. The GSAW is a low-frequency exposure event (i.e., annually) relative to the outcome observation events (i.e., ARTI visits), so the effect could be confounded by (1) other time-varying exposures or (2) other explanatory factors that influenced these latent behavioral factors in the past (e.g., past education or training) but change in distribution over the time course of the study (e.g., as the population changes in our dataset). There is the added complication that I do not observe these latent behavioral factors – I only observe repeated antibiotic prescribing opportunities on patients and clinicians (i.e., repetitions of the indicator of the utility of antibiotics: $I(U_{AB})$ in the causal diagram), which I use to estimate these latent factors.

According to this causal modeling paradigm, I would have to adjust for factors that are causally associated with (i.e., arrows linking into) both the predictor (i.e., the onset of GSAW activities: $I_{GSAW\text{-}activities}$) and the outcomes (i.e., latent behavioral factors Y_{CLBF}, Y_{PLBF} or their surrogate measures $I(U_{AB})$) because they could confound the association (e.g., X_{CF} is a confounding factor in the diagram). In addition, I would be well advised to adjust for explanatory factors that are causally associated with latent behavioral factors (or their surrogate measures), even if they are not associated with GSAW activities (e.g., $\mathrm{X}_{\mathrm{EF(Y)}}$ or $\mathrm{Z}_{\mathrm{EF(I)}}$). I would not adjust for explanatory factors that are only associated with the predictor (e.g., $X_{EF(I)}$) or are in the causal pathway of interest (e.g., X_{PWI}). This would explain away the effect of the GSAW on latent behavioral factors.

Finally, there may be explanatory factors of either pathway-of-interest variables or latent behavioral factors that, by chance, are also correlated in time with the exposure event (e.g., X_1 or $X_{2/3}$, respectively, in the diagram). We would have to adjust for these in the analysis (i.e., we would prefer not to adjust for X_1 in the analysis and we would prefer to adjust for $X_{2/3}$, according to the earlier discussion, but we would have to adjust for these to remove confounding by chance).

5.3.4 Derivation of latent-factor structural model (maximum utility over a choice set)

My utility model can be derived as the maximum utility over a choice set (i.e., antibiotics versus no antibiotics). *U's* in my model are conceptualized as the difference in utility of antibiotics versus no antibiotics. In this derivation, choice-specific covariates (such as the type of antibiotic), which does not apply for my analysis (but I have shown for completeness), have constant parameters across the choice set. Clinician-specific and patient-specific covariates, which do not vary across the choice set, must have (or are conceived as) having varying parameters for each choice. (See Equation 7)

5.3.5 Identifiability constraints

My model includes an error term and three structural terms (i.e., a disease severity term and latent behavioral factors for clinician idiosyncratic norms of best practice and a patient's demand-induced supply). I used observables in the MarketScan data to estimate the disease severity (see Section 5.3.6). However, the behavioral factors are unobserved and high-dimensional, which motivated a random effects model. Therefore, I cannot identify (or separate) their mean-model parameters from the error term, so these get bundled into the intercept. (see Equation 8)

In addition, to estimate[8] latent behavioral factors, I need repeated observations on both clinicians and on patients within clinicians[9]. Patients and clinicians are coupled together during the diagnostic-and-prescribing events, so I would need some crossing of factors (i.e., clinicians visiting multiple patients, and patients visiting multiple clinicians – this latter constraint applies

---

[8] Or, more accurately stated, predict these factors – i.e., these are modelled as random variables. I will use the terms "estimate" and "predict" interchangeably in this context.

[9] I relax this latter constraint in my revised model, so that I only need repeated operations on patients (and not necessarily within clinicians).

primarily to my MELR algorithm) to identify (or separate) their latent behavioral factors. These are implicit constraints imposed on the data by my model. Therefore, after exploring the MarketScan data, I limited the analysis to visits where patients with ≥ 3 ARTI cases in the year and providers with ≥ 25 cases in the year.

Equation 7: Derivation of latent-factor structural model (maximum utility over a choice set).

Structural model of antibiotic prescribing

(i) Utility of choices during the patient-clinician interaction:

$$U_{ijc} = \beta_1^c \cdot X_i + \beta_2^c \cdot X_j + \beta_3 \cdot X_{ijc} + \lambda_i^c + \theta_j^c + \epsilon_{ij}^c$$

Indices:

$c \in \{0\text{=no antibiotics, 1=antibiotics}\}$

i, j: patient i seen by clinician j

Terms:

X_i : measured patient-level covariates

X_j: measured clinician-level covariates

X_{ijc}: measured features of the choice (does not apply to my application, but shown for completeness)

λ_i^c : unmeasured patient-level covariates

θ_j^c : unmeasured clinician-level covariates

ϵ_{ij}^c : unobserved error term

(ii) Utility maximization (rational action):

$$U_{ij1} \geq U_{ij0} \Rightarrow \text{patient is prescribed antibiotics} \Rightarrow$$

$$\Delta U_{ij} = U_{ij1} - U_{ij0} \geq 0 \Rightarrow \text{patient is prescribed antibiotics}$$

where (by definition and relabeling):

$$\begin{aligned}
\Delta U_{ij} &= U_{ij1} - U_{ij0} \\
&= (\beta_1^1 \cdot X_i + \beta_2^1 \cdot X_j + \beta_3 \cdot X_{ij1} + \lambda_i^1 + \theta_j^1 + \epsilon_{ij}^1) - (\beta_1^0 \cdot X_i + \beta_2^0 \cdot X_j + \beta_3 \cdot X_{ij0} + \lambda_i^0 + \theta_j^0 + \epsilon_{ij}^0) \\
&= (\beta_1^1 - \beta_1^0) \cdot X_i + (\beta_2^1 - \beta_2^0) \cdot X_j + \beta_3 \cdot (X_{ij1} - X_{ij0}) + (\lambda_i^1 - \lambda_i^0) + (\theta_j^1 - \theta_j^0) + (\epsilon_{ij}^1 - \epsilon_{ij}^0) \\
&= \beta_1^* \cdot X_i + \beta_2^* \cdot X_j + \beta_3 \cdot \Delta X_{ij} + \lambda_i^* + \theta_j^* + \epsilon_{ij}^*
\end{aligned}$$

Discrete-choice model (econometrician perspective)

$$\begin{aligned}
P(A_{ijt} = I(\Delta U_{ij} \geq 0) = 1|\theta, \lambda) = P(\Delta U_{ij} \geq 0) &= S_{\epsilon^*}\{\beta_1^* \cdot X_i + \beta_2^* \cdot X_j + \beta_3 \cdot \Delta X_{ij} + \lambda_i^* + \theta_j^*\} \\
&= S_\epsilon\{\mu + \beta_1^* \cdot X_i + \beta_2^* \cdot X_j + \beta_3 \cdot \Delta X_{ij} + \lambda_i^* + \theta_j^*\} \\
&= g_{inv-logit}\{\mu + \beta_1^* \cdot X_i + \beta_2^* \cdot X_j + \beta_3 \cdot \Delta X_{ij} + \lambda_i^* + \theta_j^*\}
\end{aligned}$$

where (by assumptions and definitions):

S_ϵ^* is the survival function of ϵ_{ij}^*

$\epsilon_{ij}^* = \epsilon_{ij}^1 - \epsilon_{ij}^0 = (\mu^1 - \delta_{ij}^1) - (\mu^0 - \delta_{ij}^0) = (\mu^1 - \mu^0) - (\delta_{ij}^1 - \delta_{ij}^0) = \mu - \epsilon_{ij}$

$\delta_{ij}^{\{0,1\}} \sim GEV(\text{type I Gumbel}) \Rightarrow \epsilon_{ij} \sim \text{Logistic}(location = 0, scale = 1)$

The "provider ID" field in the MarketScan database is overloaded in the sense that it may encode (or identify) an individual clinician or, alternatively, an institution. However, the level of the provider ID (i.e., subject versus institutional) is not exposed in the database. Therefore, I also limited the maximum number of provider-level cases ≤ 1000 cases in the year to focus on (or concentrate for) clinicians instead of institutions. Throughout, when discussing analyses of the

MarketScan data, I will use the term “provider” instead of “clinician” because a small subset of provider IDs in my analysis may be institutional-level IDs.

Equation 8: Identifiability constraints.

Identifiability constraint

$$P(A_{ijkt} = 1|\theta, \lambda) = g_{inv-logit}\{\beta_0 + \beta_1 \cdot X^{ds}_{ikt} + \theta^*_{jk} + \lambda^*_{i(j)k}\}$$
$$\text{where: } \beta_0 = \mu + \mu^C_k + \mu^P_k$$

Identifiable latent-factor distributions

$$\begin{pmatrix} \lambda^*_{ik} \\ \theta^*_{jk} \end{pmatrix} \sim \text{Normal}\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_P(k) & \rho_k \\ \rho_k & \sigma_C(k) \end{pmatrix} \right)$$

5.3.6 Disease severity model: estimation and validation (MarketScan: 2007)

The MarketScan database does not include a measure of disease severity. Therefore, I constructed and validated a surrogate estimate on 2007 data, the year prior to the first GSAW event. I used stepwise backward-elimination logistic regression to model the baseline propensity for antibiotic prescribing as a function of covariates in the MarketScan database (with elimination criterion p-value > 0.001). I used the same-day (ICD9-coded) comorbid diseases and symptoms for ARTI. The number of categories is very large, so I first performed a factor-analytic decomposition (i.e., a principal component analysis) for each of these variables [100]. I included the 3 largest factors for each decomposition (i.e., I included 6 factors in total: 3 factors corresponding to the largest eigenvalues of co-morbid disease, and 3 factors corresponding to the largest eigenvalues of symptoms).

I also included patient, clinician, and health-system level covariates that are likely associated with antibiotic prescribing. I motivated these by extending my conceptual model (see Figure 3) into a causal model, which I discussed in greater depth above (see Section 5.3.3). Leveraging my causal model, I included the following covariates: diagnosis (acute bronchitis, acute pharyngitis, acute sinusitis, common cold or acute URTI (NOS)), sex, age (18-34, 35-44, 45-54, 55-64), plan type (comprehensive, EPO, HMO, POS, PPO, POS with capitation, CDHP, HDHP), occupational industry, state identifiers, the cumulative number of years of state-level funding, and the cumulative number of years since state-level funding terminated (for states that had received prior funding). I combined low-frequency categories into one group (i.e. if the frequency was < 5%).

I fit a (stepwise backward elimination) logistic regression model to a (50% subsample) training dataset from 2007. I estimated error rates (to predict antibiotic prescribing) on a (50% holdout) test dataset from 2007. I summarized the prediction error using the ROC curve and the area under curve (AUC) [101].

After estimating parameters based on 2007 data, I used my disease-severity model to predict antibiotic prescribing for ARTI cases in 2008-2012. I used the prediction as a surrogate for disease severity., which I first converted to the scale of the latent behavioral factors in my structural model (i.e., by using the logit-link function). (See Equation 9)

Equation 9: Logistic regression model for baseline propensity for antibiotic prescribing.

Disease-severity model

$$
\begin{aligned}
P(A_{ijt} = 1|\theta, \lambda) &= g_{\text{inv-logit}}\{\beta_0 + \beta_1 \cdot X_{it}^{ds}\} \\
&= g_{\text{inv-logit}}\{\beta_0 + \beta_1 \cdot Z_{ij}^{\text{comorbid factors}} + \beta_2 \cdot Z_{ij}^{\text{symptom factors}} + \beta_3 \cdot Z_{j}^{\text{clinician}} + \beta_4 \cdot Z_{i}^{\text{patient}} + \beta_5 \cdot Z_{j}^{\text{system}}\}
\end{aligned}
$$

X_{it}^{ds} : disease severity

$Z_{ij}^{\text{comorbid factors}}$: ICD9-based comorbidity factors

$Z_{ij}^{\text{symptom factors}}$: ICD9-based symptom factors

$Z_{j}^{\text{clinician}}$: clinician-level factors

Z_{i}^{patient} : patient-level factors

Z_{j}^{system} : health system-level factors

Process for model estimation and validation

1. Randomly split 2007 dataset, which is prior to the first year of GSW, into 50% training and test datasets.
2. Perform a factor decomposition on the training dataset of ICD9-based comorbidities and symptoms - retain the top 3 factors ranked by eigenvalues.
3. Fit logistic regression model to the 50% training sample from 2007, the year prior to the first GSW.
4. Use factor loadings to compute the top 3 factors for the hold-out test dataset.
5. Make out-of-sample predictions for antibiotic Rx in the 50% hold-out test dataset.
6. Use predictions to estimate false positive (FP) and false negative (FN) error rates and summarize via ROC curves and the AUC.
7. Low FP and FN error rates support the prediction model.

5.3.7 Conditional Logistic Regression

I attempted to use conditional logistic regression (CLR) with random effects to estimate patient-level effects, but CLR failed to converge on my dataset. However, I present the CLR method for contrast to mixed-effects logistic regression (MELR), which was my final analytic approach (see Section 5.3.8). CLR conditions away clinician-specific information and focuses on within-clinician variability to estimate patient-level effects. Using the model in Equation 6 as my reference, there are two levels of conditioning. I condition on clinician-level random effects (i.e., I condition on the set of clinicians observed in my dataset and treat them as fixed effects in this stage). In the second level of conditioning, I condition on sufficient statistics for the clinician-level fixed effects, which results in a CLR model that retains within-clinician covariates (i.e., the severity of disease and patient-level random effects)[10] [102]. I then mix the conditional distribution over the patient-level random effects and use (partial) maximum likelihood to estimate parameters in the model. Finally, I estimate patient-level random effects (or, in structural terms, their latent behavioral factors) using the Best Linear Unbiased Predictors (BLUPs) [103-105].

In the linear setting, if patient-level and provider-level effects are correlated, it is appropriate to treat provider-level effects as fixed effects and focus on within-provider variability to avoid biased estimates. In the non-linear setting, the parallel is to condition on the provider-level sufficient statistic. In our setting, N (i.e., the number of patients) could be expected to get large, but not T (i.e., the number of repeated measures on a patient), so it is also necessary to treat the patient-level effects as a random effect for consistency of estimates when fitting the CLR model (i.e., in the first stage).

In the second stage, I estimate clinician-level random effects using maximum likelihood and BLUPs. However, I condition on patient-level random effects (i.e., condition on the set of patients and treat them as fixed effects in this stage of the algorithm) and plug-in their BLUPs (rather than conditioning on sufficient statistics for the patient-level fixed effects). (See Equation 10)

---

[10] Conditioning on the sufficient statistic is the "conditional" in conditional logistic regression.

However, if there is self-selection by patients into like-minded clinicians, and the clinician-level and patient-level random effects are highly correlated by self-selection, then there might not be a sufficient amount of variability in prescribing within a clinician-patient pair to separate their subject-level effects by CLR (or by MELR, see the next section).

Equation 10: Conditional logistic regression model and algorithm.

Conditional logitistic regression (with latent factors)

Step 1: condition on $\{clinician's\ j\}$ random effect (i.e., treat as a fixed effect) and clinician-level counts (i.e., sufficient statistic to eliminate clinician-level fixed effects):

$$P\left(\boldsymbol{A}_{\boldsymbol{I_j jk}} = \{a_{\cdot jk}\} \mid \boldsymbol{\lambda}_{\boldsymbol{I_j k}}, \sum_{i=i_j}^{I_j} A_{ijk} = k_{jk}\right) = \frac{exp\left(\sum_{i=i_j}^{I_j} a_{ijk} \cdot \left(\beta_1 \cdot X_{ikt}^{ds} + \lambda_{ik}^{*}\right)\right)}{\sum_{\boldsymbol{d_{jk}} \in S_{jk}} exp\left(\sum_{i=i_j}^{I_j} d_{ijk} \cdot \left(\beta_1 \cdot X_{ikt}^{ds} + \lambda_{ik}^{*}\right)\right)}$$

Step 2: condition on $\{paiient's\ i\}$ random effect and plug-in estimates from step 1:

$$P(A_{ijkt} = 1 | \theta, \lambda^{*} = \hat{\lambda}^{BLUP}) = g_{inv-logit}\{\beta_0 + \beta_1 \cdot X_{ikt}^{ds} + \theta_{jk}^{*} + \hat{\lambda}_{ik}^{BLUP}\}$$

5.3.8 Mixed-effects logistic regression

The previously discussed CLR algorithm failed to converge, so I also considered a more parsimonious structural model with patient-indexed terms that are not nested within clinician (i.e., $\{\lambda_i\}$ versus $\{\lambda_{i(j)}\}$). I estimated features using a mixed-effects logistic regression (MELR) model (i.e., fixed effects for disease severity and random effects for the latent behavioral factors) [106]. This assume a patient's demand-induced supply that is the same across all their clinicians (i.e., they are equally influential on all clinicians). I estimated subject-level random effects using the BLUPs, and then explored for a change in these channels with respect to time (i.e., years) or with respect to observable covariates in the MarketScan database. CLR conditions away between-clinician information to estimate the patient-level random effects. MELR leverages this information. However, the consequence is there is more statistical dependence between the subject-level estimates, by construction (i.e., the estimates of clinician-level and patient-level effects are necessarily positively correlated, because they are averages of the same or overlapping data – in some sense). (See Equation 11)

I attempted to explore self-selection mechanisms (e.g., by patients into like-minded clinicians) by visualizing the correlation between clinician-level and patient-level random effects that co-occur during (or are coupled by) a visit even though I modeled them as independent[11]. However, as discussed with reference to CLR, if there is self-selection by patients into like-minded clinicians, and the random effects are highly correlated by self-selection, then there might not be a sufficient amount of variability in prescribing within a clinician-patient pair to separate their subject-level effects. MELR would seem to compound this problem, because I am drawing on more overlapping data (as compared to CLR) to estimate the subject-level effects, so the clinician-level and patient-level estimates are statistically dependent (i.e., positively correlated) by construction.

5.3.9 Finite mixture modeling

The distribution of estimates (i.e., BLUPs) for patient-level and provider-level random effects appeared multi-model (even though I modelled them as a Gaussian random variable). Therefore, as a final stage of my analysis, I fit finite mixture models (FMM) to estimate the size and location of these modes (or clusters). I used maximum likelihood to estimate the FMM parameters (e.g., the proportion and mean of each cluster) and the BIC criterion to select the number of clusters in the mixture [107]. I explored for a shift in location and size of each cluster with respect to time and covariates.

Prior to fitting the FMM, to facilitate interpretation, I first projected my estimates of the subject-level random effects onto the probability-of-antibiotics scale (around the population average). I tried clustering assuming a Weibull-distributed FMM and, alternatively, a Beta-distributed FMM. These better accommodate a 0-1 support compared to a Gaussian FMM.

[11] On first pass, I model these as independent, but linked them based on co-occurrence during a visit. In future analyses, I plan to extend my DPG model to allow for (and estimate) parameters that capture the correlation.

Equation 11: Parsimonious model for antibiotic prescribing.

Revised structural model of antibiotic prescribing

(i) Structural model:

$$U_{ijkt} = \beta_1 \cdot X^{ds}_{ikt} + \theta_{jk} + \lambda_{ik} + \epsilon^*_{ijkt}$$

Indices:

i, j, k, t: patient i, seen by clinician j, in period $k \in$ {time period; e.g., year}, at time t

Terms

X^{ds}_{ikt} : disease severity
θ_{jk} : clinician's idiosyncratic norm of best practice term
λ_{ik} : patient's demand-induced supply term (not within a clinician)
ϵ^*_{ijkt} : unobserved (to the econometrician) error term

(ii) Model features:

$$A_{ijkt} = I(U_{ijkt} \geq 0) = 1 \Rightarrow \text{patient is prescribed antibiotics}$$
$$\lambda_{ik} = 0 \Rightarrow \text{patient has no influence}$$
$$\lambda_{ik} > 0 \Rightarrow \text{patient has preferences that increase propensity to receive antibiotics}$$

Discrete-choice model (econometrician perspective)

$$\begin{aligned} P(A_{ijpt} = 1|\theta, \lambda) = E(A_{ijkt}) &= S_\epsilon\{\mu + \beta_1 \cdot X^{ds}_{ipt} + \theta_{jk} + \lambda_{ik}\} \\ &= g_{inv-logit}\{\mu + \beta_1 \cdot X^{ds}_{ikt} + \theta_{jk} + \lambda_{ik}\} \end{aligned}$$

where:

$$\epsilon^*_{ijkt} = \mu - \epsilon_{ijkt}$$
$$\epsilon_{ijkt} \sim \text{Logistic}(location = 0, scale = 1)$$
S_ϵ is the survival function of ϵ_{ijkt}

Identifiability constraints

$$P(A_{ijkt} = 1|\theta, \lambda) = g_{inv-logit}\{\beta_0 + \beta_1 \cdot X^{ds}_{ikt} + \theta^*_{jk} + \lambda^*_{ik}\}$$
$$\text{where: } \beta_0 = \mu + \mu^C_k + \mu^P_k$$

Identifiable latent-factor distributions

$$\begin{pmatrix} \theta^*_{jk} \\ \lambda^*_{ik} \end{pmatrix} \sim \text{Normal}\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_C(k) & \rho_k \\ \rho_k & \sigma_P(k) \end{pmatrix} \right)$$

On this first-pass analysis, I constrain the latent-factor correlation: $\rho^k := 0$

5.3.10 Bayesian approach

As a second alternative, I used a Bayesian approach to estimate features in my latent-factor structural model. Bayesian methods include prior information (i.e., prior distributions) and inference is based on the posterior distribution. The Bayesian paradigm combines study data with prior information to inform statistical inference. A benefit of a Bayesian approach is that algorithms are general purpose and easier to extend (in an operational sense) to non-linear and hierarchical models. However, the trade-off is that the model must be specified to ensure that prior information is appropriately weighted in relation to the study data, and it is necessary to verify adequate sampling from the posterior distribution(s). I used non-informative or weakly-informative priors to minimize the weight attributed to prior information (see Equation 12). And I used Markov-Chain Monti Carlo (MCMC) methods to draw samples from posterior distributions and the Raftery-Lewis test and diagnostic plots to check for convergence and adequate mixing of MCMC chains [108][12]. I used medians of the posterior to estimate latent-factor random effects. Bayesian methods are computational intensive, so I explored this analysis on a subset of the data to check (or support) my mixed-effects modeling approach.

Equation 12: Bayesian (non-informative priors).

$$\beta_{\{0,1\}} \sim \text{Normal}(0, 1e^6)$$
$$\sigma_{\{C,P\}}(k) \sim \text{uniform}(0, 5)$$
$$\rho_k \sim \text{uniform}(-1, 1)$$

All analyses were performed in SAS 9.3 using PROCS: GLIMMIX, PHREG, MCMC, FACTOR, and FMM.

5.4 RESULTS

5.4.1 Baseline disease severity model: estimation and validation (MarketScan: 2007)

My surrogate model for disease severity (i.e., the probability of antibiotics) produced an area under the curve (AUC) of 0.72 on the holdout test dataset (see Figure 9). ICD9-coded comorbidities and symptoms were not well captured. Although they were associated with antibiotic prescribing, they were dropped from the final model by stepwise backward-elimination (i.e., p-value ≤ 0.001 for inclusion). The final covariates included in my model are provided in the Appendix (see Table 37).

[12] Specifically, I used SAS Proc MCMC, which implements a Metropolis-Hastings algorithm to implement the random walk and sample from the posterior distribution.

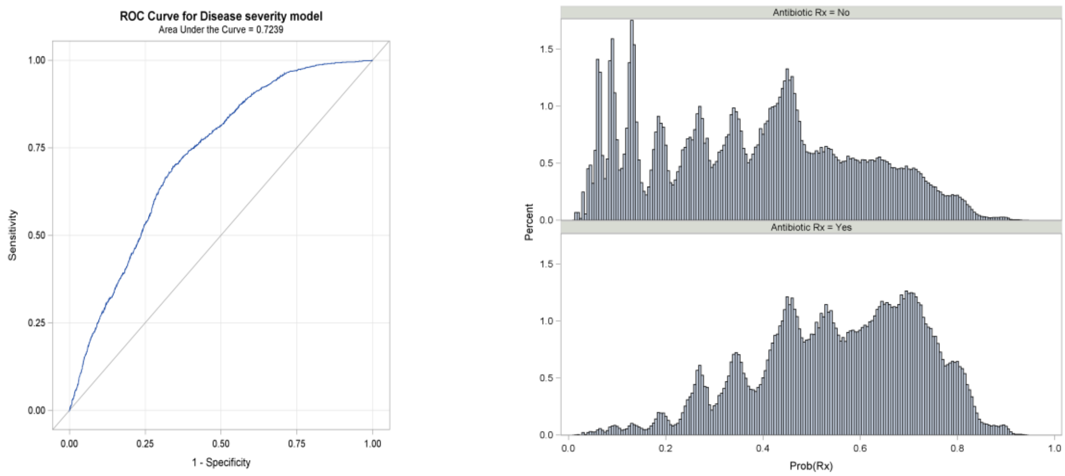


Figure 9: ROC curve and disease-severity predictions (i.e., Prob(Rx)) stratified by truth.
(Marketscan, holdout validation dataset: 2007)

5.4.2 Descriptive statistics: (MarketScan: 2008-2012)

Approximately 8M (35%) of the 23M ARTI cases had a recorded provider ID (see Appendix, Table 34). Of these, there were 52K providers (or, more accurately, provider-years) with a case load ≥ 25 and ≤ 1000 (see Table 13 and Appendix, Table 35). These providers treated a total of 5M ARTI cases (i.e., on an average ~100 ARTI cases per year). The antibiotic prescribing rates did not vary by case load (57-58%).

Table 13: Providers stratified by case-load counts in a year.

Case load*	Provider-years		Cases		Rx rates
	N	%	N	%	
Provider case load >= 25 and =< 1000 (in a year)					
25	1713	3.3	42825	1	0.57
(25,100]	37483	72	1838070	37	0.58
(100,1000]	12874	24.7	3035732	62	0.58
All	52070	100	4916627	100	0.58

Table 14: Patients stratified by case-burden counts in the year.

Cases*	Patient-years		Providers**				Cases	
			1	2	3	4		
	N	%	%				N	%
Patient case burden >= 3 (in a year)								
3	88357	93	68	27	5	.	265071	91
4	6059	6	64	27	7	2	24236	8
5	149	0	62	30	9	.	745	0
All	94565	100	68	27	6	0	290052	100

There were 95K patients (or, more accurately, patient-years) with a case burden ≥ 3 (see Table 14 and Appendix, Table 36). These patients were treated for total of 290K ARTI cases (i.e., an average of ~3 cases per year). Thirty-three percent of these patients saw more than one provider and patients had at most 5 ARTI cases in a year.

I plotted histograms of antibiotic prescribing rates for the 52K providers and for the 95K patients, along with their average predicted prescribing rates and subject-level residuals (see Figure 10 and Figure 11, respectively). Provider-level residuals appear to have a Gaussian distribution. Patient-level residuals appear to have 3 modes. In part, this is attributable to the granularity of possible (observed) prescribing rates because patients had at most 5 cases in a year. The residuals suggest heterogeneity in both prescribing and demand, which I discuss in more detail in the discussion section.

My final analysis dataset focused on ARTI cases where both the provider had ≥ 25 ARTI cases in a year and the patient had ≥ 3 cases in a year, which further reduced the analysis dataset to 190K cases (see Table 15 and Table 16). I plotted the bivariate density (or, rather, a contour plot) of these 190K cases by their provider-level and patient-level residuals (see Figure 11). The residuals provide insight as to the information in the data for separating and estimating subject-level random effects by MELR. The subject-level residuals are highly correlated and cluster into 3 modes. There is not a lot variability within horizontal and vertical slices (i.e., holding the provider-level and patient-level residuals fixed, respectively), which suggests there is not an abundance of independent information to separate and estimate subject-level random effects using MELR.

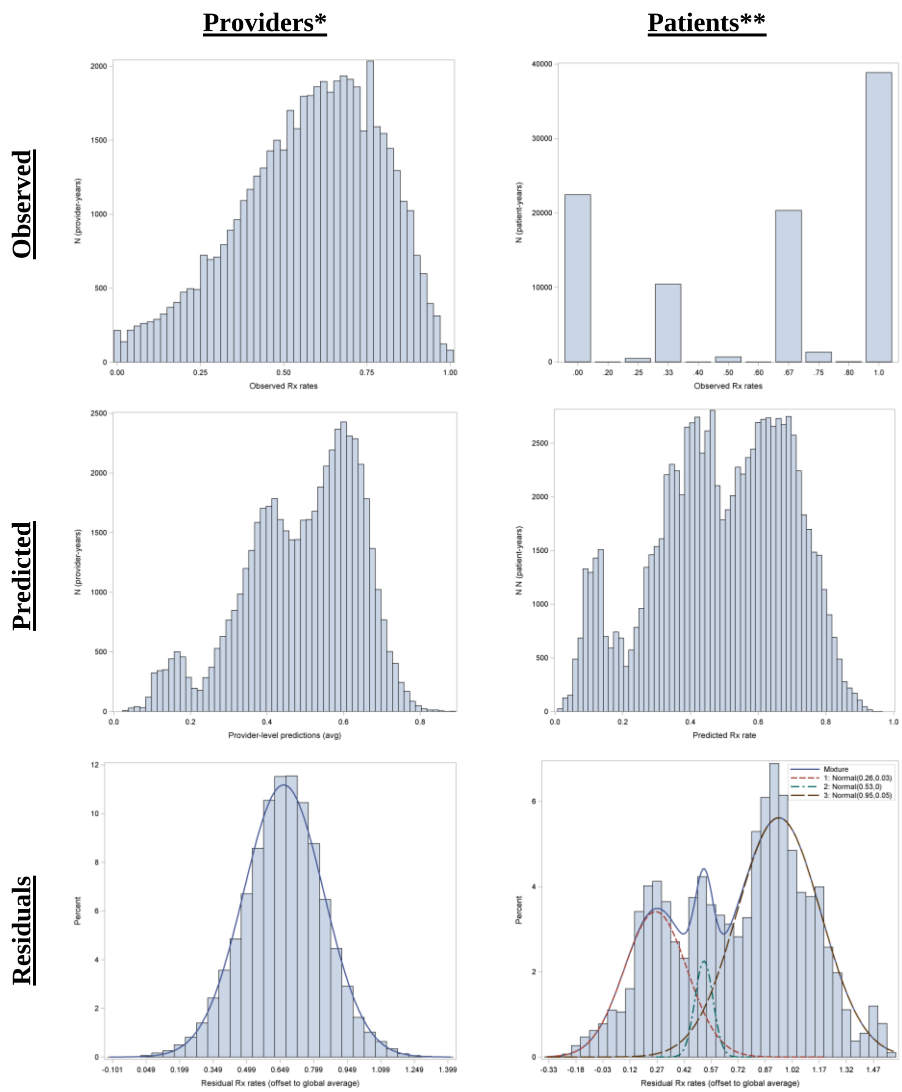


Figure 10: Histograms of subject-level antibiotic Rx rates.
*provider case load ≥ 25 and ≤ 1000; **patient case burden ≥ 3

Table 15: Providers stratified by case-load counts in a year (final analysis dataset).

Case load*	Provider-years		Cases		Rx rates
	N	%	N	%	
Provider case load >= 25 and =< 1000 **AND** Patient case burden >= 3 (in a year)					
1	3922	12.6	3922	2	0.59
(1,25]	26367	84.7	157532	82	0.61
(25,100]	825	2.7	30878	16	0.61
(100,1000]	1	0	110	0	0.41
All	31115	100	192442	100	0.61

Table 16: Patients stratified by case-burden counts in a year (final analysis dataset).

Cases*	Patient-years		Providers**				Cases	
			1	2	3	4		
	N	%	%				N	%
Provider case load >25 and =< 1000 AND Patient case burdern >= 3 (in a year)								
1	5253	8	100	.	.	.	5253	3
2	7033	10	80	20	.	.	14066	7
3	52748	77	77	19	4	.	158244	82
4	3606	5	75	19	4	1	14424	7
5	91	0	68	27	4	.	455	0
All	68731	100	79	18	3	0	192442	100

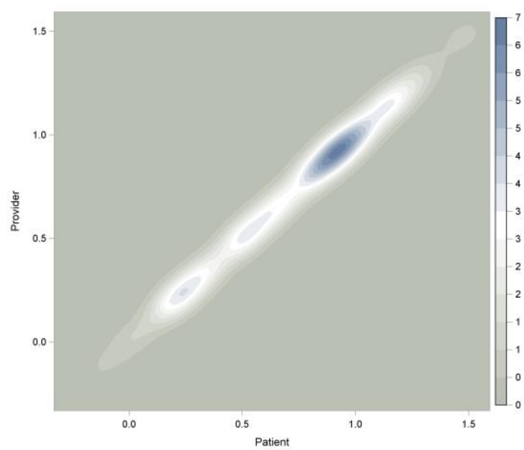


Figure 11: Bivariate density of cases by their subject-level residuals.
Note: provider case load ≥ 25 cases and ≤ 1000 cases **AND** patient case burden ≥ 3 in a year.

5.4.3 Mixed-effects analysis

5.4.3.1 Overall analysis (across all years and covariates).

The CLR algorithm failed to converge. MELR, by contrast, converged onto a distribution of random effect estimates that have 3-4 modes clustered around prescribing rates of 0.35, 0.55, 0.75, and 0.90 for both the provider-level random effects and the patient-level random effects (see Figure 12). I plotted the bivariate random effects density of cases (i.e., by their provider-level and patient-level random effect estimates). The subject-level random effects are correlated with 3 modes (see Figure 13), which appears similar to the density based on residuals (recall Figure 11). I would anticipate a high-level of correlation because only 21% of these patients visited more than one provider (recall Table 16), so it is difficult to separate their random effects. I revisit this topic in the discussion section. My preliminary Bayesian analysis and posterior samples looked similar in distribution (data not shown).

Provider Patient

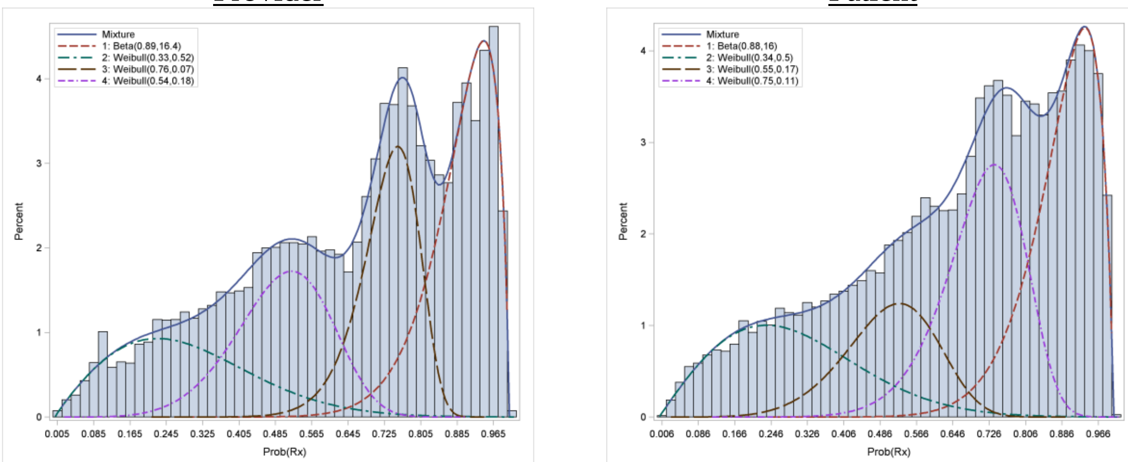


Figure 12: Histograms of subject-level random effects and mixture models.

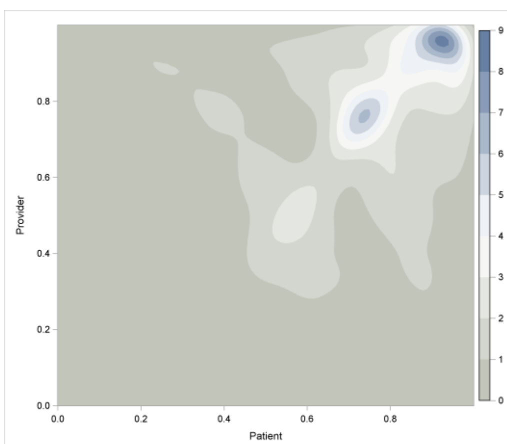


Figure 13: Bivariate random-effects density of cases.
Note: cases where provider ≥ 25 cases and ≤ 1000 cases per year **AND** patient ≥ 3 cases per year.

5.4.3.2 Exploratory analysis stratified by year.

I explored the distribution of provider-level and patient-level random effects, stratified with respect to year. There appears to be a change in the distributions across years, with the main shift occurring between 2009 and 2010 (see Figure 14). Visually, there appears to be shift into the cluster centered around 0.75 from, perhaps, both low and high clusters. This was somewhat supported by the clustering analysis (see Table 17).

Providers Patients

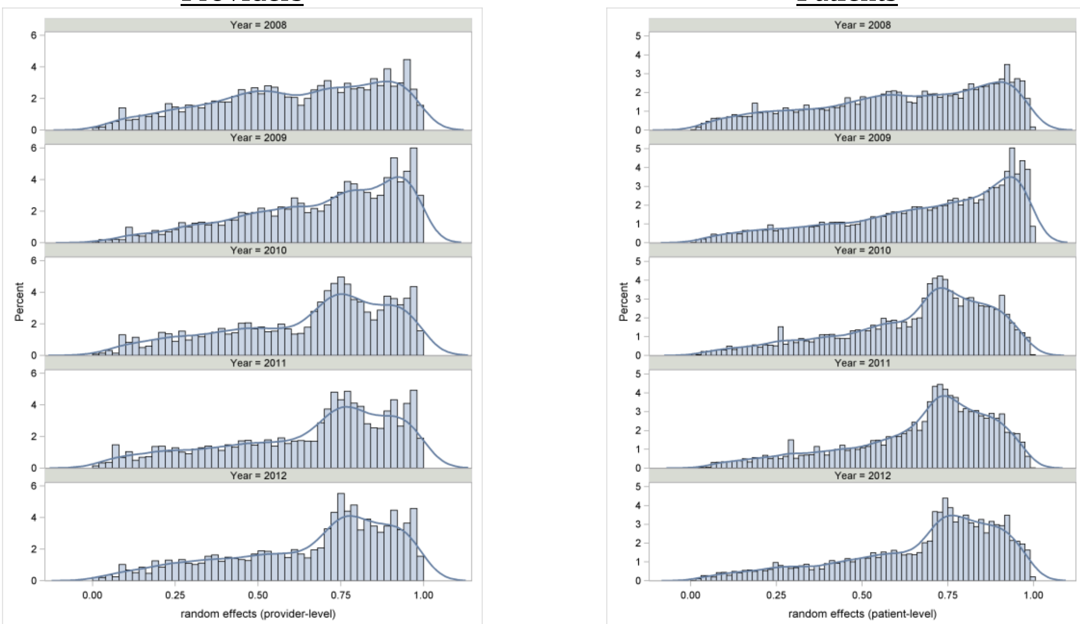


Figure 14: Histogram of subject-level random effects stratified by year.

This pattern could be attributable to contemporary socio-economic changes (e.g., the great recession) or changes to the health care marketplace (e.g., the affordable care act). However, during this period (i.e., from 2009 to 2010), there was also a sudden, large and sustained drop (~60-65%) in year-over-year ARTI cases because of missing provider IDs, with a big jump in antibiotic prescribing rates from ~55% to ~70% (see Table 18). However, for ARTI cases overall (i.e., cases with + without recorded provider IDs), the year-over-year case count and associated antibiotic prescribing rates were relatively stable or only slightly increasing (see Figure 24, Figure 26, and Table 28). These trends may be an artifact of the data collection, but I could not find documentation on the MarketScan database.

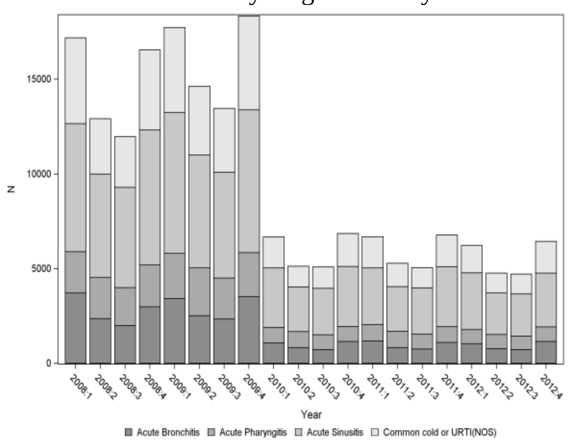
Table 17: Mixture model parameters combined and by year.

Year	Parameter	Patient Component 1	2	3	4	Global*	Provider Component 1	2	3	4	Global*
All	Mean	0.34	0.55	0.75	0.88	0.68	0.33	0.54	0.76	0.89	0.68
	Proportion	0.20	0.16	0.29	0.35		0.18	0.23	0.25	0.35	
2008	Mean	0.30	0.64		0.86	0.65	0.21	0.54		0.81	0.64
	Proportion	0.22	0.41		0.37		0.09	0.42		0.49	
2009	Mean	0.38	0.72		0.91	0.71	0.51	0.80		0.96	0.74
	Proportion	0.23	0.38		0.39		0.36	0.42		0.23	
2010	Mean	0.46		0.81		0.71	0.47	0.75		0.89	0.67
	Proportion	0.28		0.72			0.42	0.28		0.30	
2011	Mean	0.45		0.81		0.72	0.44	0.78		0.95	0.69
	Proportion	0.25		0.75			0.37	0.40		0.23	
2012	Mean	0.47		0.84		0.73	0.47	0.78		0.94	0.70
	Proportion	0.30		0.70			0.38	0.37		0.25	

* FMM model-based global mean

Table 18: Case counts with recorded provider IDs and satisifying selection criteria.

Case counts by diagnosis and year



Case counts and Rx rates by diagnosis and year

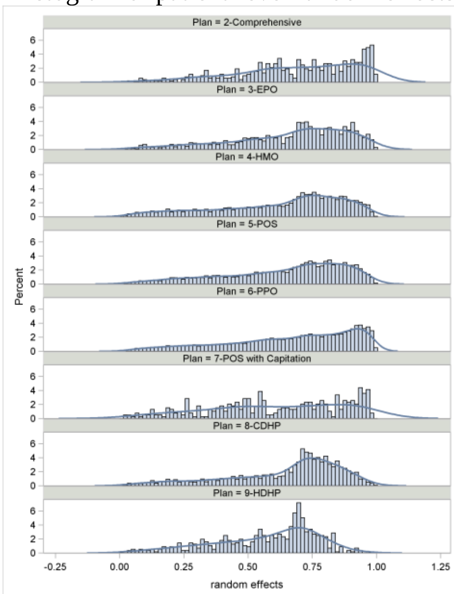
Diagnosis		Year 2008	2009	2010	2011	2012	All
Acute Bronchitis	N	11072	11784	3793	3867	3694	34210
	Col %	19	18	16	16	17	18
	Rx rate	0.55	0.59	0.73	0.75	0.74	0.63
Acute Pharyngitis	N	8524	9389	3234	3336	2973	27456
	Col %	15	15	14	14	13	14
	Rx rate	0.51	0.55	0.62	0.64	0.64	0.57
Acute Sinusitis	N	24667	26528	11120	10977	10244	83536
	Col %	42	41	47	46	46	43
	Rx rate	0.58	0.63	0.76	0.78	0.75	0.67
Common cold or URTI(NOS)	N	14361	16441	5595	5612	5231	47240
	Col %	24	26	24	24	24	25
	Rx rate	0.45	0.48	0.61	0.64	0.62	0.52
All	N	58624	64142	23742	23792	22142	192442
	Row %	30	33	12	12	12	100
	Rx rate	0.53	0.57	0.7	0.73	0.71	0.61

5.4.3.3 Exploratory analysis stratified by plan type (and other covariates)

I explored the distribution of provider-level and patient-level random effects, stratified with respect provider-level and patient-level covariates, respectively. Across all other potentially explanatory covariates, the only noticeable change was a relatively small change over time in the distribution of patients across plan type, with higher-deductible plans (CDHP and HDHP) having relatively higher antibiotic prescribing rates and less heterogeneity (see Table 19). This might make sense if patients are already paying the deductible (for the visit) they may be inclined to pressure their provider for antibiotics. Additional plots of random effect distributions, stratified by other provider-level and patient-level covariates are provided in the Appendix (see Section A.3.2).

Table 19: Stratification by plan type.

Histogram of patient-level random effects



Case counts and Rx rates by year

Plan		Year					All
		2008	2009	2010	2011	2012	
Comprehensive	N	521	474	123	130	139	1387
	Col %	0.9	0.7	0.5	0.5	0.6	0.7
	Rx rate	0.51	0.58	0.65	0.53	0.83	0.58
EPO	N	585	547	1003	993	376	3504
	Col %	1	0.9	4.2	4.2	1.7	1.8
	Rx rate	0.62	0.69	0.79	0.81	0.79	0.75
HMO	N	8992	9355	4423	4306	3287	30363
	Col %	15	15	19	18	15	16
	Rx rate	0.64	0.68	0.76	0.76	0.77	0.7
POS	N	7862	7548	3670	2685	2530	24295
	Col %	13	12	15	11	11	13
	Rx rate	0.5	0.5	0.83	0.83	0.83	0.62
PPO	N	39249	44548	13084	13530	13595	124006
	Col %	67	69	55	57	61	64
	Rx rate	0.51	0.56	0.63	0.67	0.65	0.57
POS with Capitation	N	371	351	86	112	89	1009
	Col %	0.6	0.5	0.4	0.5	0.4	0.5
	Rx rate	0.39	0.35	0.56	0.66	0.62	0.44
CDHP	N	907	1093	1090	1639	1713	6442
	Col %	1.5	1.7	4.6	6.9	7.7	3.3
	Rx rate	0.69	0.72	0.79	0.83	0.82	0.79
HDHP	N	137	226	263	397	413	1436
	Col %	0.2	0.4	1.1	1.7	1.9	0.7
	Rx rate	0.71	0.76	0.79	0.79	0.81	0.78
All	N	58624	64142	23742	23792	22142	192442
	Row %	30	33	12	12	12	100
	Rx rate	0.53	0.57	0.70	0.73	0.71	0.61

5.4.3.4 Exploratory analysis stratified by number of (provider) switches.

I explored the bivariate random effects density of cases, stratified by the number of switches between providers prior to (and including) the case (see Figure 15). By the forth switch to a new provider, a new mode emerges. A first-pass interpretation is that low-demand patients ended up switching into high-prescribing providers. I would have anticipated the opposite. That is, low-demand patients switching into low-prescribing providers, and high-demand patients switching into high-prescribing clinicians over time. However, I think the pattern reflects a lack of independence between provider-level and patient-level random effect estimates, by construction. For example, a patient may appear as low-demand by their fourth switch because, rather, their previous providers were low-prescribing. Therefore, they were not prescribed antibiotics during their first 3 visits, and the patient would appear as low-demand. This again supports the point that the patient-level effect was hard to tease out from the provider-level effect (in this data).

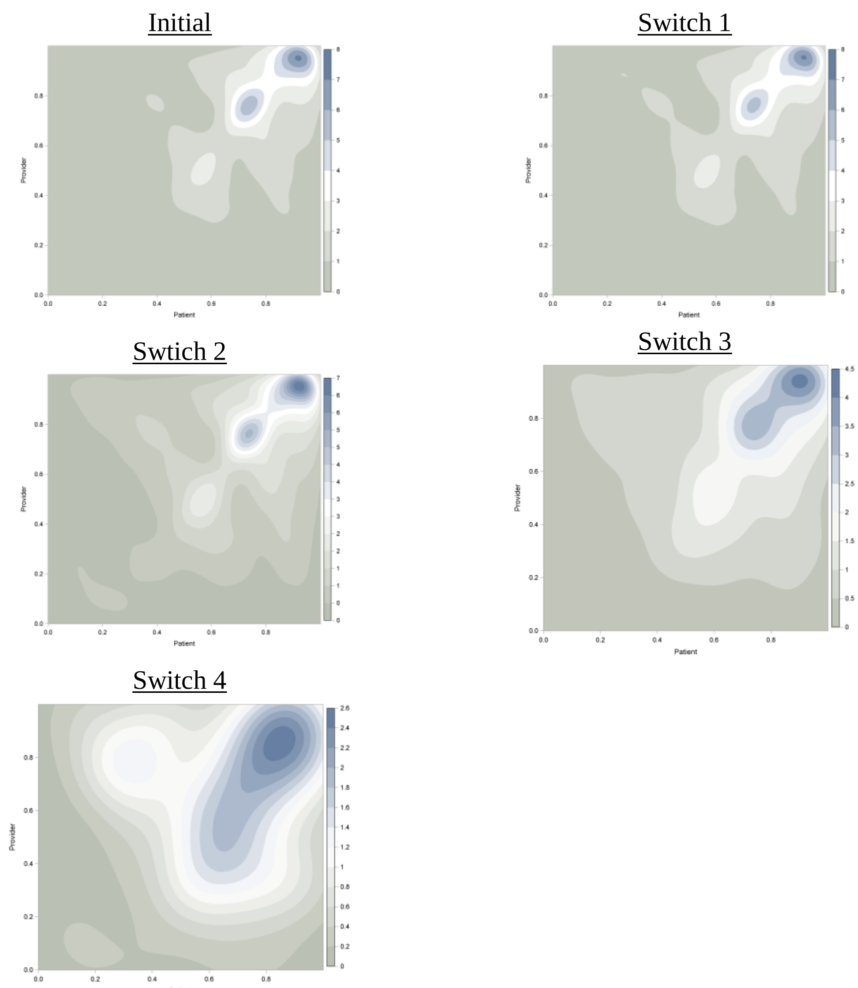


Figure 15: Bivariate random-effects density of cases, stratified by the number of provider switches (prior to and including the case).

5.5 Discussion

5.5.1 Overview

My goal was to explore clinician-level and patient-level latent behavioral factors, which I also refer to as channel effects. I operationalized these concepts as clinician-level and patient-level random effects, and then attempted to use conditional logistic regression (CLR) to estimate the patient-level effects from within-clinician information (i.e., controlling for the clinician-level effect by adjusting for the sufficient statistic). However, CLR did not adequately converge. As an alternative, I specified a more parsimonious mixed-effects logistic regression (MELR) model that assumed the patient-induced demand was the same across a patient's clinicians, which seems less likely. The advantage is that the MELR model leverages more information in the data (i.e., between-clinician information or variability) to estimate patient-level effects. However, the disadvantage is that estimates of the clinician-level and patient-level effects are more statistically dependent (i.e., positively correlated), by construction.

5.5.2 Information and estimates of patient-level and clinician-level effects

To better understand the analyses (and shortcomings), it is worth a deeper discussion on the sources of information in the data. At a conceptual level, variability in prescribing that travels with the clinician would be supportive of a clinician-level effect (after accounting for patient-level effects). And similarly, variability that travels with a patient would be supportive of patient-level effects. A more operational expression of these concepts:

1. (a) Variability in prescribing across clinicians, but (b) not within a clinician would be suggestive of a clinician-level effect (unless clinicians had differences in their patients, see point 3, which addresses this).
2. (a) Variability across patients, but (b) not within a patient would be suggestive of a patient-level effect (unless patients had differences in their clinicians, see point 4).
3. For a specific clinician, (a) variability in prescribing across their patients, but (b) not within repeated visits from a patient would be suggestive of a patient-level effect.
4. For a specific patient, (a) variability in prescribing across their clinicians, but (b) not within repeated visits to a specific clinician would be suggestive of a clinician-level effect.

I attempted to visualize some of these concepts in the data by plotting residuals – or unexplained variation after accounting for known sources of variability (i.e., after adjusting for an estimate of the case-level probability of antibiotics, which I used as a surrogate for disease severity). I had repeated measures on a subset of clinicians[13] and patients. These allowed me to estimate their subject-level prescribing rates and their residuals (from their subject-level predicted prescribing rates). For example, the histograms of subject-level residuals (recall Figure 10) visualizes concepts (1a) and (2a) in the data, which reveal unexplained variation or heterogeneity in prescribing that suggests there are channel effects. Though not provided, a histogram of case-level residuals within

[13] Or, more accurately, 'providers' when referring to the MarketScan data.

clinicians would visualize concept (1b). And a plot of these case-level residuals for clinicians versus their subject-level residuals (i.e., x-y plots of residuals for x=(1a) versus y=(1b)) would visualize point (1), overall. However, I did not provide case-level residual plots because these tend to be too granular and less visually informative for binary data.

An obvious, but important point: outcome observations (i.e., antibiotic prescribing) on patients and clinicians are coupled together[14]. Therefore, the clinician-level and patient-level residuals cannot be statistically independent, by construction. They are not completely dependent – i.e., decoupling occurs because clinicians see multiple patients and patients visit multiple clinicians. I would have to take additional steps to visualize 'independent' residual information in the data for these subject-level effects. For example, I could have constructed patient-level residuals within a clinician (i.e., that are adjusted for clinician-level effects). I could then use these to visualize concept (3) in the data. These would speak to information in the data that is leveraged by CLR, which estimates patient-level effects from within-clinician variability[15]. CLR uses statistically independent aspects of the data to separate and estimate patient-level effects from clinician-level effects. However, CLR did not adequately converge on my dataset, so I did not pursue this visual analysis[16].

Instead, I presented the bivariate density of cases according to their clinician-level and patient-level residuals (see Figure 11), which are more relevant to the MELR model because it does not exclusively focus on within-clinician variability to estimate patient-level effects. MELR estimates

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[14] A thought experiment highlights the point. We could imagine two separate experiments. One evaluating clinician-level effects, with complete knowledge, measurement, and adjustment for patient-level covariates. The other evaluating patient-level effects, with complete knowledge, measurement, and adjustment for clinician-level covariates. In this context, the variability in clinician-level residuals relative to case-level residuals, would reveal if there was a clinician-level effect (or lack thereof) overall. And analyses of clinician-level residuals in an unsupervised sense[14] (e.g., clustering) or in a supervised sense (e.g., with respect to time or other covariates) would reveal if there were dominant latent subgroups or covariates that are driving these effects, respectively. And similarly, for patients. However, I did not have two separate experiments, or an oracle to provide complete knowledge on confounding covariates, so I had to build these estimates leveraging the same data.

[15] And similarly, there are clinician-level residuals within a patient corresponding to concept (4), although these are unlikely to be very informative because of the limited number of clinicians within a patient (recall Table 14).

[16] In fact, I did a deeper analysis of the residuals that adjusted for competing subject-level effects. I decided not to provide them in this monograph because, as we might expect, they revealed limited information within-clinician information and the plots were too distracting – some pictures do not say 1000 words!

patient-level effects simultaneous with (and adjusted for) clinician-level effects, so it uses both between and within-clinician variability to inform patient-level estimates. Another interpretation contrasting CLR versus MELR:

(i) The CLR model looks at how much a patient outcome deviates from other patients treated by their (same) clinician. In some sense, it averages across their within-clinician deviations from multiple visits to infer their patient-level estimate.

(ii) The MELR model also looks at how much a patient deviates from other patients, but instead considers those patients treated by the group of clinicians that prescribe like their clinician (i.e., have the same clinician-level effect). It averages across their within-clinician-group deviations from multiple visits to infer their patient-level estimate.

Another point that I have not addressed until now, by fitting these as random effects, in statistical parlance, I am "borrowing information" across both patients and clinicians to smooth out (or further stabilize) the subject-level estimates. The bivariate density plot (of residuals) suggests that cases have subject-level effects that are highly positively correlated, and there is not a lot of variation along horizontal and vertical cross sections. From the low variability along the horizontal cross-section, it appears that patients with similar clinicians (in terms of prescribing rates) seem to have similar antibiotic rates (as compared to patients of other, less similar clinicians). The positive correlation is, in part, by construction – these are patient-level and clinician-level average rates that are estimated from overlapping data. However, the correlation seemed very high, which suggests there is limited information to separate the channel effects. We might have suspected as much because, although all clinicians saw more than 25 patients, only 33% of patients visited more than one clinician[17].

More conceptually, a primary mechanism by which a patient may exert influence on their clinician is through selection: i.e., the implicit threat or act of switching clinicians. However, by using MELR, I am leveraging (and relying on) some of the patients selecting their clinician independent

[17] The residuals in Figure 11 are for the subset of cases in my final analysis dataset, but they were constructed from the full set of data corresponding to Table 13 and Table 14.

of prescribing behavior, otherwise their latent behavioral factors would be too correlated and impossible to separate in the data.

5.5.2.1 Clustering analysis

The clustering analysis (a form of unsupervised learning – i.e., arriving at conclusions based on the shape of the distribution rather than the association between variables) suggests 3-4 latent underlying types of providers or patients, which would seem the most interesting pattern in the data. However, it was difficult to tease out provider-level from patient-level effects and assign these to a channel. The clustering seemed to concentrate over time (i.e., reduced heterogeneity), coinciding with socio-economic events (i.e., the great recession) and changes in the health insurance market (i.e., the Affordable Care Act). However, the pattern could be explained by the pattern missing data (i.e., missing provider IDs).

5.5.2.2 Conceptual and Causal modeling

The most challenging aspect of specific aim 3, in terms of reproducible science, was developing a conceptual model and then translating it into a full causal model, which I then used to motivate covariates in my regression analysis. For anyone that has participated in such a process, it is one of the least reproducible (across analysts) aspects of health services research and social sciences in general. Specifying a causal model for social processes is difficult for a variety of reasons, including: systems have complex hierarchical organization, states change on different time scales, processes occur on different time scales, and "structural" relations can be ephemeral. There is no established framework for dealing with these challenges through a cohesive, reproducible process. I would rarely advocate for another framework – a search of the literature produces and abundance of references to social science frameworks. However, it does seem an area where a new causal modeling framework might improve reproducibility. Useful organizing concepts could include:

a. Explicit coding of systems, their hierarchy (e.g., clinicians, patients, health system), and their embedding in the environment (i.e., top level of the hierarchy).
b. Explicit coding of the type and subtype of variables observed on these systems (beyond statistical concepts such as dichotomous versus continuous): type could equal a state of a system or environment (e.g., subtype could be a categorical state, integrated state variable, change in the state variable), a process within systems, or interaction between these systems.

c. Explicit coding of the type causal associations, processes, or interactions between these systems (that influence state), e.g.: interaction between systems on the same hierarchy, interaction between systems on different hierarchical levels, or an internal process of a system.
d. Explicit treatment of time in the causal model, e.g.: calendar time of the study (absolute time frame), time frame (or duration) of each system, time scales of their variables, time scales of their interactions, and explicit notation of and treatment of endogenous processes (e.g., shown as feedback versus unfolded left-to-right).

This is a cursory list of thoughts, but it does highlight that there is known information that can be conceptually organized and, therefore, reproducibly checked off during the process of specifying conceptual model and translating into a causal model.

APPENDIX A: ADDITIONAL FIGURES

A.1 Data Sources

A.1.1 MEPS

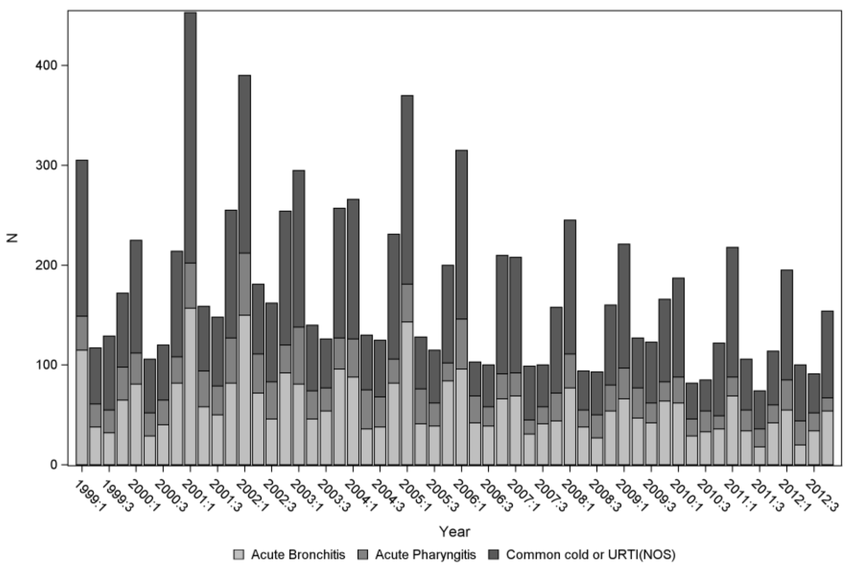

Figure 16: Counts of office-diagnosed ARTIs.

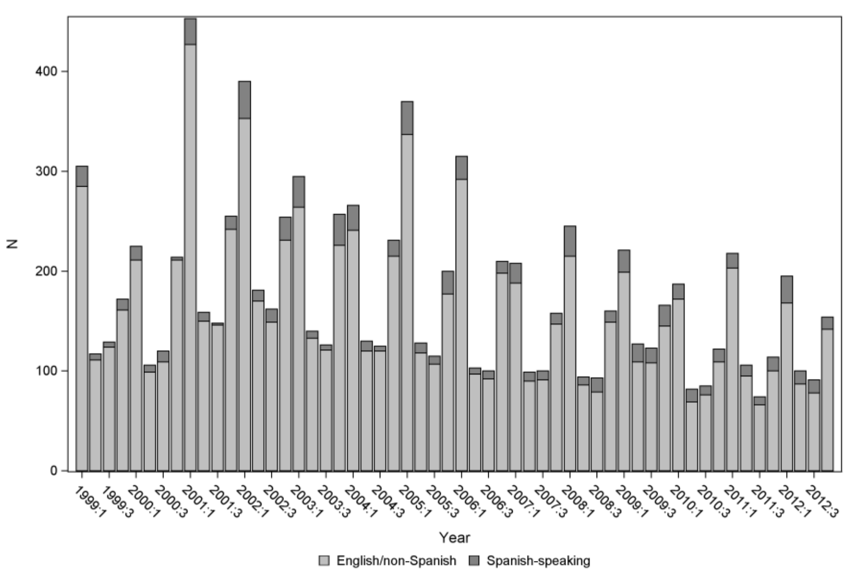

Figure 17: Counts of office-diagnosed ARTIs by primary language.

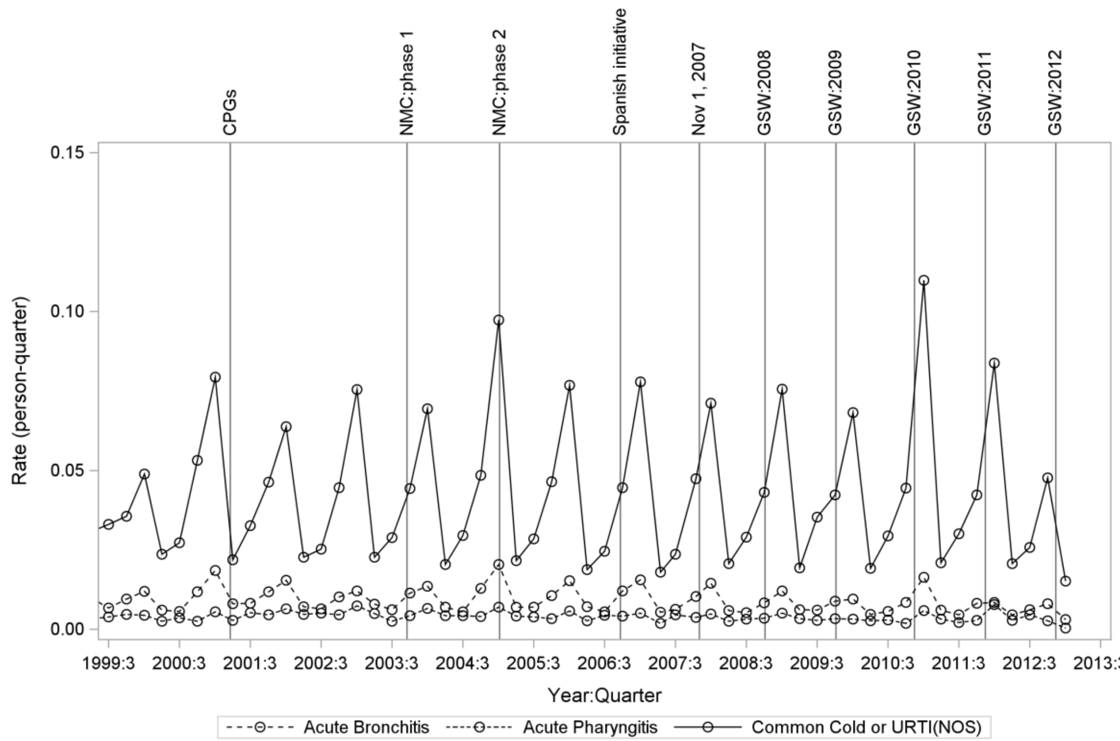

Figure 18: Incidence of ARTIs by condition (self-reported + Dx).

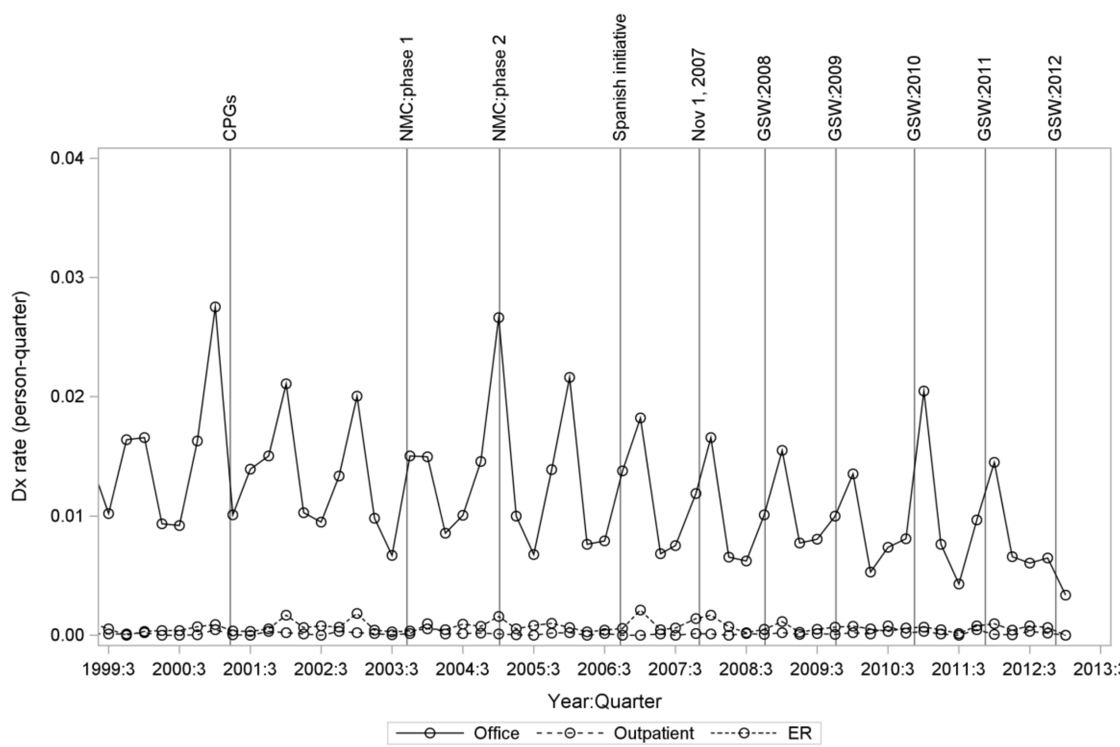

Figure 19: Incidence of ARTIs by visit type.

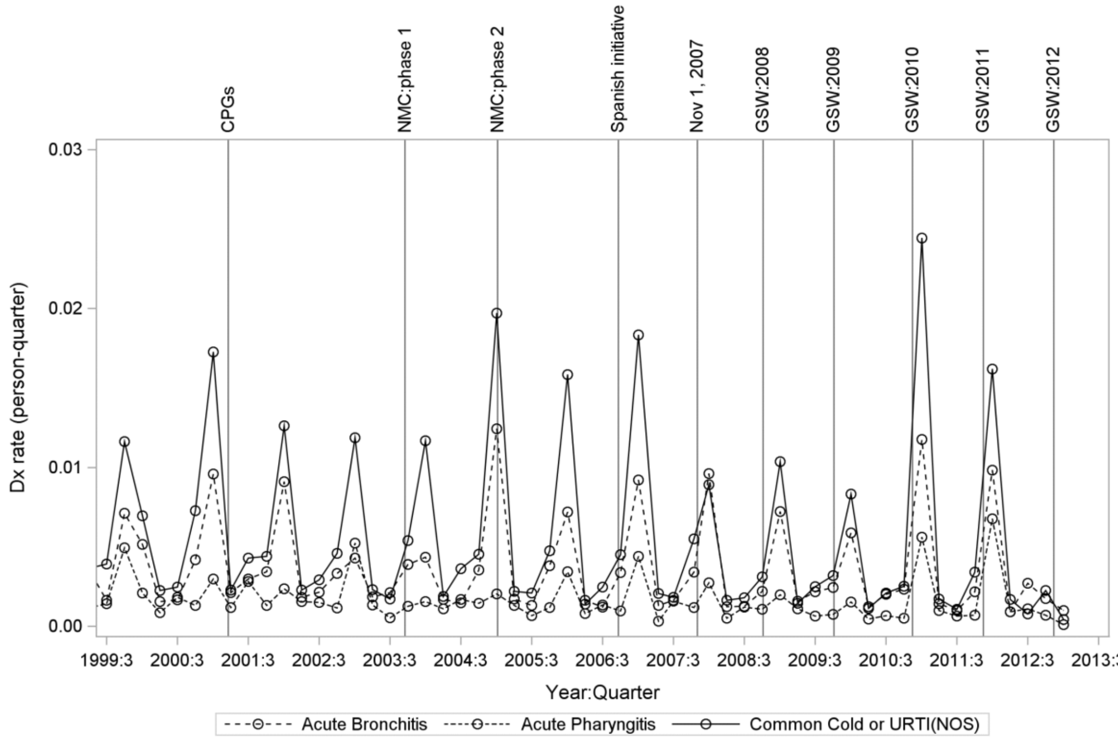

Figure 20: Office-diagnosed incidence of ARTIs by condition.

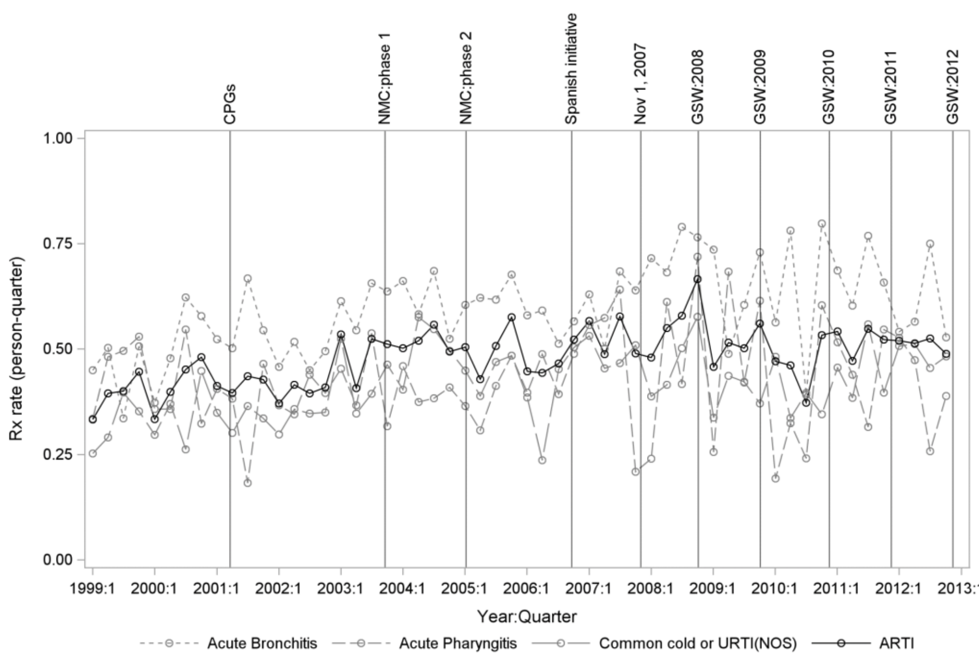

Figure 21: Office-diagnosed ARTI antibiotic Rx rates.

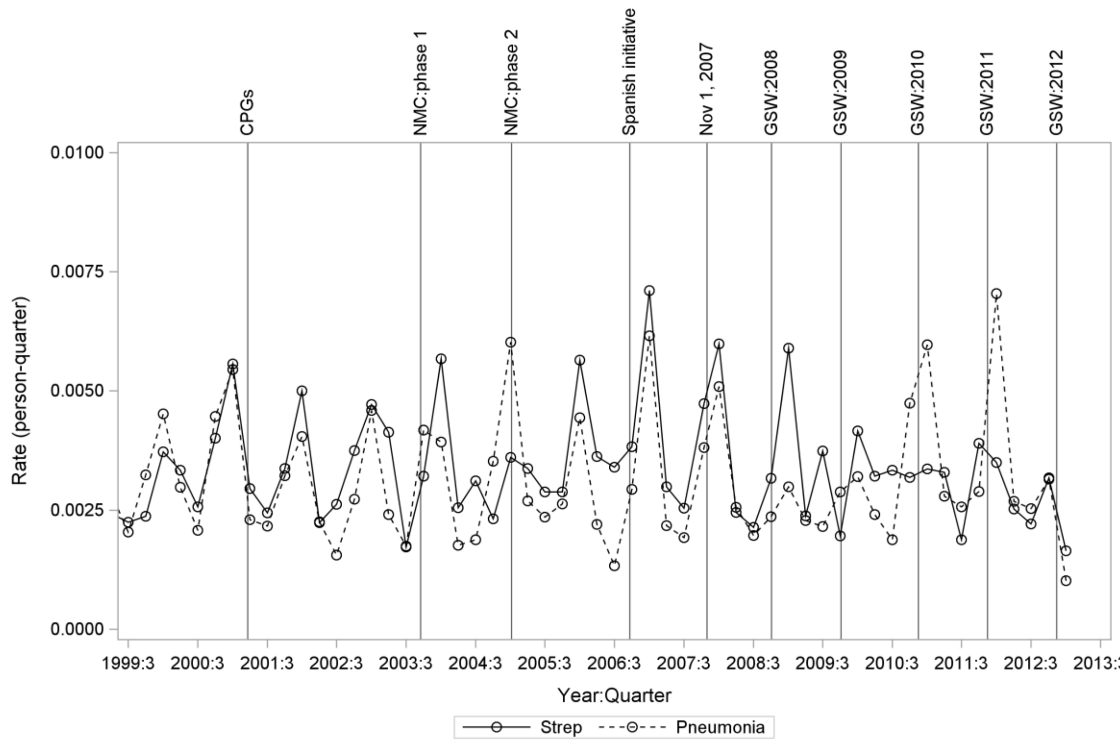

Figure 22: Incidence of Streptococcal pharyngitis and Pneumonia (self-reported + Dx).

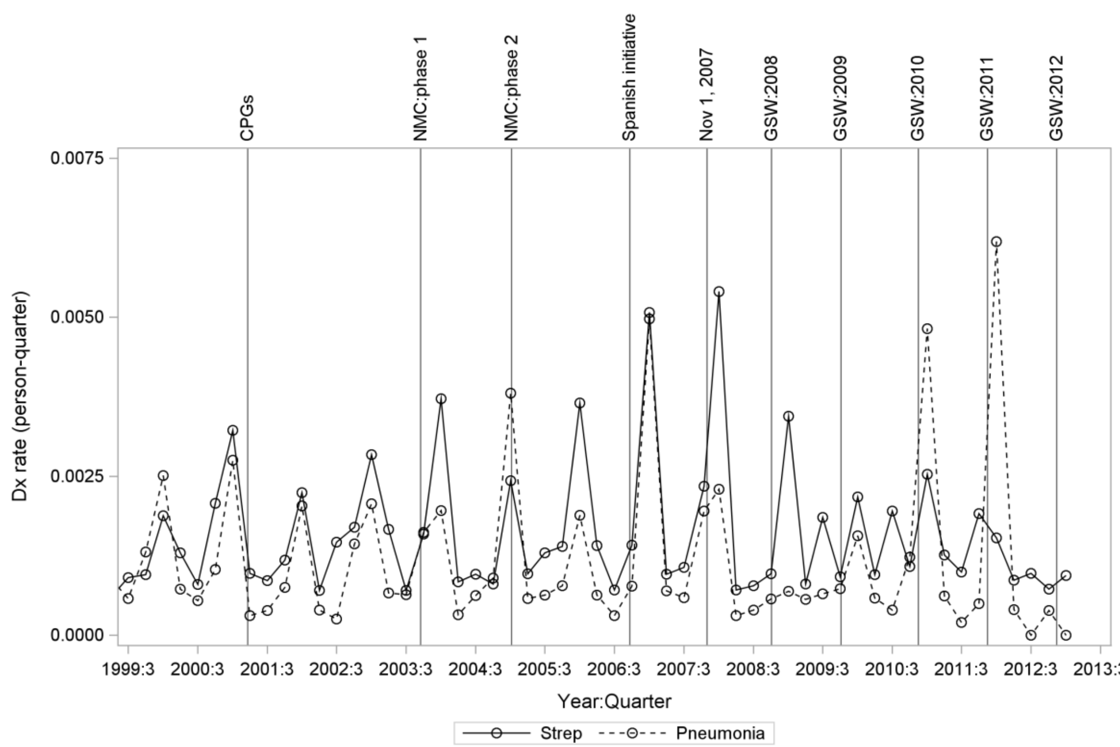

Figure 23: Office-diagnosed incidence of Streptococcal pharyngitis and Pneumonia.

A.1.2 MarketScan

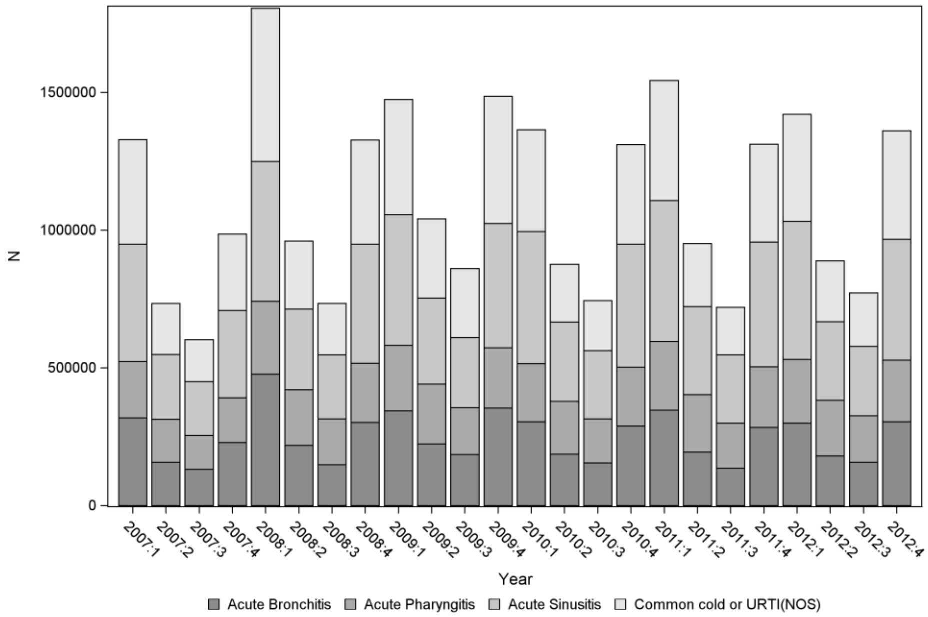

Figure 24: Office-diagnosed counts of ATIs.

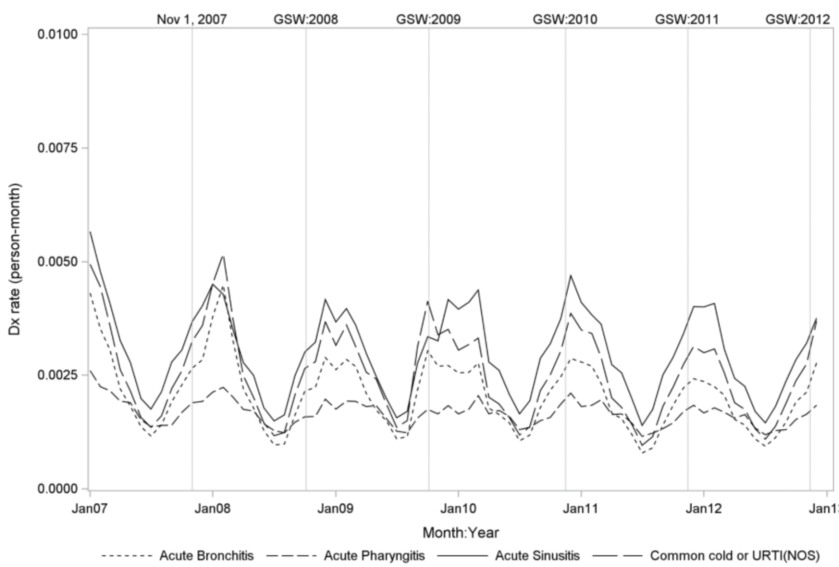

Figure 25: Office-diagnosed incidence of ARTIs.

*Note: This Marketscan plot is person-month incidence. The corresponding MEPS plot is person-quarter incidence.

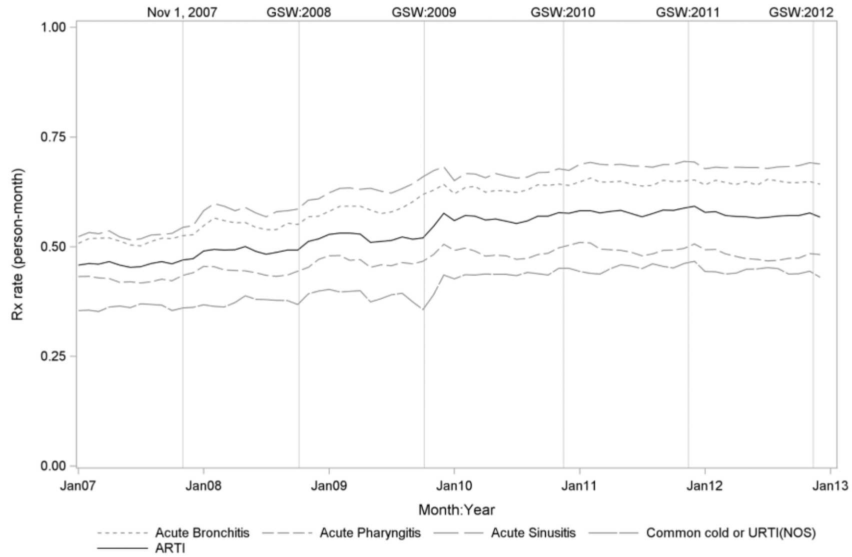

Figure 26: Antibiotic Rx rates by office-diagnosed condition.

A.2 Specific Aim 2 (State-Focused Activities)

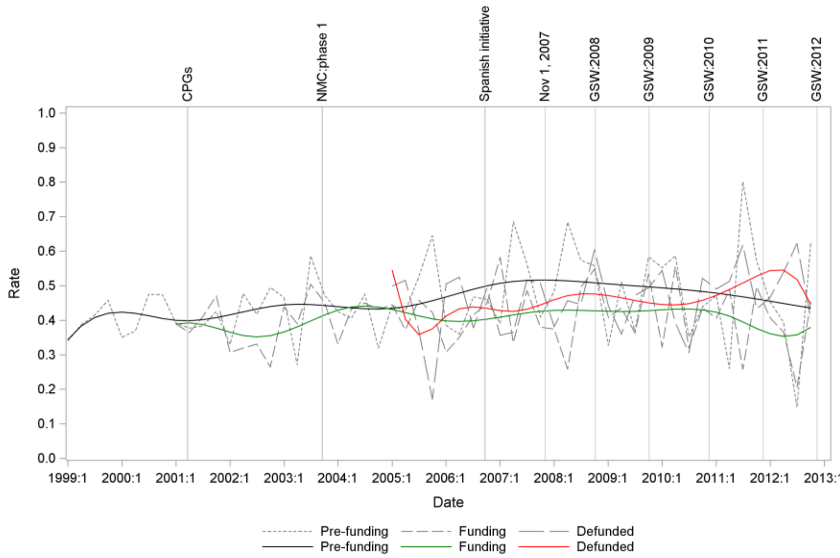

Figure 27: Office-based antibiotic Rx rates by GSA state funding status.
(MEPS, restricted access states)

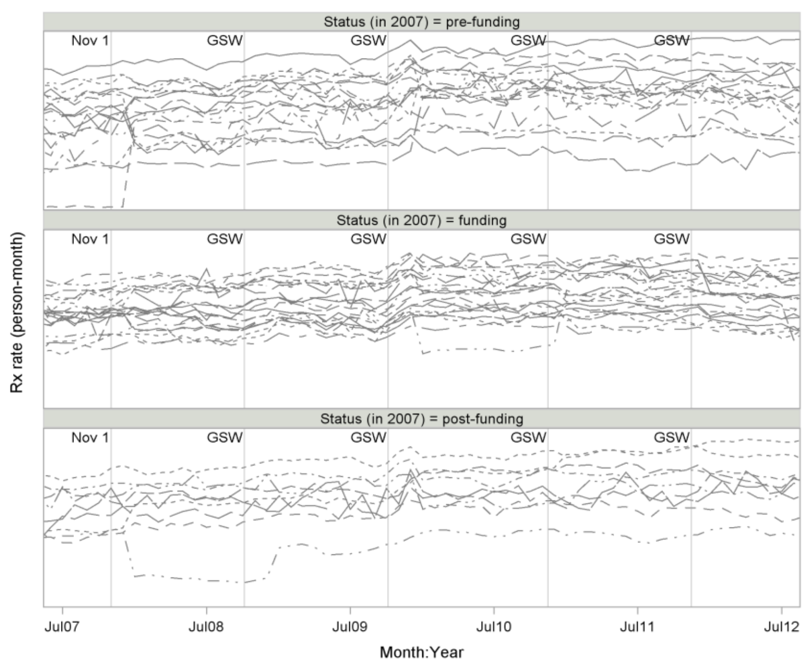

Figure 28: State-level antibiotic Rx rates by GSA state funding status (MarketScan).

A.3 Specific Aim 3: Latent-Factor Structural Model

A.3.1 Causal model

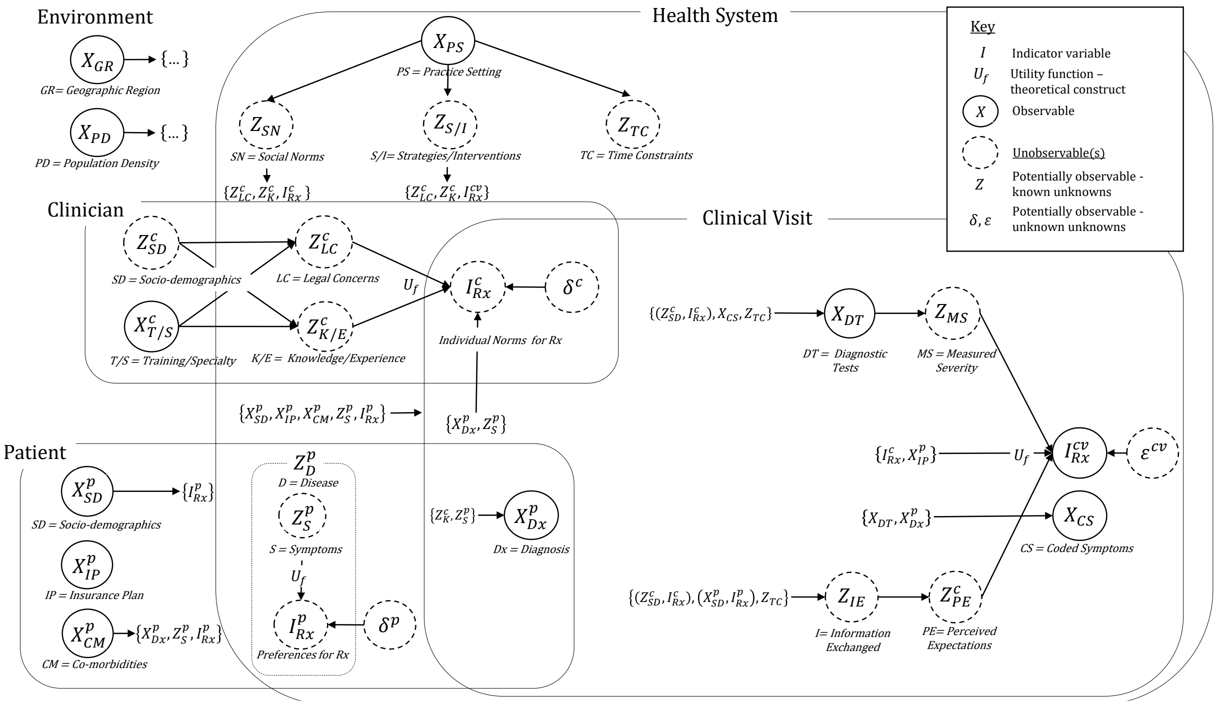

Figure 29: Causal model (directed acyclic graph) of antibiotic prescribing.

A.3.2 Distribution of random effects: stratified by provider-level and patient-level covariates.

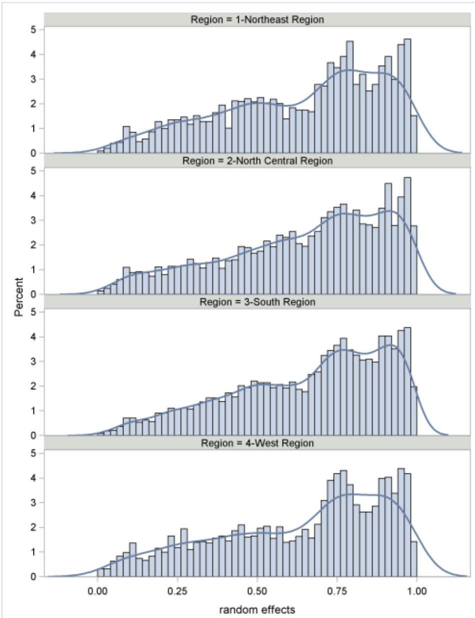

Figure 30: Histogram of provider-level random effects by region.

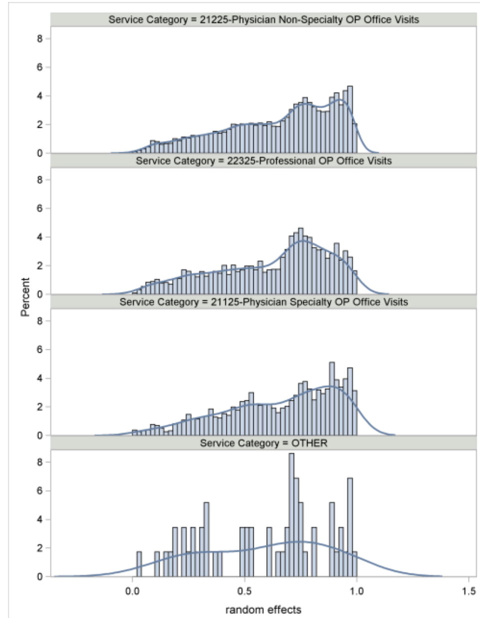

Figure 32: Histogram of provider-level random effects by service category.

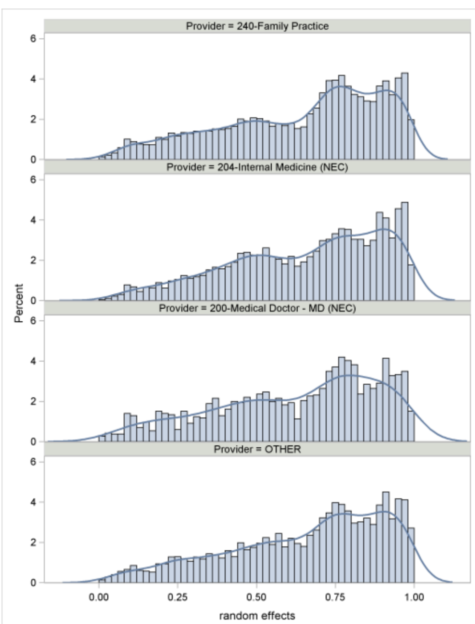

Figure 31: Histogram of provider-level random effects by provider type.

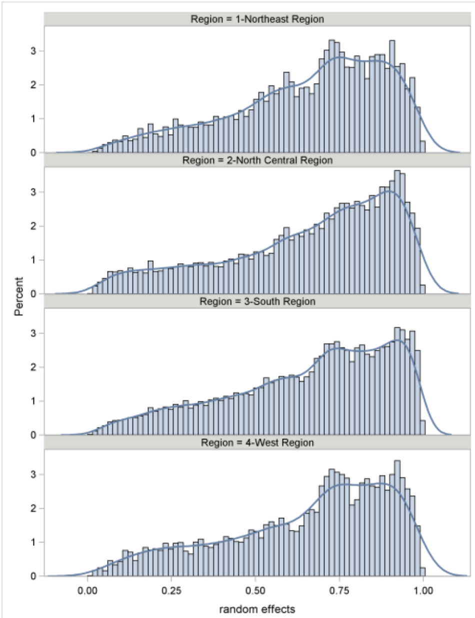

Figure 33: Histogram of patient-level random effects by region.

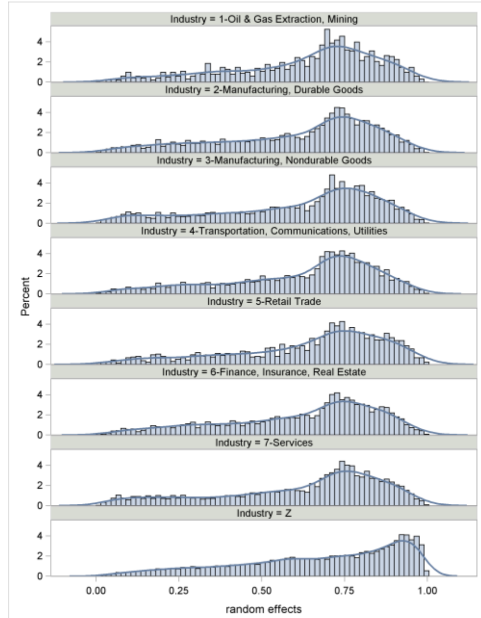

Figure 35: Histogram of patient-level random effects by industry.

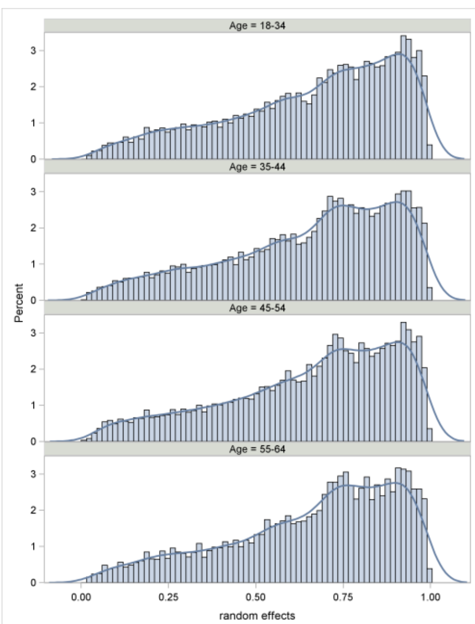

Figure 34: Histogram of patient-level random effects by age.

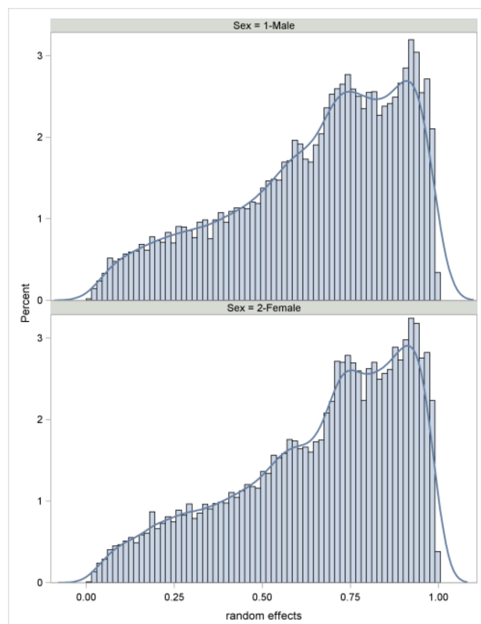

Figure 36: histogram of patient-level random effects by sex.

APPENDIX B: ADDITIONAL TABLES

B.1 DATA SOURCES

Table 20: ARTIs and ICD9 coding and inclusion and exclusion criteria.

Get Smart CPG / academic detailing sheets		ICD9 Codes		Datasource		Sensitivity	Notes
#	description	Acute	NOS	MEPS	Marketscan		
	ARTIs non-indicated for antibiotics			Index visit is defined as no previous non-indicated ARTI Dx within 2 months prior. Antibiotic Rx within 7 days of index visit (Marketscan).			Preliminary look at shorter duration of antibiotics Rx (3 days) did not suggest any differences.
1.	Acute bronchitis (uncomplicated)	466.0	490	466.[01]*	✓	Exclude NOS	MEPS also includes 466.1: Acute Bronchiolitis, which mostly affects infants and is also not indicated for non-complicated conditions. Focus is on adults, so should not impact the analysis.
2.	Acute pharyngitis (non-strep)	462		✓	✓		
3.	Acute sinusitis (uncomplicated)	461.[012389]*		✓	✓		Detail sheets indicate antibiotics may be appropriate if symptoms longer than 7 days and have maxillary facial pain and purulent nasal secretions.
4.	Common cold or Acute URTI						
	Common cold (acute rhino/naso-pharyngitis)	460		✓	✓		
	Acute URTI	465.[089]*		✓	✓		465[089] are exhaustive
	Exclusion Criteria						
#	description						
1.	Antibiotic appropriate RTIs			Co-diagnosis	Co-Dx or within 2 months prior		
	Otitis media (suppurative)	382		✓	✓		
	Otitis media (nonsuppurative)	381.[0-4]		381.[0-9]*	✓		MEPS analysis excludes 381[0-9], which extends exclusion to eustachian tube disorders. Focus is on adults, so should not impact the analysis.
	Pertussis	033		✓	✓		
	Pneumonia (bacterial)	48[1-6]		✓	✓		
	Streptococcal (GABHS) pharyngitis	034		✓	✓		
2.	Antibiotic appropriate (other)			Co-diagnosis	Co-Dx or within 2 months prior		
	Soft tissue infection	68[0-6]		✓	✓		
	UTIs	595		✓	✓		Could have considered 599.0, but we decided these were rare Dx.
	Infectious and parasitic diseases	001-139		✓	✓		This code range also catches pertussis and strep and HIV, which I explicitly break out.
3.	Chronic RTIs			Co-diagnosis or within 6 months prior			
	Rhinitis (non-allergic), Pharyngitis, Nasopharyngitis	472		✓	✓		
	Sinusitis	473		✓	✓		
	Tonsillitis and Adenoids	474		✓	✓		
	COPD			✓	✓		
	Bronchitis/Bronchiectasis	491, 49[4-6]	490	✓	✓		
	Emphysema	492		✓	✓		
	Asthma (chronic)	493		✓	✓		
4.	Immuno-compromising conditions			Co-diagnosis or within 6 months prior			
	Cancer	140-149, 209, 230-239		✓	✓		
	HIV	049		✓	✓		
	Organ transplantation	V42		✓	✓		
	Asplenia	759.0		759.[0-9]*	✓		MEPS analysis excludes 759.[0-9], which extends exclusion to rare congenital events. Focus is on adults, so should not impact the analysis.
	Disorders of the immune system	279		✓	✓		

B.2 Specific Aim 1 (Nationally-Focused Activities)

Table 21: Descriptive statistics for ARTI cases diagnosed in office-based setting. (MEPS: 1999-2009)

	ARTI cases		
	N	%	Rx rates
Diagnosis			
Acute Bronchitis	2789	34	0.57
Acute Pharyngitis	1306	16	0.41
Common cold or URTI (NOS)	4011	49	0.40
Sex			
Male	2902	36	0.47
Female	5204	64	0.46
Age			
18 - 24	1211	15	0.42
25 - 44	3677	45	0.46
45 - 64	3218	40	0.49
Race			
White	6921	85	0.48
Black	834	10	0.36
Other	351	4.3	0.36
Education			
No degree	1144	14	0.39
GED or High school degree	4110	51	0.47
Bachelor's	1458	18	0.48
Master's or Doctorate	709	8.7	0.47
Other degree	685	8.5	0.47
Employment			
< Full employment	1996	25	0.42
Full employment	6110	75	0.48
MSA			
Non-MSA	1661	20	0.49
MSA	6445	80	0.46
Census region			
Northeast	1423	18	0.46
Midwest	1882	23	0.49
South	3125	39	0.49
West	1676	21	0.39
General health			
Missing/NA	1288	16	0.40
Fair/Poor	924	11	0.44
Excellent/Very Good/Good	5894	73	0.48
Insured			
Yes	7213	89	0.47
No	893	11	0.42
Rx med insurance			
Yes	5883	73	0.48
No	2223	27	0.41
Spanish			
English/non-Spanish	7480	92	0.47
Spanish-speaking	626	7.7	0.38
All	8106	100	0.46

Table 22: Complete regression analysis of non-indicated ARTI antibiotic Rx rates. (MEPS: 1999-2008)

Variable	Level (categorical variables)	CPG models*		NMC models**		SI models***	
		OR	P-value	OR	P-value	OR	P-value
Diagnosis	Acute Bronchitis	1.84	<.001	1.91	<.001	2.01	<.001
	Acute Pharyngitis	1.27	0.06	0.94	0.57	0.88	0.27
years		1.36	0.01	1.20	0.02	0.94	0.22
Clinical Practice Guidelines							
post-CPGs		0.68	0.01				
post-CPGs X years		0.93	0.58				
	joint test		0.03				
NMC: initial phase							
post-NMC				1.18	0.30		
post-NMC X year				0.76	0.01		
	joint test				0.01		
Spanish Initiative (SI)							
Spanish-speaking X post-SI						0.59	0.37
Spanish-speaking X post-SI X years						1.19	0.61
	joint test						0.58
Additional Spanish-speaking covariates							
post-SI						1.35	0.04
post-SI X years						1.03	0.70
Spanish-speaking		0.77	0.47	0.67	0.29	1.54	0.29
Spanish-speaking X years		0.90	0.46	1.14	0.28	0.88	0.58
Additional covariates							
General health	Fair/Poor	1.23	0.15	1.00	0.97	0.69	0.00
	Missing/NA	1.28	0.10	0.88	0.46	0.77	0.09
Sex	Female	1.15	0.07	1.00	0.98	0.87	0.103
Age	25 - 44	1.00	0.99	0.99	0.93	1.18	0.14
	45 - 64	0.98	0.86	1.11	0.39	1.25	0.05
Race	Other	0.62	0.10	0.66	0.06	0.76	0.17
	Black	0.50	<.001	0.69	0.00	0.79	0.08
Education	GED or High school diploma	1.34	0.02	1.35	0.01	1.18	0.14
	Bachelor's	1.37	0.05	1.51	0.01	1.09	0.55
	Master's or Doctorate	0.95	0.82	1.23	0.24	1.27	0.14
	Other	1.31	0.12	1.29	0.18	1.05	0.77
Employment	Full employment	1.17	0.14	1.16	0.09	1.13	0.21
MSA	Non-MSA	1.09	0.36	1.05	0.61	1.04	0.66
Region	Northeast	0.94	0.51	0.90	0.33	0.84	0.11
	Midwest	0.80	0.02	0.93	0.47	1.07	0.52
	West	0.69	0.001	0.78	0.04	0.69	0.00
Rx insurance	Yes	1.34	<.001	1.18	0.09	1.17	0.10

* CPG dataset dates: September 17, 2003 (+/-) 2.5 years

** NMC dataset dates: September 17, 2003 (+/-) 2.5 years

**** SI dataset dates: September 20, 2006 (+/-) 2.5 years

B.3 Specific Aim 2 (State-Focused Activities)

B.3.1 MEPS

Table 23: Descriptive statistics for ARTI cases diagnosed in office-based setting. (MEPS, all states: 1999-2012)

	All			MEPS-encyrpted state						Missing		
				Yes			No					
	N	%	Rx rates	N	%	Rx rates	N	%	Rx rates	N	%	Rx rates
Diagnosis												
Acute Bronchitis	3346	34	0.59	455	37	0.65	2738	34	0.58	153	33	0.53
Acute Pharyngitis	1564	16	0.42	195	16	0.42	1281	16	0.42	88	19	0.41
Common cold or URTI(NOS)	4913	50	0.41	575	47	0.43	4111	51	0.41	227	49	0.43
Sex												
Male	3498	36	0.48	440	36	0.54	2892	36	0.47	166	35	0.49
Female	6325	64	0.47	785	64	0.49	5238	64	0.47	302	65	0.45
Age												
18 - 24	1458	15	0.42	200	16	0.51	1189	15	0.40	69	15	0.49
25 - 44	4434	45	0.47	538	44	0.50	3694	45	0.47	202	43	0.39
45 - 64	3931	40	0.50	487	40	0.52	3247	40	0.49	197	42	0.53
Race												
White	8286	84	0.49	1062	87	0.52	6816	84	0.48	408	87	0.47
Black	1064	11	0.36	94	7.7	0.36	928	11	0.36	42	9	0.42
Other	473	4.8	0.40	69	5.6	0.56	386	4.7	0.38	18	3.8	0.33
Education												
No degree	1346	14	0.39	187	15	0.48	1104	14	0.37	55	12	0.48
GED or High school degree	4915	50	0.48	641	52	0.51	4035	50	0.48	239	51	0.43
Bachelor's	1811	18	0.49	207	17	0.60	1512	19	0.47	92	20	0.54
Master's or Doctorate	901	9.2	0.47	102	8.3	0.49	768	9.4	0.47	31	6.6	0.35
Other degree	850	8.7	0.50	88	7.2	0.39	711	8.7	0.51	51	11	0.51
Employment												
< Full employment	2465	25	0.43	250	20	0.50	2079	26	0.43	136	29	0.43
Full employment	7358	75	0.48	975	80	0.51	6051	74	0.48	332	71	0.47
MSA												
Non-MSA	1866	19	0.49	497	41	0.50	1271	16	0.48	98	21	0.50
MSA	7957	81	0.47	728	59	0.52	6859	84	0.47	370	79	0.45
Census region												
Northeast	1692	17	0.47	92	7.5	0.35	1523	19	0.48	77	16	0.57
Midwest	2283	23	0.49	367	30	0.54	1821	22	0.48	95	20	0.52
South	3757	38	0.50	344	28	0.52	3209	39	0.50	204	44	0.44
West	2091	21	0.40	422	34	0.52	1577	19	0.37	92	20	0.34
General health												
Missing/NA	1416	14	0.40	166	14	0.41	1224	15	0.40	26	5.6	0.58
Fair/Poor	1127	11	0.45	128	10	0.42	940	12	0.45	59	13	0.47
Excellent/Very Good/Good	7280	74	0.49	931	76	0.54	5966	73	0.48	383	82	0.46
Insured												
Yes	8698	89	0.47	1063	87	0.51	7202	89	0.47	433	93	0.46
No	1125	11	0.46	162	13	0.48	928	11	0.45	35	7.5	0.46
Rx med insurance												
Yes	7069	72	0.49	878	72	0.52	5843	72	0.48	348	74	0.50
No	2754	28	0.42	347	28	0.49	2287	28	0.42	120	26	0.32
Spanish												
English/non-Spanish	9008	92	0.48	1163	95	0.51	7407	91	0.47	438	94	0.45
Spanish-speaking	815	8.3	0.37	62	5.1	0.45	723	8.9	0.35	30	6.4	0.72
All	9823	100	0.47	1225	100	0.51	8130	100	0.47	468	100	0.46

Table 24: Descriptive statistics for ARTI cases by GSA state funding status.
(MEPS, restricted-access states: 1999-2012)

	All			Funding status								
				Pre-funding			Funding			Defunded		
	N	%	Rx rates	N	%	Rx rates	N	%	Rx rates	N	%	Rx rates
Diagnosis												
Acute Bronchitis	2738	34	0.58	1023	34	0.53	1198	34	0.59	517	33	0.65
Acute Pharyngitis	1281	16	0.42	486	16	0.46	558	16	0.41	237	15	0.33
Common cold or URTI(NOS)	4111	51	0.41	1497	50	0.37	1789	50	0.40	825	52	0.49
Sex												
Male	2892	36	0.47	1051	35	0.44	1278	36	0.46	563	36	0.53
Female	5238	64	0.47	1955	65	0.44	2267	64	0.47	1016	64	0.52
Age												
18 - 24	1189	15	0.40	411	14	0.39	557	16	0.41	221	14	0.40
25 - 44	3694	45	0.47	1421	47	0.45	1565	44	0.46	708	45	0.54
45 - 64	3247	40	0.49	1174	39	0.45	1423	40	0.50	650	41	0.55
Race												
White	6816	84	0.48	2578	86	0.46	2947	83	0.48	1291	82	0.54
Black	928	11	0.36	321	11	0.28	393	11	0.40	214	14	0.45
Other	386	4.7	0.38	107	3.6	0.31	205	5.8	0.39	74	4.7	0.46
Education												
No degree	1104	14	0.37	379	13	0.33	526	15	0.37	199	13	0.46
GED or High school degree	4035	50	0.48	1535	51	0.44	1753	49	0.49	747	47	0.54
Bachelor's	1512	19	0.47	534	18	0.47	645	18	0.44	333	21	0.51
Master's or Doctorate	768	9.4	0.47	287	9.5	0.44	327	9.2	0.48	154	9.8	0.51
Other degree	711	8.7	0.51	271	9	0.48	294	8.3	0.48	146	9.2	0.59
Employment												
< Full employment	2079	26	0.43	735	24	0.38	938	26	0.44	406	26	0.50
Full employment	6051	74	0.48	2271	76	0.46	2607	74	0.47	1173	74	0.53
MSA												
Non-MSA	1271	16	0.48	483	16	0.47	564	16	0.49	224	14	0.48
MSA	6859	84	0.47	2523	84	0.44	2981	84	0.46	1355	86	0.53
Census region												
Northeast	1523	19	0.48	903	30	0.46	421	12	0.53	199	13	0.47
Midwest	1821	22	0.48	693	23	0.44	791	22	0.50	337	21	0.52
South	3209	39	0.50	1103	37	0.47	1234	35	0.49	872	55	0.56
West	1577	19	0.37	307	10	0.32	1099	31	0.37	171	11	0.45
General health												
Missing/NA	1224	15	0.40	838	28	0.39	260	7.3	0.38	126	8	0.49
Fair/Poor	940	12	0.45	304	10	0.43	463	13	0.46	173	11	0.46
Excellent/Very Good/Good	5966	73	0.48	1864	62	0.46	2822	80	0.47	1280	81	0.54
Insured												
Yes	7202	89	0.47	2737	91	0.45	3112	88	0.47	1353	86	0.52
No	928	11	0.45	269	8.9	0.36	433	12	0.46	226	14	0.58
Rx med insurance												
Yes	5843	72	0.48	2242	75	0.47	2503	71	0.48	1098	70	0.53
No	2287	28	0.42	764	25	0.35	1042	29	0.43	481	30	0.52
Spanish												
English/non-Spanish	7407	91	0.47	2786	93	0.45	3221	91	0.47	1400	89	0.53
Spanish-speaking	723	8.9	0.35	220	7.3	0.34	324	9.1	0.31	179	11	0.42
All	8130	100	0.47	3006	100	0.44	3545	100	0.47	1579	100	0.53

Table 25: Descriptive statistics for ARTI cases by GSA Week.
(MEPS, restricted-access states: 2007-2012, 4-month window)

	All			GSW Participant											
				No						Yes					
				GSW						GSW					
				No			Yes			No			Yes		
	N	%	Rx rate	N	%	Rx rate	N	%	Rx rate	N	%	Rx rate	N	%	Rx rate
Diagnosis															
Acute Bronchitis	487	34	0.68	220	33	0.68	100	37	0.66	92	29	0.63	75	36	0.76
Acute Pharyngitis	189	13	0.45	91	14	0.32	27	9.9	0.50	44	14	0.49	27	13	0.73
Common cold or URTI(NOS)	776	53	0.45	348	53	0.48	145	53	0.46	177	57	0.40	106	51	0.40
Sex															
Male	532	37	0.54	248	38	0.59	95	35	0.55	117	37	0.45	72	35	0.52
Female	920	63	0.53	411	62	0.50	177	65	0.54	196	63	0.51	136	65	0.63
Age															
18 - 24	211	15	0.38	105	16	0.34	34	13	0.51	46	15	0.35	26	13	0.40
25 - 44	637	44	0.55	281	43	0.54	117	43	0.57	143	46	0.50	96	46	0.61
45 - 64	604	42	0.57	273	41	0.60	121	44	0.53	124	40	0.53	86	41	0.63
Race															
White	1173	81	0.55	537	81	0.54	218	80	0.56	249	80	0.49	169	81	0.62
Black	186	13	0.41	87	13	0.44	39	14	0.36	31	9.9	0.44	29	14	0.34
Other	93	6.4	0.47	35	5.3	0.44	15	5.5	0.65	33	11	0.42	10	4.8	0.39
Education															
No degree	198	14	0.41	90	14	0.37	30	11	0.40	54	17	0.47	24	12	0.49
GED or High school degree	683	47	0.52	327	50	0.52	115	42	0.57	142	45	0.43	99	48	0.56
Bachelor's	272	19	0.60	113	17	0.60	64	24	0.61	58	19	0.52	37	18	0.68
Master's or Doctorate	169	12	0.56	77	12	0.62	35	13	0.48	35	11	0.49	22	11	0.60
Other degree	130	9	0.55	52	7.9	0.46	28	10	0.53	24	7.7	0.69	26	13	0.65
Employment															
< Full employment	385	27	0.48	169	26	0.44	81	30	0.54	85	27	0.47	50	24	0.50
Full employment	1067	73	0.55	490	74	0.56	191	70	0.55	228	73	0.49	158	76	0.62
MSA															
Non-MSA	187	13	0.50	105	16	0.50	37	14	0.44	22	7	0.50	23	11	0.58
MSA	1265	87	0.54	554	84	0.54	235	86	0.57	291	93	0.48	185	89	0.60
Census region															
Northeast	273	19	0.52	126	19	0.42	48	18	0.61	57	18	0.58	42	20	0.66
Midwest	318	22	0.59	139	21	0.62	63	23	0.58	78	25	0.54	38	18	0.60
South	572	39	0.57	311	47	0.58	142	52	0.53	65	21	0.48	54	26	0.67
West	289	20	0.41	83	13	0.39	19	7	0.33	113	36	0.36	74	36	0.50
General health															
Missing/NA	120	8.3	0.45	61	9.3	0.44	22	8.1	0.37	23	7.3	0.54	14	6.7	0.46
Fair/Poor	161	11	0.49	67	10	0.43	31	11	0.56	36	12	0.39	27	13	0.63
Excellent/Very Good/Good	1171	81	0.55	531	81	0.55	219	81	0.56	254	81	0.49	167	80	0.60
Insured															
Yes	1259	87	0.53	573	87	0.54	238	88	0.53	267	85	0.48	181	87	0.58
No	193	13	0.57	86	13	0.51	34	13	0.70	46	15	0.51	27	13	0.68
Rx med insurance															
Yes	1007	69	0.54	458	69	0.54	186	68	0.57	216	69	0.49	147	71	0.60
No	445	31	0.50	201	31	0.50	86	32	0.48	97	31	0.47	61	29	0.58
Spanish															
English/non-Spanish	1284	88	0.54	585	89	0.54	247	91	0.56	269	86	0.50	183	88	0.61
Spanish-speaking	168	12	0.34	74	11	0.38	25	9.2	0.34	44	14	0.28	25	12	0.34
All	1452	100	0.53	659	100	0.53	272	100	0.55	313	100	0.49	208	100	0.59

Table 26: Complete regression results of state-funding and ARTI antibiotic Rx rates.
(MEPS, restricted-access states: 1999-2012)

Variable	Level (categorical variables)	Combined		Acute Bronchitis		Acute Pharyngitis		Common Cold	
		OR	P-value	OR	P-value	OR	P-value	OR	P-value
Diagnosis	Acute Bronchitis	1.96	<.001						
	Acute Pharyngitis	1.07	0.43						
years		1.09	0.44						
Funding terms									
Funded		1.22	0.07	1.14	0.48	1.37	0.23	1.22	0.17
Funded X years		0.96	0.03	0.96	0.21	0.95	0.25	0.94	0.06
	joint test		0.01		0.35		0.29		0.06
Defunding terms									
Defunded		1.16	0.23	1.18	0.45	0.66	0.17	1.33	0.11
Defunded X years		1.05	0.24	0.97	0.57	1.05	0.60	1.11	0.06
	joint test		0.08		0.71		0.38		0.004
GSAW term									
GSAW (cummulative participation years)		1.54	0.02	1.81	0.04	3.22	0.02	1.02	0.95
Clinical Practice Guideline terms									
CPGs		0.64	0.01	0.81	0.49	0.59	0.24	0.50	0.01
CPGs * years		1.22	0.13	1.29	0.21	1.09	0.80	1.28	0.26
	joint test		0.01		0.37		0.45		0.02
National Media Campaign terms									
NMC		0.99	0.93	0.89	0.64	0.85	0.61	0.99	0.97
NMC * years		0.76	0.001	0.80	0.14	0.99	0.97	0.64	0.002
	joint test		<.001		0.25		0.81		<.001
Spanish-speaking covariates									
Spanish-speaking		0.66	0.02						
Spanish-speaking * years		1.00	0.99						
Additional covariates									
General health	Fair/Poor	0.89	0.20						
	Missing/NA	0.92	0.45						
Sex	2 FEMALE	1.00	0.97						
Age	25 - 44 AGE	1.25	0.01						
	45 - 64 AGE	1.29	0.01						
Race	Asian or Native Hawaiian/Pacific Islander	0.80	0.11						
	Black	0.61	<.001						
Education	2/3 GED or HIGH SCHOOL DIPLOMA	1.25	0.01						
	4 BACHELOR'S DEGREE	1.13	0.27						
	5/6 MASTER'S DEGREE or DOCTORATE DEGREE	1.11	0.40						
	7 OTHER DEGREE	1.37	0.01						
Employment	Full employment	1.16	0.02						
MSA	0 NON-MSA	0.95	0.57						
Rx insurance	1 YES	1.16	0.03						

*Note: State and Month effects not shown.

Table 27: Complete regression results of GSA Week and ARTI antibiotic Rx rates.
(MEPS, restricted-access states: 2007-2012, 4-month window)

Variable*	Level (categorical variables)	Combined	
		OR	P-value
Diagnosis	Acute Bronchitis	2.82	<.0001
	Acute Pharyngitis	1.04	0.86
GSAW term			
GSAW participant		0.70	0.11
Post-GSAW		1.10	0.75
GSAW participant X Post-GSAW		1.42	0.22
Spanish-speaking covariates			
Spanish-speaking		0.46	0.01
Additional covariates			
General health	Fair/Poor	0.79	0.40
	Missing/NA	0.96	0.89
Sex	2 FEMALE	0.93	0.57
Age	25 - 44 AGE	1.75	0.01
	45 - 64 AGE	2.05	0.001
Race	Other	0.95	0.88
	Black	0.55	0.004
Education	2/3 GED or HIGH SCHOOL DIPLOMA	1.04	0.86
	4 BACHELOR'S DEGREE	1.41	0.24
	5/6 MASTER'S DEGREE or DOCTORATE DEGREE	1.30	0.40
	7 OTHER DEGREE	1.24	0.46
Employment	Full employment	1.15	0.36
MSA	0 NON-MSA	0.74	0.19
Rx insurance	1 YES	0.97	0.83

* Note: State, Year, Month, Funding, and Defunding effects not shown.

B.3.2 MarketScan

Table 28: Counts and Rx rates by diagnosis and year (MarketScan: 2007-2012).

Diagnosis		**Year**						**All**
		2007	2008	2009	2010	2011	2012	
Acute Bronchitis	N	837416	1146757	1107917	935743	962084	942570	5932487
	Col %	23	24	23	22	21	21	22
	Rx rate	0.52	0.56	0.6	0.63	0.65	0.65	0.6
Acute Pharyngitis	N	645802	847127	844575	775014	839485	825369	4777372
	Col %	18	18	17	18	19	19	18
	Rx rate	0.43	0.45	0.47	0.49	0.5	0.48	0.47
Acute Sinusitis	N	1173123	1467460	1492185	1463978	1534356	1476741	8607843
	Col %	32	30	31	34	34	33	32
	Rx rate	0.53	0.59	0.64	0.67	0.69	0.68	0.64
Common cold or URTI(NOS)	N	995567	1368199	1419348	1121971	1193246	1198367	7296698
	Col %	27	28	29	26	26	27	27
	Rx rate	0.36	0.38	0.39	0.44	0.45	0.44	0.41
All	N	3651908	4829543	4864025	4296706	4529171	4443047	26610000
	Row %	14	18	18	16	17	17	100
	Rx rate	0.46	0.5	0.53	0.57	0.58	0.57	0.54

Table 29: Descriptive statistics for ARTI cases by year (MarketScan: 2007-2012).

	All			Year					
				2007	2008	2009	2010	2011	2012
	N	Col %	Rx rates	Col %					
Diagnosis									
Acute Bronchitis	5932487	22	0.60	23	24	23	22	21	21
Acute Pharyngitis	4777372	18	0.47	18	18	17	18	19	19
Acute Rhino-sinusitis	8607843	32	0.64	32	30	31	34	34	33
Common cold or URTI(NOS)	7296698	27	0.41	27	28	29	26	26	27
Sex									
Male	9967294	37	0.54	37	38	37	37	38	38
Female	16650000	63	0.54	63	62	63	63	62	62
Age									
18-34	8768749	33	0.51	32	32	33	32	34	34
35-44	6585150	25	0.55	25	25	25	25	24	24
45-54	6413603	24	0.55	24	25	24	25	24	23
55-64	4846898	18	0.55	18	18	18	19	19	18
Region*									
Northeast Region	3731800	14	0.45	8.9	16	14	15	15	15
North Central Region	6935109	26	0.55	28	27	26	24	26	25
South Region	12220000	46	0.57	51	44	46	47	44	45
West Region	3726583	14	0.50	12	13	13	14	15	16
Work industry									
Oil & Gas Extraction, Mining	267145	1	0.69	0.8	0.9	1.1	1.3	0.9	1
Manufacturing, Durable Goods	2915620	11	0.63	12	11	11	12	11	10
Manufacturing, Nondurable Goods	1406057	5.3	0.64	4.9	4.8	4.8	5.7	5.7	5.7
Transportation, Communications, Utilities	2185561	8.2	0.66	7.2	8.4	8.3	9	8.2	8
Retail Trade	773454	2.9	0.56	2.2	2.9	3	3.1	2.9	3.2
Finance, Insurance, Real Estate	2062210	7.7	0.62	5.5	7.8	8.1	8.7	8.1	7.8
Services	3402653	13	0.51	5.6	12	13	15	15	15
Missing	13600000	51	0.48	62	53	51	45	48	49
Plan type									
Comprehensive	428226	1.6	0.58	2.3	1.8	1.4	1.6	1.3	1.3
EPO	506798	1.9	0.45	0.7	1	1.1	3.1	3.2	2.3
HMO	3266812	12	0.58	16	16	13	11	9.9	9.1
POS	2113065	7.9	0.54	9.7	9.1	8.5	7.9	6.6	6.1
PPO	18610000	70	0.53	69	67	71	69	71	73
POS with Capitation	159665	0.6	0.47	0.8	0.8	0.7	0.6	0.5	0.3
CDHP	1029539	3.9	0.61	2.2	3	3.2	5.2	4.8	4.6
HDHP	502691	1.9	0.55	0	0.8	1.3	2.4	3.1	3.5
All	26610000	100	0.54						

Table 30: Descriptive statistics for ARTI cases by GSA state funding status.
(Marketscan: 2007-2012)

	All			Funding status								
				Pre-funding			Funding			Post-funding		
	N	%	Rx rates	N	%	Rx rates	N	%	Rx rates	N	%	Rx rates
Diagnosis												
Acute Bronchitis	5932487	22	0.60	1432556	22	0.58	1844694	23	0.59	2655237	22	0.62
Acute Pharyngitis	4777372	18	0.47	1163062	18	0.44	1395279	18	0.46	2219031	18	0.49
Acute Rhino-sinusitis	8607843	32	0.64	2138078	33	0.62	2535273	32	0.62	3934492	32	0.66
Common cold or URTI(NOS)	7296698	27	0.41	1692120	26	0.39	2145557	27	0.36	3459021	28	0.45
Sex												
Male	9967294	37	0.54	2388554	37	0.52	2972447	38	0.52	4606293	38	0.56
Female	16650000	63	0.54	4037262	63	0.52	4948356	62	0.51	7661488	62	0.56
Age												
18-34	8768749	33	0.51	2150799	33	0.49	2526086	32	0.48	4091864	33	0.53
35-44	6585150	25	0.55	1594496	25	0.53	1968526	25	0.53	3022128	25	0.57
45-54	6413603	24	0.55	1544306	24	0.53	1923421	24	0.53	2945876	24	0.58
55-64	4846898	18	0.55	1136215	18	0.53	1502770	19	0.54	2207913	18	0.58
Region*												
Northeast Region	3731800	14	0.45	1609824	25	0.47	802367	10	0.53	1319609	11	0.37
North Central Region	6935109	26	0.55	2799959	44	0.52	2234046	28	0.60	1901104	15	0.55
South Region	12220000	46	0.57	1937406	30	0.55	2364610	30	0.48	7918892	65	0.60
West Region	3726583	14	0.50	78627	1.2	0.57	2519780	32	0.47	1128176	9.2	0.56
Work industry												
Oil & Gas Extraction, Mining	267145	1	0.69	34994	0.5	0.71	55882	0.7	0.65	176269	1.4	0.71
Manufacturing, Durable Goods	2915620	11	0.63	656043	10	0.63	1073400	14	0.61	1186177	9.7	0.64
Manufacturing, Nondurable Goods	1406057	5.3	0.64	372229	5.8	0.64	436810	5.5	0.62	597018	4.9	0.65
Transportation, Communications, Utilities	2185561	8.2	0.66	435926	6.8	0.66	707000	8.9	0.63	1042635	8.5	0.68
Retail Trade	773454	2.9	0.56	196301	3.1	0.56	227995	2.9	0.53	349158	2.8	0.57
Finance, Insurance, Real Estate	2062210	7.7	0.62	452656	7	0.63	651075	8.2	0.61	958479	7.8	0.64
Services	3402653	13	0.51	675953	11	0.55	1366548	17	0.49	1360152	11	0.50
Missing	13600000	51	0.48	3601714	56	0.45	3402093	43	0.44	6597893	54	0.52
Plan type												
Comprehensive	428226	1.6	0.58	115791	1.8	0.46	179283	2.3	0.61	133152	1.1	0.65
EPO	506798	1.9	0.45	61419	1	0.45	157600	2	0.43	287779	2.3	0.46
HMO	3266812	12	0.58	692977	11	0.53	1318901	17	0.57	1254934	10	0.61
POS	2113065	7.9	0.54	622103	9.7	0.60	417255	5.3	0.64	1073707	8.8	0.46
PPO	18610000	70	0.53	4558170	71	0.51	5377871	68	0.49	8671563	71	0.56
POS with Capitation	159665	0.6	0.47	81692	1.3	0.37	29248	0.4	0.56	48725	0.4	0.57
CDHP	1029539	3.9	0.61	186896	2.9	0.59	303320	3.8	0.59	539323	4.4	0.63
HDHP	502691	1.9	0.55	106768	1.7	0.58	137325	1.7	0.47	258598	2.1	0.59
All	26610000	100	0.54	6425816	100	0.52	7920803	100	0.52	12270000	100	0.56

Table 31: Descriptive statistics for ARTI cases by GSA Week.

(Marketscan: 2007-2012, 4-window window)

	All			Post-GSAW											
				No						Yes					
				GSAW participant						GSAW participant					
				no			yes			no			yes		
	N	%	Rx rates	N	%	Rx rates	N	%	Rx rates	N	%	Rx rates	N	%	Rx rates
Diagnosis															
Acute Bronchitis	2529022	23	0.59	1297285	22	0.56	640153	23	0.62	249531	22	0.61	342053	23	0.62
Acute Pharyngitis	1901656	17	0.46	1024959	18	0.45	443918	16	0.49	200162	18	0.45	232617	16	0.47
Acute Rhino-sinusitis	3623202	32	0.62	1871882	32	0.58	910068	32	0.67	363592	33	0.65	477660	32	0.66
Common cold or URTI(NOS)	3160347	28	0.40	1593226	28	0.39	846926	30	0.44	300171	27	0.37	420024	29	0.38
Sex															
Male	4138709	37	0.53	2127185	37	0.50	1059440	37	0.56	403869	36	0.53	548215	37	0.54
Female	7075518	63	0.52	3660167	63	0.50	1781625	63	0.56	709587	64	0.53	924139	63	0.54
Age															
18-34	3681911	33	0.49	1921777	33	0.48	916930	32	0.53	375140	34	0.49	468064	32	0.50
35-44	2805017	25	0.54	1455957	25	0.51	707194	25	0.57	276002	25	0.54	365864	25	0.55
45-54	2696269	24	0.54	1392463	24	0.51	687789	24	0.58	261373	23	0.56	354644	24	0.56
55-64	2031030	18	0.54	1017155	18	0.51	529152	19	0.58	200941	18	0.56	283782	19	0.56
Region															
Northeast Region	1444494	13	0.45	649782	11	0.45	466877	16	0.42	147836	13	0.51	179999	12	0.52
North Central Region	2970268	26	0.53	1454619	25	0.47	563750	20	0.55	411792	37	0.60	540107	37	0.61
South Region	5373070	48	0.55	3096915	54	0.52	1625924	57	0.61	279854	25	0.50	370377	25	0.51
West Region	1426395	13	0.49	586036	10	0.50	184514	6.5	0.55	273974	25	0.46	381871	26	0.47
Work industry															
Oil & Gas Extraction, Mining	109824	1	0.69	60330	1	0.69	37853	1.3	0.72	5025	0.5	0.60	6616	0.4	0.63
Manufacturing, Durable Goods	1229645	11	0.63	641272	11	0.64	284846	10	0.65	131273	12	0.60	172254	12	0.61
Manufacturing, Nondurable Goods	578817	5.2	0.64	292024	5	0.64	144408	5.1	0.66	62490	5.6	0.63	79895	5.4	0.64
Transportation, Communications, Utilities	889043	7.9	0.66	438854	7.6	0.66	232413	8.2	0.69	93398	8.4	0.64	124378	8.4	0.65
Retail Trade	303461	2.7	0.57	142673	2.5	0.60	81708	2.9	0.56	34033	3.1	0.54	45047	3.1	0.54
Finance, Insurance, Real Estate	800486	7.1	0.63	363649	6.3	0.64	216827	7.6	0.64	93472	8.4	0.61	126538	8.6	0.62
Services	1251304	11	0.52	446191	7.7	0.56	312636	11	0.52	211459	19	0.49	281018	19	0.49
Missing	6051647	54	0.45	3402359	59	0.41	1530374	54	0.51	482306	43	0.48	636608	43	0.49
Plan type															
Comprehensive	195154	1.7	0.57	110691	1.9	0.53	35583	1.3	0.59	21489	1.9	0.64	27391	1.9	0.65
EPO	180535	1.6	0.47	67179	1.2	0.52	51016	1.8	0.47	28142	2.5	0.40	34198	2.3	0.42
HMO	1423277	13	0.58	777002	13	0.58	289246	10	0.58	149086	13	0.57	207943	14	0.58
POS	936062	8.3	0.53	553048	9.6	0.51	269110	9.5	0.53	48790	4.4	0.62	65114	4.4	0.63
PPO	7836969	70	0.51	4010291	69	0.48	1990178	70	0.56	792796	71	0.52	1043704	71	0.52
POS with Capitation	70736	0.6	0.48	41797	0.7	0.49	21321	0.8	0.43	3295	0.3	0.59	4323	0.3	0.60
CDHP	398536	3.6	0.62	174941	3	0.63	119400	4.2	0.63	45447	4.1	0.59	58748	4	0.60
HDHP	172958	1.5	0.56	52403	0.9	0.59	65211	2.3	0.59	24411	2.2	0.48	30933	2.1	0.49
All	11210000	100	0.52	5787352	100	0.50	2841065	100	0.56	1113456	100	0.53	1472354	100	0.54

Table 32: Complete regression results of non-indicated ARTI antibiotic Dx rates and state funding (MarketScan: 2007-2012).

Variable	Level (categorical variables)	Combined		Acute Bronchitis		Acute Pharyngitis		Actue Sinusitis		Common Cold	
		OR	P-value	OR	P-value	OR	P-value	OR	P-value	OR	P-value
Diagnosis	Acute Bronchitis	2.66	<.001								
	Acute Pharyngitis	1.33	<.001								
	Acute Sinusitis	2.95	<.001								
years	years	1.09	<.001								
Funding terms											
Funded		0.98	0.30	0.97	0.23	1.00	0.49	0.91	0.004	1.09	0.002
Funded X years		0.97	<.001	0.95	<.001	0.99	0.01	0.95	<.001	1.00	0.48
Defunding terms											
Defunded		0.99	0.32	1.02	0.14	0.97	0.04	1.01	0.18	1.00	0.40
Defunded X years		0.99	0.07	0.99	0.05	1.00	0.43	0.97	<.001	1.01	0.004
Additional GSA terms											
Cumulative # GSAWs (participated)		1.02	0.001								
Additional covariates*											
Sex	Women	1.00	0.05								
Age	35-44	1.15	<.001								
	45-54	1.16	<.001								
	55-64	1.13	<.001								
Occupation industry	Oil & Gas Extraction, Mining	1.32	<.001								
(ref=Services)	Manufacturing, Nondurable Goods	1.37	<.001								
	Manufacturing, Nondurable Goods	1.43	<.001								
	Transportation, Communications, Utilities	1.57	<.001								
	Retail trade	1.10	<.001								
	Finance, Insurance, Real estate	1.48	<.001								
	Other	0.66	<.001								
Health plan type	Comprehensive	0.93	0.01								
(ref=PPO)	EPO	0.68	<.001								
	HMO	1.36	<.001								
	POS	1.24	<.001								
	POS with capitation	1.12	<.001								
	CDHP	0.95	<.001								
	HDHP	0.96	0.02								

*Note: State and Month effects not shown.

Table 33: Complete regression results of non-indicated ARTI antibiotic Dx rates and the GSA Week (MarketScan: 2007-2012).

Variable	Level (cateogrical variables)	Combined		Acute Bronchitis		Acute Pharyngitis		Actue Sinusitis		Common Cold	
		OR	P-value	OR	P-value	OR	P-value	OR	P-value	OR	P-value
Diagnosis	Acute Bronchitis	2.79	<.001								
	Acute Pharyngitis	1.35	<.001								
	Acute Rhinosinusitis	3.10	<.001								
GSAW terms											
GSAW participant	yes	1.02	0.02	1.02	0.15	1.01	0.30	1.04	0.001	1.01	0.18
Post-GSAW	post-exposure	0.99	<.001	0.98	0.06	0.97	0.004	1.00	0.34	0.99	0.06
GSAW participant X Post-GSAW	post-exposure & yes	1.00	0.29	1.01	0.26	1.05	<.001	1.01	0.31	0.99	0.19
Funding terms											
Funded		1.05	0.15								
Funded X years		0.96	<.001								
Defunding terms											
Defunded		1.00	0.44								
Defunded X years		1.00	0.40								
Additional covariates*											
Sex	Women	0.99	0.02								
Age	35-44	1.17	<.001								
	45-54	1.20	<.001								
	55-64	1.17	<.001								
Occupation industry	Oil & Gas Extraction, Mining	1.29	<.001								
(ref=Services)	Manufacturing, Nondurable Goods	1.39	<.001								
	Manufacturing, Nondurable Goods	1.42	<.001								
	Transportation, Communications, Utili	1.58	<.001								
	Retail trade	1.12	<.001								
	Finance, Insurance, Real estate	1.48	<.001								
	Other	0.65	<.001								
Health plan type	Comprehensive	0.97	0.11								
(ref=PPO)	EPO	0.65	<.001								
	HMO	1.35	<.001								
	POS	1.23	<.001								
	POS with capitation	1.12	<.001								
	CDHP	0.95	<.001								
	HDHP	0.98	0.18								

*Note: State and Month effects not shown.

B.4 Specific Aim 3: Latent-Factor Structural Model

Table 34: Covariate distribution by Provider ID missing versus present.
(MarketScan: 2008-2012)

	All			Provider ID					
				Present			Missing		
	N	Col %	Rx rates	N	Col %	Rx rates	N	Col %	Rx rates
Diagnosis									
Acute Bronchitis	5095071	22	0.62	1754445	22	0.64	3340626	22	0.60
Acute Pharyngitis	4131570	18	0.48	1407455	18	0.51	2724115	18	0.46
Acute Rhino-sinusitis	7434720	32	0.66	2569186	32	0.68	4865534	32	0.64
Common cold or URTI(NOS)	6301131	27	0.42	2239104	28	0.44	4062027	27	0.40
Sex									
Male	8612405	38	0.55	2908238	36	0.57	5704167	38	0.54
Female	14350000	62	0.55	5061952	64	0.57	9288135	62	0.54
Age									
18-34	7584864	33	0.52	2621100	33	0.54	4963764	33	0.50
35-44	5659170	25	0.56	1987885	25	0.59	3671285	24	0.55
45-54	5520383	24	0.57	1944382	24	0.59	3576001	24	0.56
55-64	4198075	18	0.57	1416823	18	0.58	2781252	19	0.56
Region*									
Northeast Region	3405814	15	0.44	877018	11	0.58	2528796	17	0.39
North Central Region	5905316	26	0.57	1735458	22	0.58	4169858	28	0.57
South Region	10370000	45	0.58	4336908	54	0.57	6029075	40	0.60
West Region	3285379	14	0.50	1020806	13	0.58	2264573	15	0.47
Work industry									
Oil & Gas Extraction, Mining	236116	1	0.70	91090	1.1	0.76	145026	1	0.65
Manufacturing, Durable Goods	2490382	11	0.63	587820	7.4	0.69	1902562	13	0.61
Manufacturing, Nondurable Goods	1225852	5.3	0.64	302596	3.8	0.70	923256	6.2	0.62
Transportation, Communications, Utilities	1922449	8.4	0.66	580003	7.3	0.70	1342446	9	0.65
Retail Trade	693528	3	0.55	162786	2	0.69	530742	3.5	0.50
Finance, Insurance, Real Estate	1860452	8.1	0.62	521230	6.5	0.68	1339222	8.9	0.60
Services	3198596	14	0.50	624243	7.8	0.66	2574353	17	0.46
Missing	11340000	49	0.50	5100422	64	0.51	6234695	42	0.50
Plan type									
Comprehensive	343223	1.5	0.60	67995	0.9	0.47	275228	1.8	0.64
EPO	480524	2.1	0.44	156791	2	0.69	323733	2.2	0.32
HMO	2698913	12	0.58	1332531	17	0.65	1366382	9.1	0.51
POS	1760021	7.7	0.55	832337	10	0.58	927684	6.2	0.52
PPO	16100000	70	0.54	5147756	65	0.54	10950000	73	0.54
POS with Capitation	131973	0.6	0.46	43405	0.5	0.46	88568	0.6	0.45
CDHP	948695	4.1	0.61	304411	3.8	0.72	644284	4.3	0.55
HDHP	502581	2.2	0.55	84964	1.1	0.68	417617	2.8	0.53
All	22960000	100	0.55	7970190	100	0.57	14990000	100	0.54

Table 35: Providers stratified by case-load counts in the year (MarketScan: 2008-2012).

Note: many cases were missing provider ids (~65%, Table 34)

Case load*	Provider-years		Cases		Rx rates
	N	%	N	%	
1	180008	38.8	180008	2	0.52
(1,25]	232729	50.2	1549935	19	0.55
(25,100]	37483	8.1	1838070	23	0.58
(100,1000]	12874	2.8	3035732	38	0.58
(1000,10000]	620	0.1	1246904	16	0.57
>1E4	8	0	114601	1	0.51
All	463722	100	7965250	100	0.54

* Provider case load in the year.

Table 36: Patients stratified by case-burden counts in the year (MarketScan: 2008-2012).

Note: many cases were missing provider ids (~65%, see Table 34)

Cases*	Patient-years		Providers**				Cases	
			1	2	3	4		
	N	%	%				N	%
1	6050566	87	100	.	.	.	6050566	76
2	812316	12	75	25	.	.	1624632	20
3	88357	1	68	27	5	.	265071	3
4	6059	0	64	27	7	2	24236	0
5	149	0	62	30	9	.	745	0
All	6957447	100	97	3	0	0	7965250	100

* Patient case count in the year.

** Providers in the year.

Table 37: Covariates and logistic regression results for the disease-severity model.
(MarketScan: 2007)

Covariates	N	%	Rx rate	OR	P-value
Diagnosis					
Acute Bronchitis	768271	23	0.55	2.20	<.001
Acute Pharyngitis	593227	18	0.46	1.43	<.001
Acute Sinusitis	1079436	32	0.57	2.29	<.001
Common cold or URTI (NOS)	920239	27	0.38	ref	
Sex					
Male	1246136	37	0.50	ref	
Female	2115037	63	0.49	0.96	<.001
Age					
18-34	1080935	32	0.48	ref	
35-44	849671	25	0.50	1.06	<.001
45-54	826075	25	0.50	1.02	<.001
55-64	604492	18	0.50	0.98	<.001
Region					
Northeast Region	283128	8.4	0.54		
North Central Region	941927	28	0.47		
South Region	1736594	52	0.49		
West Region	399524	12	0.52		
Work industry					
Oil & Gas Extraction, Mining	30912	0.9	0.67	1.26	<.001
Manufacturing, Durable Goods	421401	13	0.64	1.13	<.001
Manufacturing, Nondurable Goods	179535	5.3	0.63	1.10	<.001
Transportation, Communications, Utilities	260838	7.8	0.64	1.26	<.001
Retail Trade	78959	2.3	0.63	1.07	<.001
Finance, Insurance, Real Estate	197802	5.9	0.64	1.18	<.001
Services	195899	5.8	0.61	ref	
Other	1995827	59	0.40	0.46	<.001
Plan type					
Comprehensive	82715	2.5	0.51	0.88	<.001
EPO	26232	0.8	0.62	1.33	<.001
HMO	559316	17	0.58	1.59	<.001
POS	347747	10	0.50	0.80	<.001
PPO	2238403	67	0.46	ref	
POS with Capitation	27490	0.8	0.52	1.48	<.001
CDHP	79160	2.4	0.63	1.48	<.001
HDHP	110	0	0.60	2.82	0.002
Location					
Office	3361173	100	0.49		
Provider					
Family Practice	1857741	55	0.52	ref	
Internal Medicine (NEC)	694547	21	0.48	0.93	<.001
Medical Doctor - MD (NEC)	212714	6.3	0.48	0.78	<.001
Other	596171	18	0.41	0.63	<.001
Service					
Physician Non-Specialty OP Office Visits	3037251	90	0.49	ref	
Professional OP Office Visits	191884	5.7	0.57	1.67	<.001
Physician Specialty OP Office Visits	127808	3.8	0.46	1.40	<.001
Other	4230	0.1	0.68	2.17	<.001
All	3361173	100	0.49		

Covariates	N	%	Rx rate	OR	P-value
State					
04-Connecticut	33297	1	0.60	1.15	<.001
05-Maine	4117	0.1	0.54	0.54	<.001
06-Massachusetts	24008	0.7	0.58	0.77	<.001
07-New Hampshire	6190	0.2	0.60	0.72	<.001
08-Rhode Island	3959	0.1	0.57	0.70	<.001
09-Vermont	1769	0.1	0.51	0.54	<.001
11-New Jersey	46369	1.4	0.56	0.69	<.001
12-New York	81801	2.4	0.47	0.66	<.001
13-Pennsylvania	81618	2.4	0.57	0.98	0.14
16-Illinois	280916	8.4	0.16	0.21	<.001
17-Indiana	66015	2	0.63	1.09	<.001
18-Michigan	136159	4.1	0.62	0.86	<.001
19-Ohio	104721	3.1	0.62	0.96	<.001
20-Wisconsin	28733	0.9	0.51	0.67	<.001
22-Iowa	173493	5.2	0.59	0.90	<.001
23-Kansas	36891	1.1	0.66	1.45	<.001
24-Minnesota	19230	0.6	0.52	0.62	<.001
25-Missouri	58020	1.7	0.62	1.12	<.001
26-Nebraska	15440	0.5	0.60	0.90	<.001
27-North Dakota	1903	0.1	0.58	0.75	<.001
28-South Dakota	20406	0.6	0.64	1.32	<.001
32-Delaware	20043	0.6	0.62	1.32	<.001
33-Florida	99747	3	0.54	0.79	<.001
34-Georgia	136572	4.1	0.63	1.37	<.001
35-Maryland	178161	5.3	0.32	0.46	<.001
36-North Carolina	66784	2	0.60	0.89	<.001
37-South Carolina	169165	5	0.40	0.63	<.001
38-Virginia	87256	2.6	0.45	0.62	<.001
39-West Virginia	9815	0.3	0.66	1.30	<.001
41-Alabama	61221	1.8	0.66	1.55	<.001
42-Kentucky	32850	1	0.65	1.08	<.001
43-Mississippi	55577	1.7	0.70	3.05	<.001
44-Tennessee	113055	3.4	0.67	1.70	<.001
46-Arkansas	23588	0.7	0.63	1.14	<.001
47-Louisiana	32900	1	0.64	1.30	<.001
49-Texas	649860	19	0.42	0.72	<.001
52-Arizona	24464	0.7	0.61	0.89	<.001
53-Colorado	28177	0.8	0.57	0.85	<.001
54-Idaho	5026	0.1	0.54	0.78	<.001
55-Montana	17091	0.5	0.40	0.75	<.001
56-Nevada	16240	0.5	0.60	1.26	<.001
57-New Mexico	50980	1.5	0.45	0.78	<.001
58-Utah	8474	0.3	0.54	0.67	<.001
59-Wyoming	2877	0.1	0.59	1.12	0.07
61-Alaska	3098	0.1	0.55	0.87	0.02
62-California	179748	5.3	0.52	ref	
64-Oregon	22019	0.7	0.51	0.87	<.001
65-Washington	41330	1.2	0.55	0.66	<.001

Covariates	N	%	Rx rate	OR	P-value
Month					
1	471141	14	0.49	ref	
2	404888	12	0.49	1.03	<.001
3	346364	10	0.49	1.04	<.001
4	269969	8	0.50	1.05	<.001
5	233219	6.9	0.49	1.03	<.001
6	173464	5.2	0.48	1.01	0.30
7	152414	4.5	0.48	1.03	0.01
8	176705	5.3	0.49	1.02	0.06
9	224723	6.7	0.50	1.07	<.001
10	260925	7.8	0.49	1.03	<.001
11	311635	9.3	0.50	1.09	<.001
12	335726	10	0.50	1.11	<.001

Table 38: Covariate distribution by year.
(MarketScan, 2008-2012: provider ≥ 25 cases and ≤ 1000 cases per year **AND** patient ≥ 3 cases per year)

	All		Year				
			2008	2009	2010	2011	2012
Covariates	N	%					
Diagnosis							
Acute Bronchitis	34210	18	19	18	16	16	17
Acute Pharyngitis	27456	14	15	15	14	14	13
Acute Sinusitis	83536	43	42	41	47	46	46
Common cold or URTI (NOS)	47240	25	24	26	24	24	24
Sex							
Male	59172	31	31	31	30	31	31
Female	133270	69	69	69	70	69	69
Age							
18-34	59806	31	30	32	31	31	31
35-44	51766	27	27	27	27	27	26
45-54	47836	25	26	24	25	24	25
55-64	33034	17	17	16	17	18	18
Region							
Northeast Region	18100	9.4	7.2	7.8	13	13	13
North Central Region	40431	21	26	24	14	14	13
South Region	118792	62	61	62	62	62	63
West Region	15119	7.9	6.1	6.2	11	11	11
Work industry							
Oil & Gas Extraction, Mining	2778	1.4	0.8	1.1	2.4	2.3	2.5
Manufacturing, Durable Goods	12870	6.7	5.9	5.2	7.8	9.7	8.6
Manufacturing, Nondurable Goods	8183	4.3	3.1	3.2	5.9	6.4	6.3
Transportation, Communications, Utilities	14330	7.4	6.9	6.5	10	9.3	6.4
Retail Trade	3480	1.8	1.8	1.6	1.8	2	2.1
Finance, Insurance, Real Estate	11043	5.7	5	4.6	9.1	8.4	4.7
Services	12500	6.5	6	6.3	5.6	8.4	7.4
Other	127258	66	71	72	57	53	62
Plan type							
Comprehensive	1387	0.7	0.9	0.7	0.5	0.5	0.6
EPO	3504	1.8	1	0.9	4.2	4.2	1.7
HMO	30363	16	15	15	19	18	15
POS	24295	13	13	12	15	11	11
PPO	124006	64	67	69	55	57	61
POS with Capitation	1009	0.5	0.6	0.5	0.4	0.5	0.4
CDHP	6442	3.3	1.5	1.7	4.6	6.9	7.7
HDHP	1436	0.7	0.2	0.4	1.1	1.7	1.9
Provider							
Missing	9300	4.8	5.3	7.1	2.8	2.4	1.7
Family Practice	110788	58	59	56	56	58	58
Internal Medicine (NEC)	32098	17	17	17	18	16	15
Medical Doctor - MD (NEC)	8361	4.3	3.3	3.3	7.2	5.2	6
Other	31895	17	15	16	16	18	19
Service							
Physician Non-Specialty OP Office Visits	170092	88	90	90	87	85	84
Professional OP Office Visits	16020	8.3	6.4	7.3	9.1	11	12
Physician Specialty OP Office Visits	6176	3.2	3.2	3.2	3.3	3.2	3.4
Other	154	0.1	0.1	0.1	0.1	0.2	0.1
All	**192442**						

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