Antibiotic Prescribing Patterns for Acute Sinusitis in Nova Scotian Adults

by

Jody Collin

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Dalhousie is located on Mi'kma'ki, the ancestral and
unceded territory of the Mi'kmaq. We are all treaty people.

This thesis work is dedicated to my husband, Popo, who has been a source of support, love, and most importantly laughs, during the challenges of work and school. I am thankful every day to have you in my life. In addition, I would like to thank my Mom and Dad, who taught me the value of hard work and the joy of learning. I would not be where I am without you.

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ABSTRACT

Background: Antibiotic resistance is one of the biggest threats to global health, food security, and development, yet one of the most important drivers of antibiotic resistance, inappropriate antibiotic use, is not well defined in community settings. This study describes antibiotic prescribing and practice variation in community settings using a condition commonly resulting in antibiotic therapy, acute sinusitis.

Methods: I conducted a 24-month non-interventional retrospective cross-sectional study analyzing outpatient antibiotic use for acute sinusitis in adults over 18 across Nova Scotia, Canada between October 2016 and October 2018. All Nova Scotian adult patients who had an encounter with a prescriber for acute sinusitis were included. I used administrative data from the MSI Physician Billings database, the Drug Information System, the Licensed Provider Registry, and the Insured Patients Registry datasets. Using descriptive statistics and random effects logistic regression models, association of a diagnosis of acute sinusitis with antibiotic prescribing and duration of antibiotic therapy were investigated.

Results: Antibiotics were prescribed at 62.3% of encounters, and 42.3% of those were likely unnecessary. Although there are some patient and provider variables associated with antibiotic prescribing (female patients, patients between the ages of 30 and 79, rural providers, and providers who graduated before 2010), models indicate substantial between-provider heterogeneity in antibiotic prescribing for acute sinusitis, ranging from 0 to 100%. Only 4% of providers achieved the recommended prescribing rate of 20% or less. 71.3% of dispensed antibiotic prescriptions were for more than 7 days of treatment (longer than recommended). There are some patient and provider variables associated with a prescription duration of five to seven days (female patients, fewer encounters, rural providers, and providers trained internationally), but there is significant between-provider heterogeneity which can not be explained by these variables. Amoxicillin was the most dispensed antibiotic (37.4% of dispensed prescriptions).

Interpretation: There was a large amount of unnecessary antibiotic prescribing for acute sinusitis which was driven by both patient (sex, age, and number of encounters) and provider factors (graduation year and location). However, most of the variability in prescribing rates was due to individual provider differences. There is room for improvement and a multifaceted stewardship approach including broad population-based provider initiatives and targeted initiatives for providers with the largest number of prescriptions could improve prescribing rates.

LIST OF ABBREVIATIONS USED

COPD: Chronic Obstructive Pulmonary Disease

DIS: Drug Information System

ICC: Intra-class Correlation Coefficient

ICD-9: International Classification of Diseases version 9

ID: Identification

MOR: Median Odds Ratio

MSI: Medical Services Insurance

NS: Nova Scotia

QT: the interval from the beginning of the QRS complex to the end of the T wave on an electrocardiogram

UK: United Kingdom

US: United States

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CHAPTER 1: INTRODUCTION

The World Health Organization lists antibiotic resistance as one of the biggest threats to global health, food security, and development (1). Antimicrobial resistance is the term used to describe microorganisms that are resistant to treatment by antimicrobial drugs (2,3). Since the introduction of antimicrobial therapies, antimicrobial resistance has been spreading and has become a public health concern (2). There are many reasons for the spread of resistance, but misuse of antibiotics due to poor prescribing practices and poor patient adherence are important drivers (3,4). As resistance worsens, so too does our ability to treat infections, and this has led to more hospitalizations, longer hospital stays, and thousands of deaths annually (3,5–7). Despite the threat of antimicrobial resistance, in North America, prescription rates for antibiotics continue to exceed the recommendations, and in Nova Scotia there was an overall 1.3% increase in antibiotic prescribing from 2016 to 2017 (8,9).

There is likely a considerable amount of inappropriate prescribing in the community setting; however, the degree of inappropriate prescribing in Canada is not well defined. In the US, it is estimated that up to 50% of antibiotic prescriptions in the community are unnecessary, and in the UK, overprescribing for respiratory tract infections is common (10–13) . In Canada in 2017, the majority of antimicrobial use occurred in the community setting, with 92% of all defined daily doses of antibiotics dispensed in community pharmacies (8). The most common reasons to prescribe antibiotics were for respiratory and urinary tract infections (8). Antibiotics were prescribed in 82% of acute sinusitis diagnoses (3). In Ontario, Schwartz et al. estimated that about 15% of antibiotic prescriptions were unnecessary and the common cold, acute bronchitis, acute sinusitis, and other nonbacterial infections were responsible for 80% of unnecessary prescriptions. Specifically, 48% of antibiotics prescribed for acute sinusitis were deemed unnecessary (14).

Because most cases of acute sinusitis are viral, the American Academy of Otolaryngology, the Canadian Society of Otolaryngology, and Choosing Wisely Canada recommend against antibiotic treatment and instead recommend watchful waiting for 7 to 14 days (15–20) . For bacterial sinusitis, it is also recommended to use watchful waiting for 14 days as long as there will be appropriate follow up (15,18,20,21). This is because antibiotic treatment does not shorten the duration of symptoms in most cases and many cases resolve within 2 weeks without antibiotic treatment (17,21). Despite spontaneous resolution, 1 in 5 adult prescriptions for antibiotics are for treating acute sinusitis (21). Adverse effects can occur with antibiotic treatment and this results in a number needed to harm of 8 demonstrating that the risk of harm outweighs the potential benefits (22,23).

To effectively apply antimicrobial stewardship interventions in Nova Scotia, patterns of inappropriate prescribing must first be determined. Antimicrobial stewardship is a concept that embodies the "practical, judicious use of antimicrobials to decrease adverse outcomes from antimicrobials while optimizing the treatment of bacterial infections to reduce the emergence of resistant pathogens" (24). Antimicrobial stewardship interventions include audit and feedback, a formulary of targeted antimicrobials and approved indications, education, and guideline development, among others.

I conducted a non-interventional retrospective cross-sectional study analyzing outpatient antibiotic use for acute sinusitis in adults over 18 across Nova Scotia, Canada between October 2016 and October 2018. The aims of this study are to: (1) describe antibiotic prescribing in a community setting for acute sinusitis in adults in Nova Scotia, (2) determine how much practice variation there is in how often therapeutic guidelines for acute sinusitis, as defined by the Dalhousie Academic Detailing Service document "Antibiotics: Why and Why Not", are followed for prescribing and duration, (3) determine which prescriber and patient factors affect prescribing patterns and (4) provide baseline data on antibiotic prescribing rates and patterns for acute sinusitis which can be used for feedback to prescribers. This study will help to characterize outpatient antimicrobial use for sinusitis in Nova Scotia and provide valuable information on factors associated with unnecessary antibiotic prescribing. This can be used to assist in the development of antimicrobial stewardship policy and education and to promote appropriate prescribing of antibiotics and reduce the serious consequences of antimicrobial resistance.

CHAPTER 2: LITERATURE REVIEW

2.1 ANTIMICROBIAL RESISTANCE

Antimicrobial resistance is the term used to describe microorganisms that are resistant to treatment by antimicrobial drugs (2,3). These microorganisms can include bacteria, fungi, viruses, and parasites; however, the most common form of antimicrobial resistance involves bacteria having antibiotic resistance (3). Antibiotics can occur naturally or may be manufactured semi-synthetically or synthetically (25,26). They are classified as either bacteriostatic, which can slow down or stop bacterial growth, or bactericidal, which can kill bacteria (25,26). Throughout history, bacteria have evolved various protective mechanisms in response to external threats, like antibiotics, to ensure their survival (27). Through the process of natural selection, resistant strains have been able to survive, multiply, and replace non-resistant strains of bacteria (25).

Since the discovery and distribution of penicillin in 1945, bacteria have continued to evolve, and resistance is spreading enough that antibiotic resistance has become a major public health concern (2). There are many reasons for the spread of resistance, but misuse of antibiotics due to poor prescribing practices and poor patient adherence are important drivers (3,4). As resistance worsens, so too does our ability to treat infections, and this has led to more hospitalizations, longer hospital stays, and thousands of deaths annually (3,5–7) In turn, health care costs continue to rise (3).

Antimicrobial resistance has occurred in almost all antibiotic classes, and in some cases has lead to superbugs (2,4). These bacteria are no longer sensitive to first line antibiotics and are usually resistant to multiple drugs (4). Common examples include multidrug resistant *Mycobacterium tuberculosis*, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), *Clostridioides difficile*, and fluoroquinolone resistant *Neisseria gonorrhoeae* (2,26). Superbugs cause excess hospitalizations and deaths, particularly in immunocompromised patients, and the rate of infections are growing (26). It is estimated that 10 million people will die globally each year by 2050 as a result of antimicrobial resistance, and antimicrobial resistance will surpass cancer as the leading cause of death worldwide(28).

2.2 Mechanisms and Transmission of Antimicrobial Resistance

Antimicrobial resistance can occur both within and between hosts by a variety of mechanisms (7). Some bacteria have genes that protect them from antibiotics by altering the drug targets, inactivating the drug, or decreasing the concentration of the drug (25,26). These bacteria survive and multiply quickly so that future generations of the bacteria carry the resistant genes (29). In some cases, they may also transfer the resistant genes to other bacteria through a process called horizontal gene transfer (30). As bacteria are exposed to more and more antibiotics, they become resistant to more drugs, leaving few effective treatments (31).

It is accepted that the spread of antimicrobial resistance at both the patient and population level can be attributed in large part to the misuse of antibiotics (2,32–34). In fact, antibiotic use may be the largest modifiable risk factor for antimicrobial resistance (35–38). The reasons for misuse of antibiotics are complex, but include both poor prescribing practices and inappropriate expectations and misuse of antibiotics by the general public (39). The appropriateness of prescribing, dosing and timing of antibiotics all play a role in the spread of antimicrobial resistance (7). Resistance may develop in individuals who do not have a bacterial infection, but are treated with antibiotics (7). Antimicrobial resistance appears to evolve when a dose which is too low to kill resistant strains is prescribed (7). In addition, there is evidence that long courses of antibiotics are associated with higher frequency of resistance (40–43)

In addition to human antimicrobial consumption, other drivers of antimicrobial resistance include "agricultural use of antibiotics, environmental contamination, healthcare transmission, suboptimal diagnostics, suboptimal vaccination, suboptimal dosing, mass drug administration, transmission by food, [and] increasing global trade and travel" (40–44).

2.3 IMPLICATIONS OF RESISTANCE IN PRACTICE

There are serious economic and health related costs to antimicrobial resistance and it is viewed by many as one of the primary global public health threats today. Antimicrobial resistance was listed in 2014 as one of the 50 biggest global threats by the World Economic Forum and they estimated its threat to be as severe as climate change (45). Mortality from antibiotic resistant infections is increasing each year. In Canada in 2018, approximately 26% of infections were resistant to antibiotics, over 14,000 deaths were associated with resistant infections, and 5400 of those deaths were directly attributable to antimicrobial resistance (46). It is predicted that resistance rates will gradually increase to 40%, and by 2050, this would result in 396, 000 Canadian lives lost (46). Worldwide, the numbers are estimated to rise to 10 million deaths per year by 2050 which is 1 person dying every 3 seconds (4,26,47–50).

Antimicrobial resistant infections are also associated with increased morbidity. This includes reduced quality of life, increased recurrence rates, increased complications, longer hospital admissions, higher toxicity and adverse drug reactions associated with newer drugs, and future infections with resistant organisms (25,51). Patients being treated for an antimicrobial resistant infection are up to three times as likely to get another infection from a resistant germ (52). Unnecessary antimicrobial therapy may be associated with cases of the development of obesity, allergies, renal injury, hematologic effects, hepatobiliary effects, neurologic symptoms, QT prolongation, and opportunistic infections from yeast and *C. difficile* (19,53–56). In addition, people taking antibiotics have about a 20% chance of adverse events and up to a 30% risk of allergic reactions and gastrointestinal symptoms (19,35–38).

When examining the financial impact of antimicrobial resistance, it is estimated that the world economy loses $100 trillion annually as a result (57). This is because resistant infections result in longer hospitalizations, more expensive drugs, more visits to health care providers, and disabilities (26) . In Canada, in 2018, an estimated $1.4 billion dollars were spent on resistant infections and this is expected to increase by $13 to $21 billion annually if resistance rates remain stable at 26% or gradually increase to 40% as predicted (46). This would be a loss of $396 billion in gross domestic product (GDP) by 2050 (46) .

The impact of antimicrobial resistance is not limited to the human population. Many antibiotics are used in food production, and they are largely excreted unmetabolized in the environment which can increase the resistance in any exposed bacteria. It has been demonstrated that these bacteria exist and are circulating in the soil, plants, and the food chain (4). Some of the drugs used in animals are the same or similar to those used in humans, and the consequence is increased antimicrobial resistance in humans. For instance, after the introduction of fluoroquinolone antibiotics in poultry farms in the Netherlands, there were increases in antimicrobial resistance both in the chickens and in farm workers (58) . In order to counteract this trend, some countries have imposed bans on certain antibiotics in food animals; however, these measures are not worldwide (4).

2.4 ANTIMICROBIAL USE

In North America, prescription rates for antibiotics continue to exceed the recommendations, and in seniors in Canada, prescription rates continue to rise (8,9). The Centers for Disease Control and Prevention (CDC) estimates that 50% of antibiotics prescribed in US emergency rooms are unnecessary because the infections are caused by viruses (17,26). An estimated 23 million antibiotic prescriptions are written annually in Canada (59). Whereas antibiotic prescribing for children is showing a decreasing trend, prescription rates for Canadians aged 60 years and older are increasing and they are 60% greater than in adults 15-59 years (8) . In 2017, 92.3% of people age 60 and over received a prescription for an antibiotic (8). The prescribing rates differ among provinces, and in Nova Scotia there was an overall 1.3% increase in antibiotic prescribing from 2016 to 2017 whereas some provinces showed decreases in overall prescribing (8). Nova Scotia ranked in the top five provinces regarding the total number of antibiotic prescriptions per 1000 hospital inhabitant-days at 693.2 (8). In the United States, it is estimated that 30%

of antibiotics prescribed in primary care clinics and 47 million prescriptions written in emergency departments were unnecessary (26) .

Prescribing rates also vary by indication. In adults, the most common reasons to prescribe antibiotics are for respiratory and urinary tract infections (8) . Antibiotics are prescribed in 82% of acute sinusitis diagnoses in both Canada and the US, 77% of acute bronchitis diagnoses in Canada, and 74% of pneumonia diagnoses in Canada (8,9) . Fleming-Dutra et al. found that sinusitis was the single diagnosis associated with the most prescriptions in the United States, followed by otitis media and pharyngitis (10) . When looking at all antibiotics prescribed for Canadian adults, 15-21% are prescribed for treating sinus infections.

2.5 Antimicrobial Use in Community Practice in Canada

In 2017, most antimicrobial use occurred in the community setting. Ninety-two percent of all antibiotic defined daily doses in Canada were dispensed by community pharmacies, and this equalled more than 24 million prescriptions at a cost of approximately $756 million (8). This means that on any given day, 2% of the Canadian population was likely taking an antibiotic (8) . In Ontario, 621 prescriptions for antibiotics were dispensed per 1000 people in a 1 year period (60). Most antibiotics in the community setting are for oral use and 66% are prescribed by community practitioners including family physicians and general practitioners (3) . The top three antibiotics prescribed by community practitioners were amoxicillin, azithromycin and ciprofloxacin (3). Schwartz et al. noted that there was geographic variability in prescribing rates between health regions in Ontario (60).

There is likely a considerable amount of inappropriate prescribing in the community setting; however, the degree to which this is the case in Canada is not well defined. In the US, it is estimated that up to 50% of antibiotic prescriptions are unnecessary. In the UK, overprescribing for respiratory tract infections is common (10–13) . In Ontario, it is estimated that about 15% of antibiotic prescriptions are unnecessary and the common cold, acute bronchitis, acute sinusitis, and other nonbacterial infections are responsible for 80% of unnecessary prescriptions. Specifically, 68% of acute sinusitis diagnoses received antibiotics, and a rate of 1 to 20% was considered acceptable. (14). There are approximately 30 million prescriptions for antibiotics for sinusitis in the US each year which makes it the fifth most common diagnosis for which antibiotics are prescribed (16,20). In Canada, 82% of diagnoses of acute sinusitis resulted in antibiotic recommendations and 14% of all antimicrobial recommendations were for sinusitis in 2014 (3).

2.6 SINUSITIS (EPIDEMIOLOGY, TREATMENT, GUIDELINES)

Sinusitis, also called acute rhinosinusitis (ARS), is an inflammation of the sinuses and nasal cavity which can be caused by viruses, bacteria, or fungi (20,61). The sinuses act as filters for "pollutants, microorganisms, dust, and other antigens"(61). The sinuses do this with the help of tiny hairs called cilia that line the nasal passages. They work together to push the filtered debris, mucus, and other substances towards the pharynx where it is ultimately swallowed (61). If the sinuses and nasal passages can not clear the filtered debris and mucous, inflammation and sinusitis occurs (61). Although there are several causes of chronic sinusitis, acute sinusitis is usually caused by upper respiratory tract infections or nasal allergies which cause local edema. Sinusitis is classified as acute if symptoms last less than 4 weeks (61) . The most common causes of acute sinusitis are viruses including *rhinovirus*, *adenovirus*, *influenza*, and *parainfluenza* (21) . The majority of cases of viral acute sinusitis resolve without treatment, but about 0.5 to 2.0% of cases will develop into bacterial infections in adults (21) . The common pathogens which cause bacterial acute sinusitis are S*treptococcus pneumoniae* (38%), *Haemophilus influenzae* (36%), and *Moraxella catarrhalis* (16%) (18) . Fungal infections usually only occur in immunocompromised patients (61) .

Symptoms of acute sinusitis include purulent mucous, obstruction of the nasal passages and facial pain or pressure often described as a headache (21). However, a meta-analysis found that clinical signs and symptoms were not effective at determining which patients would benefit from antibiotics (15). In order to avoid unnecessary antibiotics, clinicians must be able to distinguish between viral and bacterial infections but also be aware of "local resistance patterns and the prevalence of penicillin non-susceptible *S. pneumoniae*" (21). The Infectious Disease Society of America recommends that a bacterial infection should be suspected with the following symptoms: persistent symptoms for more than 10 days, fever >39°C and purulent discharge lasting 3-4 consecutive days, or clinical deterioration 5 or more days after the onset of symptoms (16) . The Canadian guidelines are similar with the exception of persistent symptoms for more than 7 days instead of 10 (18). There is an increased chance that the infection is bacterial if the symptoms persist beyond 10 days, there is double-sickening (the patient gets worse after initial improvement), or the patient has a high fever (15,21) . It is important to note that recurrent cases of acute sinusitis should be investigated as there may be chronic rhinosinusitis, or an underlying condition such as cystic fibrosis, asthma, ciliary dyskinesia, or an immunocompromised state (20). Considering all the above information, most cases are viral and spontaneously resolve.

Because most cases of sinusitis are viral, the American Academy of Otolaryngology, the Canadian Society of Otolaryngology, and Choosing Wisely Canada recommend against antibiotic treatment and instead recommend watchful waiting for 7 to 14 days (15–20) . There is not a consensus on the percentage of cases of acute sinusitis that require antibiotics, but Canadian Choosing Wisely guidelines state that 2 to 10% of cases require treatment, and on the more generous end, Schwartz et al. recommend 1 to 20% (14,17). Even for suspected bacterial acute sinusitis, it is recommended to use watchful waiting for 14 days as long as there will be appropriate follow up (15,18,20,21). This is because antibiotic treatment does not shorten the duration of symptoms in most cases and many cases resolve within 2 weeks without antibiotic treatment (17,21–23,62,63). One Cochrane review showed that 46% of patients had resolution of symptoms in 7 days and 64% had resolution of symptoms in 14 days without antibiotic treatment (23). Although there was a slightly higher cure rate between 7 and 15 days for those who took antibiotics, only 5 to 11% of patients had a faster cure. The number needed to treat for an additional beneficial outcome was 19 [95% CI 10-205] and the number needed to harm (mostly GI upset) was 8 [95% CI 6-12] (22,23,63). Only 5% of those patients who did not start with an antibiotic had to start an antibiotic later because their condition worsened (23). Despite spontaneous resolution and the risk of treatment outweighing the benefits, 1 in 5 adult prescriptions for antibiotics are for treating acute sinusitis (21–23).

If a bacterial infection warrants treatment, the choice of antibiotic should take allergies, risk of complications, resistance patterns, and failures of other treatments into consideration. First-line antibiotics include amoxicillin with or without clavulanate (15,16,18,20,64,65). Levofloxacin, a fluoroquinolone, should only be used for patients with no other options because it offers no benefit, is associated with a variety of adverse effects and is an overly broad-spectrum antibiotic (16,20,66,67). Other antibiotics such as macrolides, trimethoprim/sulfamethoxazole and cephalosporins have demonstrated high rates of resistance to *S. pneumoniae* and *H. influenzae* (16,20,64) . However, second generation cephalosporins, trimethoprim/sulfamethoxazole, doxycycline, and macrolides should be considered in individuals with a penicillin allergy depending on local resistance patterns (16,18,64) . Efforts should be made to confirm all penicillin allergies and reduce broad-spectrum antibiotic use. If antibiotic therapy is chosen, the optimal duration of therapy is unknown, and some sources recommend 5 to 10 days of therapy whereas others recommend 10 to 14 days or treatment 7 days beyond the resolution of symptoms (16,18,20) .

There is a 1 in 1000 chance of complications from sinusitis which can include cellulitis, thrombosis, abscesses, subdural hematoma, meningitis and subdural empyema which all have significant morbidity and mortality (21). If any complications are suspected or unusually severe symptoms are present, it is recommended that the patient promptly be referred to an otolaryngologist (18,21). Severe headache, altered mental status, systemic toxicity, swelling of the orbit, and change in visual acuity are all red flags which should lead to prompt referral (19).

Because not everyone with acute sinusitis seeks treatment, the incidence is difficult to estimate. A 2007 study in the US estimated that 26 million individuals were affected by acute sinusitis that year (68). Extrapolating this data to Canada, we can estimate that there is an annual occurrence of acute sinusitis in Canada of 2.6 million cases.

2.7 ANTIMICROBIAL STEWARDSHIP

Antimicrobial stewardship is a recent concept that embodies the "practical, judicious use of antimicrobials to decrease adverse outcomes from antimicrobials while optimizing the treatment of bacterial infections to reduce the emergence of resistant pathogens" (24). "Vital components of [antimicrobial stewardship] include appropriate testing to diagnose whether infections are viral or bacterial, and using clinical follow-up rather than antibiotics in cases where uncertainty exists" (69). This in turn, ensures less treatment failure and less consumption of unnecessary antibiotics. It also decreases adverse effects and costs associated with antimicrobial use (24) .

Strategies of antimicrobial stewardship include watchful waiting or delayed prescribing, narrowing antimicrobial spectrum, strict adherence to guidelines for dosage, duration, and timing of antibiotics, staying abreast with local resistance patterns, monitoring prescribing patterns to identify and improve sources of misuse, educational material in clinics and pharmacies, educating patients with dialogue about the consequences of misuse of antibiotics, developing clear follow up plans with patients in case their symptoms do not improve, and practicing infection control and educating patients about infection control (26). Delayed prescribing has been a successful strategy in several countries at reducing antibiotic consumption rates (70). However, not all strategies should be employed in all situations. Immunocompromised patients may require broad spectrum therapy and watchful waiting may not be appropriate (24). In most cases, timely follow up with patients is more important than antibiotic prescriptions (24).

CHAPTER 3: OBJECTIVES

3.1 OBJECTIVE

Describe antibiotic prescribing patterns for acute sinusitis in adults in community practice Nova Scotia.

3.2 RESEARCH QUESTIONS

1. What is the rate of antibiotic prescribing for a diagnosis of acute sinusitis in a community setting amongst Nova Scotian adults?

2. What is the extent of practice variation in how often therapeutic guidelines for acute sinusitis, as defined by the Dalhousie Academic Detailing Service document "Antibiotics: Why and Why Not", are followed for prescribing and duration (6)?

3. Which of the following prescriber factors affect prescribing patterns for acute sinusitis in adults in Nova Scotia: age, sex, number of years practicing, country of training, geographic location, and type of prescriber?

4. Are patient's age and sex associated with prescribing patterns for acute sinusitis in adults in Nova Scotia?

CHAPTER 4: METHODS

4.1 SETTING AND POPULATION

I conducted a 24-month non-interventional retrospective cross-sectional study analyzing outpatient antibiotic use for acute sinusitis in adults over 18 years of age across Nova Scotia, Canada between October 2016, and October 2018. All Nova Scotian adult patients who had an encounter with a provider with a diagnosis for acute sinusitis were included. Patient characteristics used in the analysis included age and sex. Age was measured in 10-year age groups, and sex was defined as male or female. Children (less than 19) were excluded because the treatment of sinusitis in pediatric patients aged 1 to 18 follows different guidelines than adults (71).

4.2 DATA SOURCES

Data on sinusitis encounters were drawn from MSI Physician Billings from October 2016 to 2018. Sinusitis encounter data was linked to a population-based drug information system (DIS), Licensed Provider Registry, and the Insured Patients Registry datasets to capture antibiotic prescribing, and to uniquely identify patients, providers, and their attributes.

The MSI Physician Billings database covers most patient encounters in Nova Scotia with a provider covered under the provincial health care system. Encounters by recent migrants insured by other provinces, or persons covered under federal program (e.g. military) are not captured in the data. Providers who shadow bill, including some non fee-for-service providers, may have incomplete billing data. All encounters record diagnostic information using the international classification of diseases version 9 (ICD-9) coding. The DIS records information on prescriptions prescribed and dispensed in all community pharmacies in Nova Scotia. It does not include drugs dispensed to correctional centres and long-term care facilities not serviced by community pharmacies, drugs dispensed by Canadian Forces pharmacies, drugs dispensed by out-of-province pharmacies, and drugs dispensed from hospital pharmacies. The Licensed Provider Registry contains demographic information regarding health services providers. The Insured Patients Registry contains four data sets which record information regarding the population of insured health care beneficiaries in Nova Scotia. Data from these databases can be linked using unique physician or patient identifiers. I extracted data to summarize patient demographic information (age, sex), antibiotic information (agent, duration), encounter diagnoses, and prescriber information (type of prescriber, age, country of training, year of graduation, sex, geographic location).

4.3 VARIABLE DEFINITIONS AND INCLUSION/EXCLUSION CRITERIA

4.3.1 Providers

Providers included nurse practitioners and medical doctors who had an encounter with a patient diagnosed with acute sinusitis in Nova Scotia from October 2016 to October 2018. Provider variables included graduation year, age, sex, geographic location, and country of training. Graduation year ranged from 1960 to 2014 and was categorized by decade (1960-1969, 1970-1979, 1980-1989, 1990-1999, 2000-2009, 2010-2014). Prescriber age and graduation year were strongly correlated so prescriber age was not used in the analysis (rho =-0.8594). Provider sex variables were male and female, and geography variables were urban and rural determined from the second digit of the provider's postal code. A provider's country of training was categorized as either Canadian or International. There were 10 providers identified as out of province providers who were excluded because they were missing all the provider factors which were examined in this study. The 1184 providers who were not identified as general practitioners were also excluded because patients seeing specialists likely had more complicated patient histories and diagnoses than those seeking treatment from general practitioners. Ear, nose, and throat specialists, who have more training in the respiratory tract, also prescribe less antibiotics than general practitioners (9) .

4.3.2 Clinical Encounters for Sinusitis

An encounter was defined as the presence of a billing claim within the MSI Physician Billings Database. A physician billing of any ICD-9 code assigned to acute sinusitis (461.0 – 461.9) was used as a diagnosis of acute sinusitis. Canadian physician billing claims for a single encounter for sinusitis have previously been shown to have a sensitivity of 0.46 (95% CI: 0.38, 0.3) and specificity of 1.00 (95% CI: 1.00, 1.00) (72). If a patient had two or more encounters for sinusitis within 30 days, only the first encounter was included in the analysis because treatment guidelines differ after an unsuccessful treatment. A sensitivity analysis was conducted to determine if excluding these encounters affected the results.

If there was more than one diagnosis for a particular encounter, and the other diagnosis(es) were also conditions which could be treated with antibiotic therapy, the encounter was excluded due to the inability to link the antibiotic to the sinusitis diagnosis (Appendix A). For example, if a patient had both cystitis and acute sinusitis at their appointment, the observation was excluded because cystitis can be treated with antibiotics. However, if a patient was diagnosed with a common cold and sinusitis, the observation was included because the common cold should not be treated with antibiotics.

4.3.3 Prescriptions

An antibiotic prescription was related to a prescriber visit (an encounter) if there was one or more antibiotics dispensed and a claim generated in the DIS within 7 days after the encounter. Because the American Academy of Otolaryngology, the Canadian Society of Otolaryngology, and Choosing Wisely Canada recommend watchful waiting for 7 to 14 days, it is possible that a prescription dispensed more than 7 days after an encounter followed the recommended guidelines (16–20). Combining these prescriptions with prescriptions that were potentially inappropriate could confound the results. In addition, because there is no way to directly link a dispensed prescription to the encounter, there is a greater chance that prescriptions filled more than a week after the encounter were not related to the diagnosis. Eligible antibiotics included oral systemic antibacterial agents from the J01 class of pharmacologic agents categorized according to the World Health Organization's Anatomic Therapeutic Classification System (73). Topical antibiotics were excluded. For each antibiotic prescription dispensed, the drug and duration of therapy was obtained from the DIS. Subgroup analysis was performed including observations with a lag time between the encounter and antibiotic dispensation of seven or more days.

4.3.4 Therapy for Acute Sinusitis

There is not a consensus on the percentage of cases of acute sinusitis that require antibiotics, but Canadian Choosing Wisely guidelines state that 2 to 10% of cases require treatment; on the more generous end, Schwartz et al. recommend 1 to 20% (14,17). The least conservative of these, 20%, was used as an upper-bound on an acceptable prescribing rate for the purposes of this study. The Dalhousie University Academic Detailing document "Antibiotics: Why and Why Not?" was used as a reference for appropriate therapeutic treatment of acute sinusitis. This document was developed by a group of local clinical experts including medical doctors and pharmacists using treatment guidelines, evidence from randomized controlled trials, local antibiogram data, Provincial stewardship resources, and national reports. A table of treatment options taken from this document can be found in Appendix B. Amoxicillin is the only first line treatment and appropriate treatment for acute sinusitis. Although there are other antibiotic choices that may be appropriate for patients who have allergies to amoxicillin, patient allergy information was not available in the dataset. Therefore, only a high-level descriptive analysis of antibiotic choices for acute sinusitis was done. Duration of the dispensed prescription was also described, and 5 to 7 days was considered appropriate. Any dispensed prescription for less than 5 days was likely an extension of a prescription written in a location which does not record dispensations on the DIS. Therefore, observations of duration less than 5 days were excluded in the analysis. Any dispensed prescription for treatment greater than 7 days was considered longer than recommended.

4.4 Statistical Analysis

Descriptive analyses were used to describe antibiotic prescribing rates for acute sinusitis encounters overall, and by patient, prescription, and provider characteristics. Antibiotic use for acute sinusitis was summarized using the rate of antibiotic prescribing per 100 encounters for acute sinusitis.

To more fully describe between-provider variation in antibiotic prescribing for acute sinusitis encounters, and the extent to which patient and provider characteristics explained that variation, multilevel logistic regression models with encounters nested within individual providers were used. The models included a random intercept for provider, while patient and provider variables were modeled as fixed effects. Ideally, encounters would also be nested within patients, but 91.1% of patients in this study only saw one provider and 65.6% of all encounters were with patients who only had one encounter for sinusitis, so the modelling treated encounters within patients as independent. The number of encounters with providers was included as a strategy to deal with the problem of not including patient random intercept in the models.

Of value from this modelling approach is the partitioning of residual variation from models into between and within provider components, from which the percent of residual variation due to providers can be calculated (i.e. the intra-class correlation coefficient (ICC) in multi-level logistic regression). By comparing the ICC between the null model (i.e. without fixed effects for patients and providers) and models with patient and provider fixed effects, the extent to which patient provider attributes account for antibiotic prescribing rates can be assessed. As well, the estimated fixed effects in the models quantify the magnitude, direction and significance of patient and provider variables. To further describe between-provider variation in antibiotic prescribing, the median odds ratio (MOR) for each model was also calculated. The MOR was calculated using the following formula and the provider variance to describe between-provider heterogeneity and the degree to which it was explained by individual-level characteristics.

$$MOR = e^{.6745*\sqrt{2\sigma_u^2}}$$

The MOR can be interpreted as the median amount by which the probability of a patient being prescribed an antibiotic will change from one provider to another. This expresses between-provider variation in an odds ratio scale, and can therefore be compared with the magnitude of fixed patient and provider effects on the models.

Two sets of random effect logit models were used in the study. For both sets of models, low volume providers (prescribed for acute sinusitis less than once a month) were excluded from the analysis. We wanted to include prescribers who had a reasonable case load and treat acute sinusitis regularly. In addition, low volume prescribers contribute very little to the prescribing problem while contributing to a biased estimate of random variation. The first set of models examined the differences in prescribing rates between providers by exploring the effects of patient factors (sex, age, number of encounters) and prescriber factors (sex, graduation year, country of training, geographic location, type of prescriber) on antibiotic prescribing. Three models were run to determine the degree to which provider prescribing rates were explained by patient and provider characteristics. The first model included whether an antibiotic was prescribed, the second added effects for patient age, sex, and number of encounters, and the third added all provider factors. The ICC and MOR were calculated for each model.

The second set of models examined variation in the duration of an antibiotic prescription and included the same patient and provider variables as in the first set of models. As with the first set of models, examination started with the variation between providers. It then examined whether this could be explained by patient or provider characteristics using a null model, followed by one with patient characteristics, and one with patient and provider characteristics.

Statistical analyses were performed in Stata version 15.

4.5 ETHICS APPROVAL

This project is a sub-study of a larger project “Characterizing Antibiotic Use in Nova Scotia” which has received ethics approval. An amendment for this project has also received approval.

Chapter 5: Results

5.1 Study Population

The data set included 69,254 encounters with a diagnosis of acute sinusitis between September 15, 2016 and October 2018. All patients who were children (under the age of 19), and all providers who were from out of province or who were not identified as general practitioners were excluded (Figure 1). Encounters were also excluded if the patient had diagnoses other than acute sinusitis which may have resulted in antibiotic therapy (Appendix A), had both relevant patient identifiers missing (sex and year of birth), if the time lapsed between their diagnosis and prescription fill date was more than 7 days, or if an encounter with an antibiotic prescription followed a previous encounter with an antibiotic prescription within 30 days. Only 0.48% of prescriptions were dispensed more than 7 days after an encounter. There were 57,740 encounters remaining for analysis.

There were 46,201 patients and 68% were female (Table 1), which follows the trend in other studies (74). Females are more likely to visit a general practitioner and also more likely to get a diagnosis of acute sinusitis (75). Acute sinusitis is most common in people aged 45-64 and, in this dataset, most patients with acute sinusitis were between 50 and 69 (76). Overall, 82.0% of patients had only one encounter for sinusitis. 63.4% of patients filled an antibiotic prescription following a diagnosis of sinusitis.

There were 1079 unique providers, most of whom (93.6%) prescribed antibiotics for sinusitis (Table 2). Although most providers prescribed antibiotics, female providers and providers living in rural areas prescribed them at a higher rate.

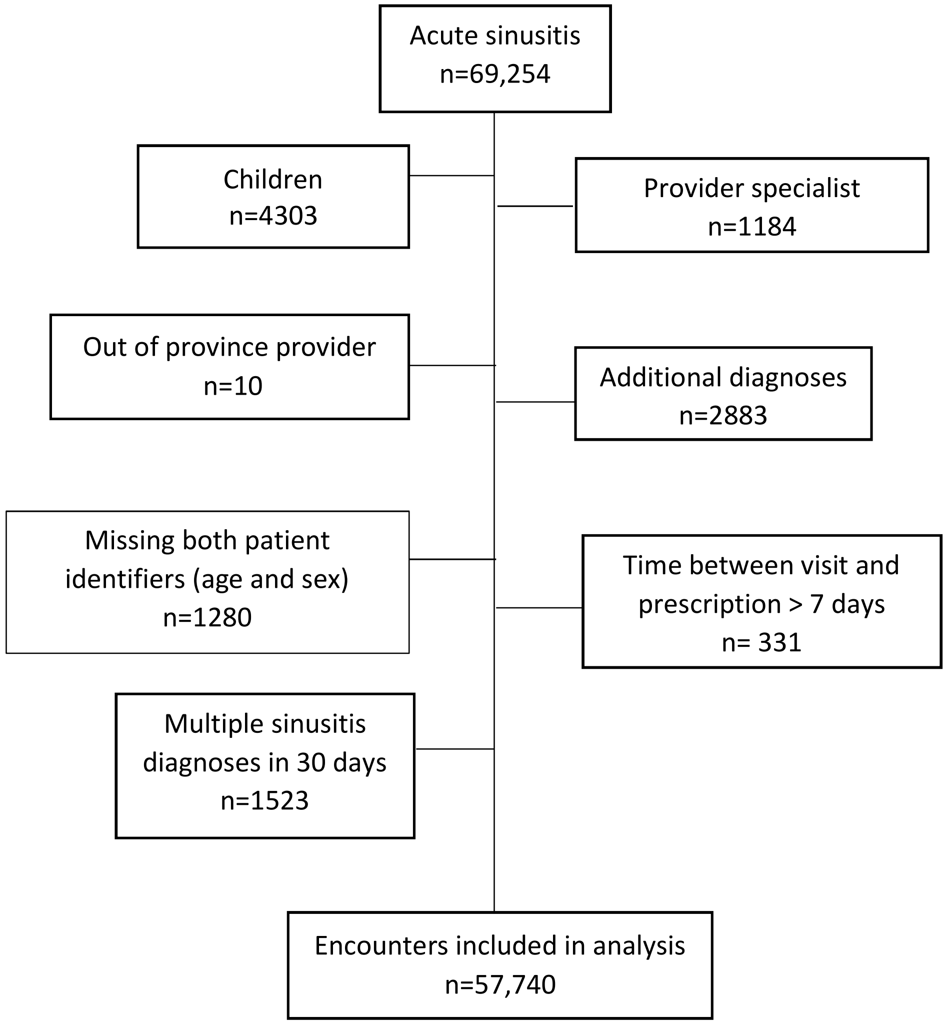


Figure 1 Flow of Inclusion and Exclusion Criteria for Acute Sinusitis

Table 1 Characteristics of patients who did or did not receive an antibiotic after a diagnosis of acute sinusitis from a general practitioner in Nova Scotia between October 2016 and October 2018

	No Antibiotic	Antibiotic	Total
	N=16,906	N=29,295	N=46,201
Sex			
Female	11,346 (36.1%)	20,074 (63.9%)	31,420
Male	5,560 (37.6%)	9,221 (62.4%)	14,781
Age Group			
19 to 29	1,909 (39.5%)	2,919 (60.5%)	4,828
30 to 39	2,518 (35.4%)	4,596 (64.6%)	7,114
40 to 49	2,810 (35.2%)	5,182 (64.8%)	7,992
50 to 59	3,670 (35.2%)	6,760 (64.8%)	10,430
60 to 69	3,407 (36.3%)	5,966 (63.7%)	9,373
70 to 79	1,845 (38.4%)	2,958 (61.6%)	4,803
80+	747 (45%)	914 (55%)	1,661
Number of Encounters for Sinusitis			
1	13,674 (36.1%)	24,214 (63.9%)	37,888
More than 1	3,232 (38.9%)	5,081 (61.1%)	8,313

Table 2 Characteristics of providers who diagnosed acute sinusitis in Nova Scotia between September 15, 2016 and October 2018

	% Prescribing an Antibiotic (95% CI)[1]	N
Total	93.6% (92.0, 95.0)	1,079
Sex		
Female	96.3% (94.3,97.7)	561
Male	90.7% (87.9,93.1)	518
Graduation Year		
1960-1969	82.6% (61.2, 95.0)	23
1970-1979	95.4% (89.6, 98.5)	109
1980-1989	94.8% (91.0, 97.3)	229
1990-1999	93.3% (89.3, 96.1)	238
2000-2009	94.8% (90.9, 97.4)	211
2010-2014	92.2% (88.3, 95.1)	269
Education		
International	91.4% (87.4, 94.5)	269
Canadian	94.4% (92.5, 95.9)	798
Missing	91.7% (61.5, 99.8)	12
Provider Type		
Medical Doctor	93.6% (91.9, 95.1)	986
Nurse Practitioner	93.5% (86.5, 97.6)	93
Provider Location		
Urban	92.9% (90.8, 94.5)	798
Rural	95.7% (92.7, 97.8)	281
Age		
less than 30	84.4% (67.2, 94.7)	32
30 to 39	93.6% (89.8, 96.3)	249
40 to 49	94.6% (91.2, 97.0)	259
50 to 59	93.3 % (89.9, 95.8)	312
60 to 69	95.4% (91.1, 98.0)	173
70 to 79	93.6% (82.5, 98.7)	47
over 79	71.4% (29.0, 96.3)	7
Encounter Volume		
Less than one per month[2]	63.9% (59.5, 68.3)	475
One per month or more	49.3% (45.3, 53.4)	604

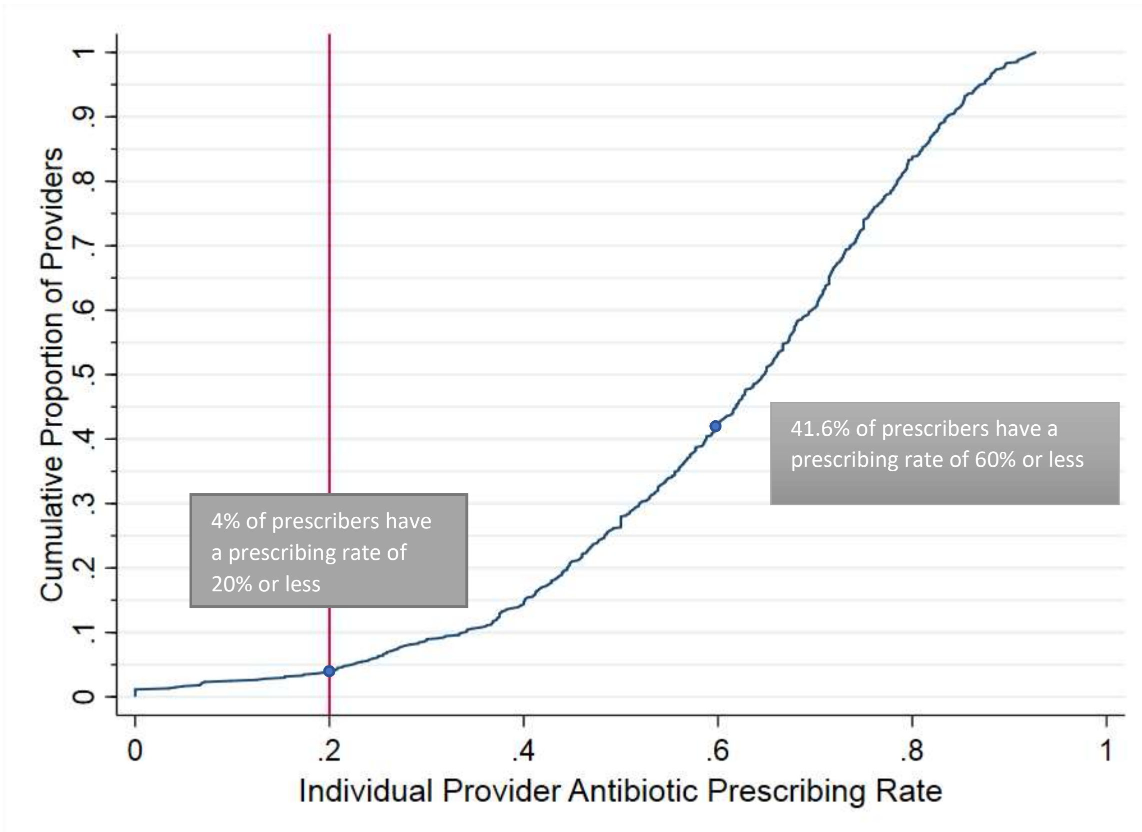
1 This column represents the percentage of providers who both diagnosed sinusitis at an encounter and prescribed an antibiotic that was filled no longer than 7 days after that encounter. Example: (96.3% of female providers who diagnosed sinusitis prescribed an antibiotic which was filled after the diagnosis encounter)

2 Volume was calculated using the total number of encounters with a diagnosis of sinusitis in the twenty-four-month study period. If there were less than 24 encounters, it was considered less than one per month. If there 24 encounters or more, it was considered one per month or more.

5.2 ANTIBIOTIC PRESCRIBING

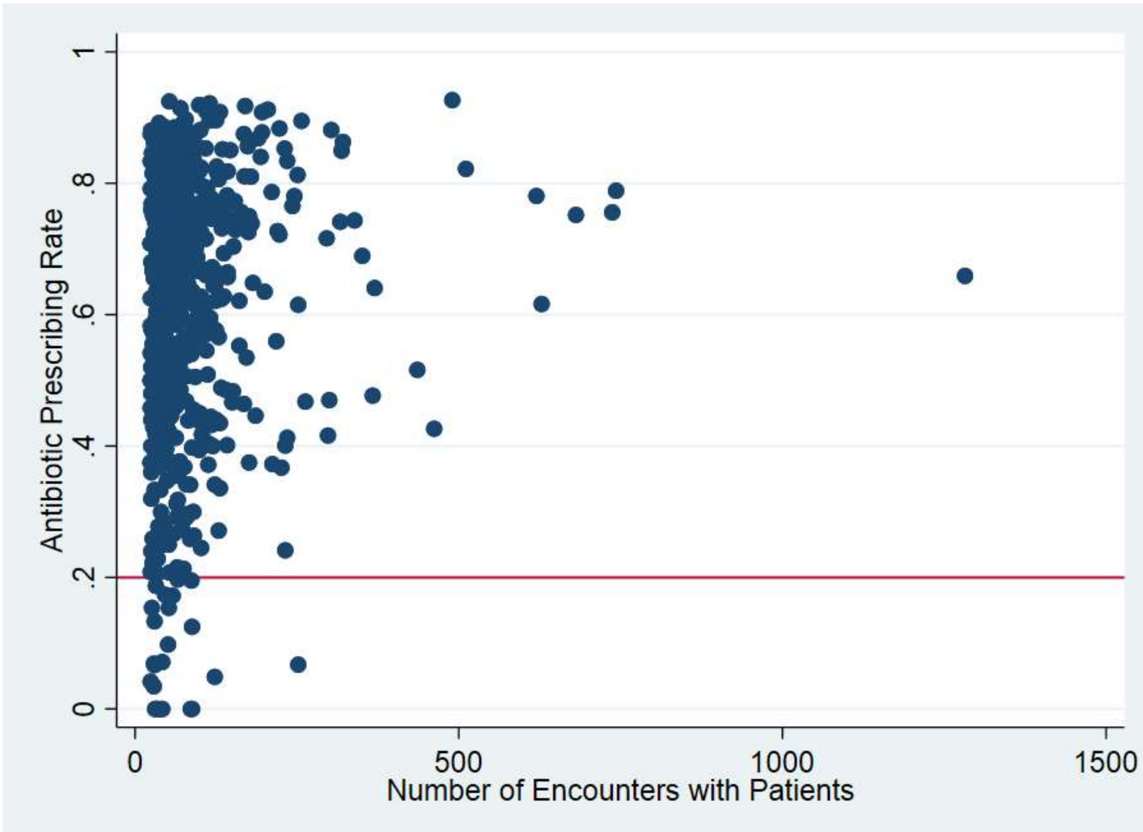
According to dispensation data (DIS), antibiotics were prescribed at 62.3% of encounters. There was a large variation in antibiotic prescribing rates amongst providers in Nova Scotia, ranging from 0% to 100%. Providers that rarely diagnose sinusitis may have contributed to this high variation, but when prescribers who diagnose sinusitis less than once per month were removed from the data, there was still a large variation in antibiotic prescribing rates (0% to 92.7%) (Figure 2). Sixty-nine % of providers had an antibiotic prescribing rate between 40 and 80% for acute sinusitis, and only 4% of providers had a prescribing rate of 20% or less. To determine if the variation in prescribing rates was related to how often a provider diagnosed sinusitis, the number of encounters was plotted against the prescribing rate (Figure 3). Providers diagnosed sinusitis a mean number of 54 times in 2 years, but there were 7 providers who diagnosed sinusitis over 500 times in the two-year study period. Those providers who diagnosed sinusitis over 500 times also had high prescribing rates, but no higher than some providers with lower numbers of encounters.

Figure 2 Antibiotic prescribing rates for acute sinusitis of individual providers who had encounters for acute sinusitis a minimum of 24 times. The prescribing rates are ranked from lowest prescribing rate to highest prescribing rate. The red line represents the maximum acceptable prescribing rate.



Provider Antibiotic Prescribing Rate	Percentage of Providers
Less than 5%	1.7
Less than 10%	2.5
Less than 20%	4.0
Less than 40%	14.3
Less than 60%	41.6
Less than 80%	83.3
Less than 100%	100

Figure 3 Provider antibiotic prescribing rate* by number of patient encounters with a diagnosis of acute sinusitis in Nova Scotia from October 2016 to October 2018. The red line represents the acceptable prescribing rate.



*Providers included in graph had encounters for acute sinusitis a minimum of 24 times

The results from the random effects logit models for antibiotic prescribing are presented in Table 3. Although there are some patient and provider variables associated with antibiotic prescribing (female patients, patients between the ages of 30 and 79, rural providers, and providers who graduated before 2010), models indicate substantial between-provider heterogeneity in antibiotic prescribing for acute sinusitis. This is indicated by the large ICCs, and the effect size of MOR compared to the effect sizes of individual patient and provider variables on antibiotic prescribing. For example, in model 2, the ICC of 0.21 indicates that the percent of variance related to between-provider variance in antibiotic prescribing rates is 21%. This effect size is large as indicated by the estimated MOR of 2.41 which is large relative to the significant relative odds for antibiotic prescribing which range from 1.14 to 1.29. In other words, the median effects on the odds of a dispensed antibiotic prescription from one provider to another is greater than the effects from patient age, sex, or number of encounters. Adjustments for patient and provider variables (models 2 and 3) only reduced the MOR from 2.42 to 2.41 and the ICC remains the same showing the between provider variation in prescribing of antibiotics can not be explained by the patient and provider variables included in this data.

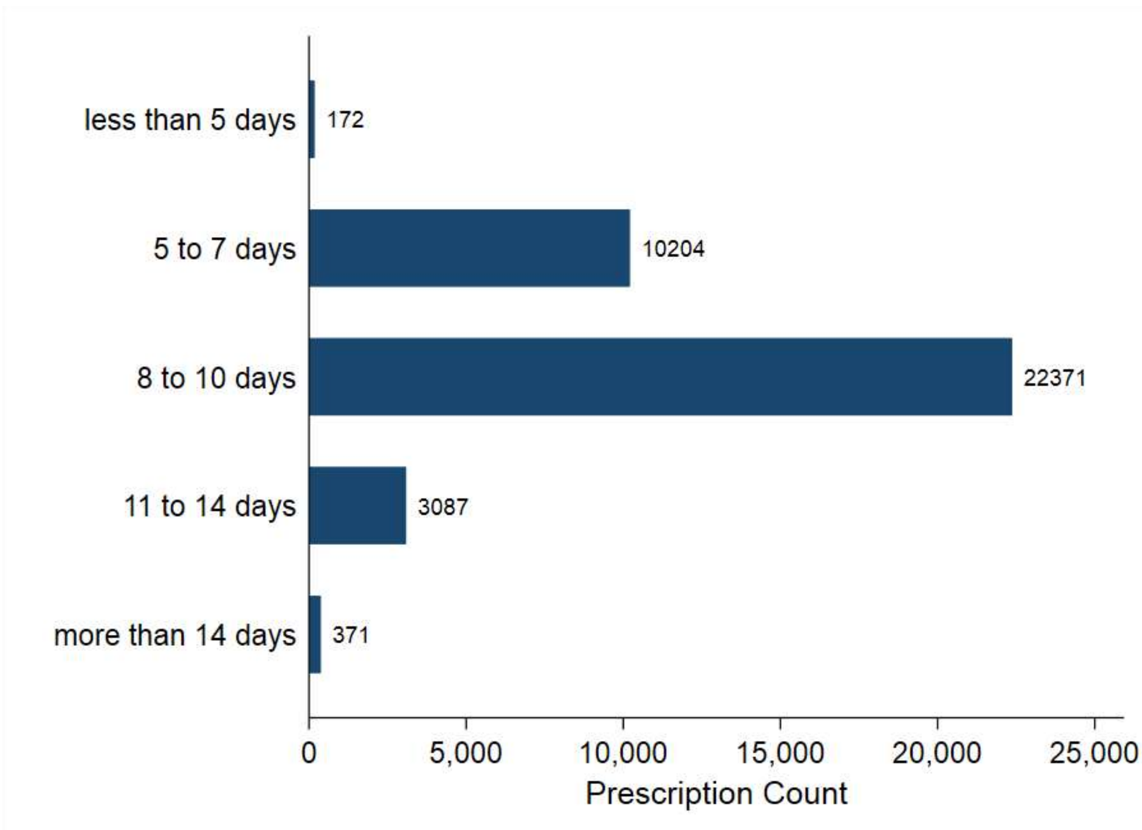
Table 3 Odds of Dispensed Antibiotic Prescription and 95% CIs for all Encounters for Acute Sinusitis in Nova Scotia between October 2016 and October 2018

Variable	Dispensed Antibiotic Prescription OR (95% CI)		
	(1) Null model	(2) Patient Age/Sex/Number of encounters	(3) All individual variables
Patient Factors			
Sex			
Female		1	1
Male		0.86 (0.83,0.90) ***	0.87 (0.83,0.90) ***
Age			
19 to 29		1	1
30 to 39		1.15 (1.06, 1.25) ***	1.15 (1.06, 1.25) ***
40 to 49		1.29 (1.19, 1.40) ***	1.29 (1.19, 1.39) ***
50 to 59		1.28 (1.18, 1.37) ***	1.28 (1.18, 1.38) ***
60 to 69		1.22 (1.13, 1.32) ***	1.23 (1.14, 1.32) ***
70 to 79		1.14 (1.04, 1.24) ***	1.14 (1.04, 1.24) **
80+		0.85 (0.75, 0.95) ***	0.85 (0.75, 0.95) ***
Number of Encounters with Provider(s)		0.95 (0.93, 0.97) ***	0.95 (0.93, 0.97) ***
Provider Factors			
Sex			
Female			1
Male			0.93 (0.78, 1.10)
Provider Type			
Medical Doctor			1
Nurse Practitioner			0.74 (0.49, 1.14)
Graduation Year			
1960-1969			1.51 (0.78, 2.92)
1970-1979			2.23 (1.64, 3.03) ***
1980-1989			3.09 (2.39, 4.01) ***
1990-1999			3.34 (2.59, 4.32) ***
2000-2009			3.26 (2.51, 4.24) ***
2010-2014			1
Education			
International			0.98 (0.82, 1.18)
Canadian			1
Provider Location			
Urban			1
Rural			1.24 (1.07, 1.44) ***
ICC	0.21 (0.19, 0.23)	0.21(0.18, 0.23)	0.21(0.19, 0.24)
MOR	2.42 (2.28, 2.58)	2.41 (2.27, 2.56)	2.41 (2.27, 2.56)

Significance levels * p<0.05 ** p <0.01 *** p <0.001
N=52,788
ICC, intra-class correlation coefficient (area share of variance); MOR, median odds ratio

The duration of antibiotic treatment ranged from 1 day to 100 days, and 28.2% of dispensed prescriptions fell between the recommended 5 and 7 days (Figure 4). 71.3% of dispensed prescriptions were for more than 7 days of treatment. Most of the dispensed prescriptions that were more than 7 days were for 10 days (85.3%), and less than 2% were for more than 14 days.

Figure 4 Duration of antibiotic treatment prescribed to adults in Nova Scotia for acute sinusitis between October 2016 and October 2018



Between-provider heterogeneity is also substantial when looking at the logistic regression models predicting prescribing antibiotics within the recommended duration of 5-7 days (Table 4). Again, there are some patient and provider variables associated with a prescription duration of five to seven days (female patients, youngest and oldest patients, fewer encounters, providers graduated 2010-2014, rural providers, and providers trained internationally), but there is large and significant between-provider heterogeneity which can not be explained by these variables. The estimated MOR of the null model, 5.67, is much larger than the largest significant relative odds, 1.94, showing that median effects on the odds of a dispensed antibiotic prescription of recommended duration from one provider to another is greater than the effects from independent patient or provider variables. The ICC in model 3 of 0.48 indicates that the percent of variance related to between-provider variance in antibiotic prescribing duration is 48%. Adjustments for patient and provider variables (models 2 and 3) only reduce the MOR from 5.67 to 5.28 and it remains significant showing that most of the between provider variation in prescribing of antibiotics can not be explained by the patient and provider variables included in this data.

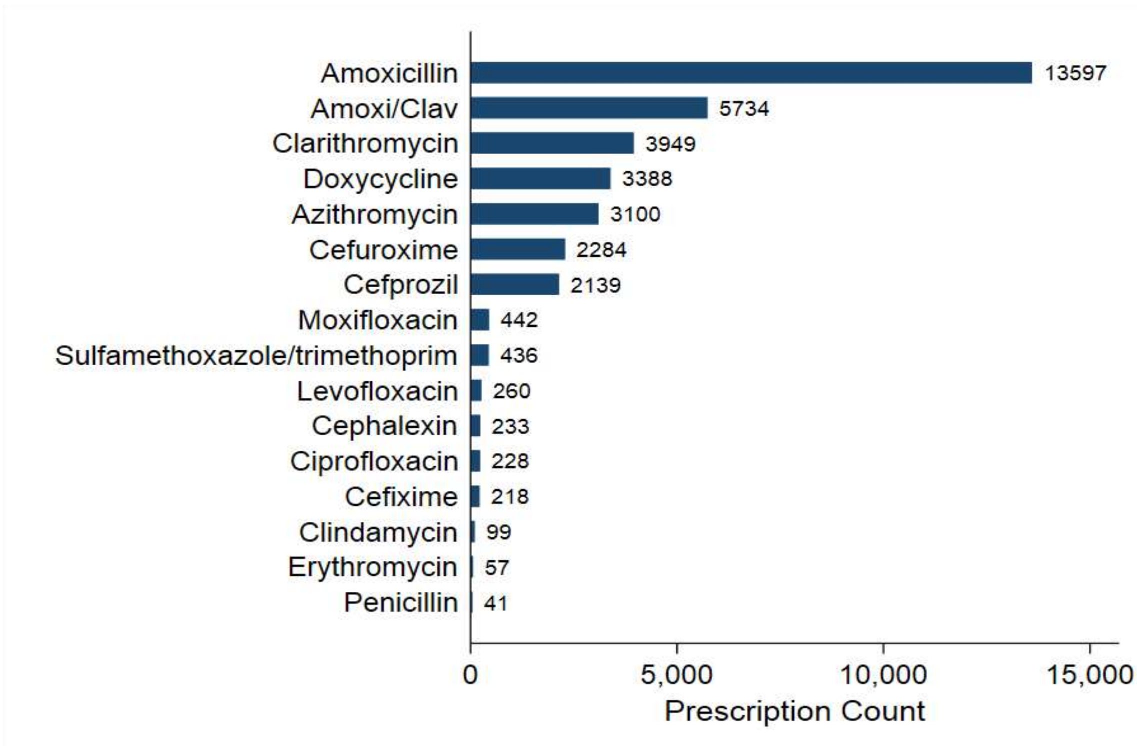
Table 4 Odds of the recommended duration of an antibiotic prescription (5 to 7 days) and 95% CI for all Encounters for Acute Sinusitis for which an antibiotic was written in Nova Scotia between October 2016 and October 2018

Variable	Recommended Duration of an Antibiotic Prescription OR (95% CI)		
	(1) Null Model	(2) Patent Age/Sex/Number of encounters	(3) All individual variables
Patient factors			
Sex Female Male		 1 0.84(0.78, 0.90) ***	 1 0.83(0.78, 0.89) ***
Age 19-29 30-39 40-49 50-59 60-69 70-79 80+		 1 0.87(0.76, 0.98)* 0.87(0.77, 0.98)* 0.84(0.74, 0.94)** 0.83(0.73, 0.93)** 0.82(0.72, 0.94) ** 1.01(0.74, 1.23)	 1 0.87(0.77, 0.99)* 0.87(0.77, 0.98)* 0.84(0.74, 0.94)** 0.83(0.73, 0.93)** 0.82(0.72, 0.94)** 1.00(0.83, 1.23)
Number of Encounters with Provider(s)		0.93 (0.90, 0.96) ***	0.93(0.90, 0.96) ***
Provider Factors			
Sex Female Male			 1 1.33 (0.97, 1.81)
Provider Type Medical Doctor Nurse Practitioner			 1 0.62(0.28, 1.37)
Graduation Year 1960-1969 1970-1979 1980-1989 1990-1999 2000-2009 2010-2014			 1.07(0.30, 3.82) 0.40(0.22, 0.72)** 0.32(0.20, 0.52)*** 0.26(0.16, 0.42)*** 0.39(0.24, 0.65)*** 1
Education International Canadian			 1.94 (1.38, 2.73)*** 1
Provider Location Urban Rural			 1 1.54(1.19, 1.99) **
ICC	0.50 (0.47, 0.54)	0.50(0.47, 0.54)	0.48(0.45, 0.52)
MOR	5.67(5.04,6.42)	5.69(5.06, 6.45)	5.28(4.71,5.95)

Significance levels * p<0.05 ** p <0.01 *** p <0.001
N = 33,753
ICC, intra-class correlation coefficient (area share of variance); MOR, median odds ratio

The antibiotics prescribed are presented in Figure 5 (Appendix C). Amoxicillin was the most dispensed antibiotic (37.4% of prescriptions) which follows the recommended guidelines. This was followed by amoxicillin/clavulanate, clarithromycin, and doxycycline.

Figure 5 Antibiotics dispensed from pharmacies in Nova Scotia for acute sinusitis from October 2016 to October 2018 (Antibiotics dispensed less than 25 times in study period are not displayed in graph. See Appendix C). N=36.205



5.3 Sensitivity Analyses

There were four sensitivity analyses completed to determine if changes in the exclusion criteria would impact the results of the logistic regressions. The results of these analyses were similar to the primary prescribing analyses.

CHAPTER 6: DISCUSSION

6.1 ANTIBIOTIC PRESCRIBING FOR ACUTE SINUSITIS

This study found that nearly two-thirds of encounters with primary care providers for acute sinusitis were dispensed an antibiotic. This is similar to rates in Ontario (67%) but lower than estimates for Canada overall (82%) (14,77). There is not a consensus on the percentage of cases of acute sinusitis that require antibiotics, but Canadian Choosing Wisely guidelines state that 2 to 10% of cases require treatment, and on the more generous end, Schwartz et al. recommend 1 to 20% (14,78). Using the least conservative of these, 20%, in two years in Nova Scotia, there were 24,424 acute sinusitis diagnoses that resulted in unnecessary antibiotic therapy.

A significant source of bias that could inflate estimated rates of antibiotic prescribing is coding bias. The use of secondary administrative data and ICD-9 coding can be influenced by provider practices, access to care, and financial considerations. ICD-coding errors can occur due to poor communication with the patient, lack of clinician knowledge or experience with the condition, lack of coder training or experience, unintentional or intentional coding errors, miscoding, unbundling, and upcoding (79). It is possible that the high rate of prescribing in this study reflects a greater propensity to code for sinusitis if an antibiotic is prescribed. Cadieux et al. looked at the accuracy of physician billing claims for identifying acute respiratory tract infections in primary care (72). They found an almost "sixfold variation between physicians in the prevalence of acute respiratory infections"(72). This translated to a sensitivity of 0.46 for acute sinusitis indicating that ICD codes correctly identify an individual with sinusitis 46% of the time. This sensitivity rate suggests that, at worst case, 54% of acute sinusitis patients were missed – 67,782 additional encounters. Some might argue that patients are missing ICD codes because they did not receive a prescription at their encounter, but even if all patients with missing ICD codes did not receive a prescription the prescription rate for acute sinusitis would still be 29%, still above the 20% maximum acceptable prescription rate. Miscoding occurs when the diagnosis and the chosen ICD code do not align (79). If a provider is familiar with only certain codes, coder-use bias may occur. They may choose to use known codes for closely related conditions rather than confirming the accurate code. For example, in this case, a provider may know the code for sinusitis, but not know the code for other acute respiratory tract conditions such as bronchitis or otitis media. If they assign the sinusitis code to all these conditions, this would result in miscoding and extra cases of sinusitis in the dataset. This could either increase or decrease the antibiotic prescribing rate in this study; however, most acute respiratory tract infections are unlikely to warrant antibiotic prescriptions, so these prescriptions may still be contributing to unnecessary antibiotic therapy.

Another source of bias that could inflate potentially inappropriate prescribing rates are unmeasured clinical patient characteristics. The study did not account for patient variables and characteristics which may warrant higher prescribing rates. Immunocompromised patients may require broad spectrum antibiotic therapy and watchful waiting may not be appropriate (24). Fourteen percent of Canadians in 2020 were considered immunocompromised (80). If fourteen percent of the cases of acute sinusitis in this study were in immunocompromised individuals and antibiotic therapy was recommended for all of them, there would still be 28% of antibiotics prescribed that were potentially inappropriate. It is important to note that many of these patients are seen by specialists, not general practitioners; therefore, it is unlikely that this many patients were included in the data.

High rates of antibiotic prescribing for acute sinusitis are a public health concern. Resistance may develop in individuals who do not have a bacterial infection, but are treated with antibiotics (7). Unnecessary antimicrobial therapy may also be associated with cases of the development of obesity, allergies, renal injury, hematologic effects, hepatobiliary effects, neurologic symptoms, QT prolongation, and opportunistic infections from yeast and *C. difficile* (19,53–56). In addition, people taking antibiotics have about 20% chance of adverse events and up to a 30% risk of allergic reactions and gastrointestinal symptoms (19,35–38). Adverse effects can occur with antibiotic treatment and this results in a number needed to harm of 8 demonstrating that the risk of harm outweighs the potential benefits (22,23).

While overall prescribing rates for acute sinusitis far exceed recommendations, the heterogeneity in antibiotic prescribing rates between providers was an important finding of this study. While antibiotic prescribing rates of providers ranged between 0% to 100%, only 4 % of providers fell within the acceptable rate of less than 20%. Because there were a small number of providers who diagnosed acute sinusitis more than 500 times each, there is concern that these providers drive a disproportionate amount of the potentially inappropriate prescribing or that they overuse the sinusitis ICD code. This could have resulted in biased estimates of between provider variation.

The high-level of heterogeneity in antibiotic prescribing rates, and the fact that most providers are prescribing at rates that exceed guidelines, has important implications for how to target antibiotic stewardship interventions. Should interventions be broad based, focusing on all providers, or targeted, focusing on providers with the highest rates? To shed light on this, if the top gross 30% of providers lowered their prescribing rates by 25%, the overall prescribing rate would drop to 51%, and strategies to lower all provider prescribing rates by 25% would result in a lower overall prescribing rate of 47% (Appendix D). Given that 96 % of providers prescribed antibiotics more than recommended, broad population-based initiatives should be considered along with targeted approaches for the top grossing providers.

Although the effect of between-provider heterogeneity was more significant than individual patient or provider variable effects, there were nonetheless some variables which were associated with antibiotic prescribing: patient sex, patient age, number of patient encounters, provider graduation year, and provider location.

Female patients were more likely to receive an antibiotic than male patients. Patient sex has been associated with prescribing rates for sinusitis and other upper respiratory tract infections (81–84). Some studies report that males are more likely to receive an antibiotic for an upper respiratory tract infection, but at least one study looking at sinusitis specifically noted that females were more likely (81,84). The gender gap in antibiotic prescribing rates may be related to differences in health seeking behaviour or to gender concordance between patient and provider (84,85). These concepts are beyond the scope of this study, and future qualitative research around sex inequality in antibiotic prescribing practices would be useful.

The youngest (less than 30) and oldest patients (over 79) in this study were less likely to get an antibiotic than patients in between 30 and 79. This is likely related to the prevalence of sinusitis in different ages. Acute sinusitis is most common in people aged

45-64, and less common in younger and older age groups (76). There may be other factors related to age that could affect whether an antibiotic is prescribed or filled. Younger patients may be less likely to have drug coverage; therefore, they may not fill a prescription if it were written. Older patients have more comorbidities, and providers may be less likely to prescribe unless it is necessary. There was no information available about comorbidities in this dataset risk for adverse consequences of acute sinusitis and strengthen their recommendation to receive antibiotics.

Counterintuitively, patients who had encounters more than once during the study period were less likely to get an antibiotic. This could be at least partially explained with watchful waiting and appropriate follow up (15–20). If a patient sees a provider for suspected acute sinusitis, the provider may advise watchful waiting and want to see the patient again for follow up. Many cases of acute sinusitis resolve within 2 weeks without antibiotic treatment (17,21–23,62,63). One Cochrane review showed that 46% of patients had resolution of symptoms in 7 days and 64% had resolution of symptoms in 14 days without antibiotic treatment(23). Only 5% of those patients who did not start with an antibiotic had to start an antibiotic later because their condition worsened (23).

Provider variables associated with antibiotic prescribing included graduation year and provider location. Providers who graduated in more recent years (2010-2014) were less likely to prescribe antibiotics, and this may reflect changes in training or curriculum over the years due to the increasing threats of antibiotic resistance. Rural providers were more likely to prescribe an antibiotic which may reflect geographical distance, transportation barriers, and differences in patient health and demographics in rural settings in Nova Scotia (86). Many rural communities in Nova Scotia have no public transportation and rely on self-transport or volunteers for transportation to health appointments(86). Poor weather and road conditions can make travelling even more difficult. Therefore, a provider may be more likely to prescribe an antibiotic with watchful waiting instructions to accommodate their patient. Rural patients are often older, have poorer health, and are of lower socioeconomic status than their urban counterparts which could influence whether or not a provider decides to prescribe an antibiotic (86).

6.2 Antibiotic Duration

The appropriateness of prescribing, dosing and timing of antibiotics all play a role in the spread of antimicrobial resistance (7). Although there were only 28.2% of dispensed prescriptions that were prescribed for the recommended duration of time in "Antibiotics: Why and Why Not" (5 to 7 days), optimal treatment duration is not consistent between guidelines. While the Dalhousie specific guideline recommends 5 to 7 days, the Canadian guidelines from 2011 and American guidelines from 2015 recommend 5 to 10 days. Short courses of antibiotics have been shown to be effective and have fewer adverse effects, better adherence, and lower potential for antibiotic resistance (41,42,87–89). Given the inconsistencies in guidelines and the significant heterogeneity in between-provider prescription duration, it is possible that different information is being used by different clinicians, and they would benefit from education on the current local recommendations as part of the aforementioned population-based stewardship initiatives. This may also present an opportunity for pharmacists to adapt the duration of prescriptions for acute sinusitis. While it is still important to reduce the overall number of prescriptions, decreasing the duration of prescriptions which were written for 10 days down to 5 days would have resulted in 224,471 fewer days of dispensed antibiotic prescriptions during the study period.

6.3 Antibiotic Choice

Not withstanding that 42% of dispensed antibiotic prescriptions were potentially inappropriate, most dispensed prescriptions were for the recommended product, amoxicillin (37.4%). The next most prescribed drugs were amoxicillin/clavulanate, clarithromycin, doxycycline, and azithromycin. Amoxicillin/clavulanate is indicated for patients who fail on amoxicillin therapy. Given that antibiotics were excluded if the patient had another antibiotic in the previous 30 days, it is expected that most therapeutic failures were excluded, implying that the use of amoxicillin/clavulanate was potentially inappropriate. However, while Dalhousie Academic Detailing and the Canadian practice guidelines recommend amoxicillin/clavulanic acid only for treatment failures, the American guidelines state that amoxicillin/clavulanate is an acceptable first line therapy (20,82,90). This suggests that there may be differences in recommendations depending on a provider's sources of information and training. Clarithromycin and doxycycline are acceptable choices in patients with beta-lactam allergies; however, it is unlikely that all of the patients prescribed these alternatives had allergies given that only about 10% of the population have penicillin allergies (91). Other antibiotics such as azithromycin and trimethoprim/sulfamethoxazole have demonstrated high rates of resistance to *S. pneumoniae* and *H. influenzae* (16,20,64), and are not recommended for treatment in any cases of sinusitis.

6.4 SUMMARY

This study demonstrates that 42.3% of dispensed antibiotic prescriptions for acute sinusitis are potentially unnecessary, and when antibiotics are prescribed, they are often given for longer than recommended. There are a variety of factors which may influence whether an antibiotic is prescribed or is taken; however, the variables used in this study could not explain all provider differences. Most of the variation in prescriber patterns were related to between-provider-heterogeneity, not patient or provider level variables. Both population-based initiatives and targeted approaches for the top grossing providers may be useful as antibiotic stewardship interventions.

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APPENDICES

8.1 APPENDIX A

Additional Diagnoses in Patients with Acute Sinusitis

ICD code (Diagnosis)	Frequency	Exclusion from primary analysis
033 (whooping cough)	2	Yes
034 (strep throat or scarlet fever)	11	Yes
088.8.1 (Lyme)	1	Yes
099 (venereal disease)	2	Yes
Other 01	132	Yes
288 (disease of white blood cells)	2	Yes
357 (inflammatory nephropathy)	4	No
360-379 (disorders of the eye)	125	Yes
380-389 (disorders of the ear)	381	Yes
460 (common cold)	87	No
462 (acute pharyngitis)	59	Yes
463 (acute tonsillitis)	15	Yes
464 (acute laryngitis)	24	Yes
465 (acute upper respiratory tract infection unspecified)	64	Yes
466 (acute bronchitis)	321	Yes
472 (chronic pharyngitis)	26	Yes
473 (chronic sinusitis)	8	Yes
474 (chronic tonsillitis)	2	Yes
476 (chronic laryngitis)	2	Yes
482-486 (pneumonia)	77	Yes
487-488 (influenza)	70	No
490 (bronchitis unspecified)	680	Yes
491 (chronic bronchitis)	18	Yes
492 (emphysema)	2	Yes
493 (asthma)	167	Yes
494 (bronchiectasis)	2	Yes
496 (COPD)	111	Yes
Other 45	75	Yes
521 (disease of hard tissue of the teeth)	4	Yes
522 (disease of the pulp of the teeth)	6	Yes
523 (gingival and periodontal disease)	4	Yes
524 (dentofacial anomalies)	9	Yes
525 (other conditions of the teeth)	3	Yes
527 (disease of the salivary glands)	2	Yes
528 (disease of the oral soft tissues)	4	Yes
531-534 (GI Ulcers)	3	No
535 (gastritis/duodenitis)	4	No
574 (cholelithiasis)	1	Yes
575 (disorders of the gallbladder)	1	Yes
577 (disease of the pancreas)	1	Yes
Other 5	188	Yes
Other 56	204	Yes
592 (kidney stones)	3	No
595 (cystitis)	11	Yes
601 (inflammation of the prostate)	1	Yes
604 (orchitis)	2	Yes
664-665 (obstetrical trauma)	1	Yes
680-686 (infection of the skin or s/c tissue)	35	Yes
Other 67	196	Yes
995 (anaphylaxis)	30	No

8.2 APPENDIX B

Therapeutic Choices for the Treatment of Acute Rhinosinusitis(19)

Treatment Choice	**Antibiotic**	**Adult Regimen (acute rhino-sinusitis)**
1st Line	Amoxicillin	500mg TID – 1000mg BID
2nd Line	Amox/Clav[1]	500 mg TID or 875 mg BID
2nd Line	Cefuroxime[2]	500 mg BID
2nd Line	Clarithromycin[3]	500 mg BID
2nd Line	Doxycycline[3]	200 mg for 1st dose, then 100 mg BID
3rd Line	Levofloxacin	500 mg once daily
3rd Line	Moxifloxacin	400 mg once daily
	Duration of therapy is 5 to 7 days **Expect symptoms to improve but not completely disappear at the end of therapy. Some persistence of symptoms is not an indication for immediate prescription for a second antibiotic.**	

1 For patients who have not improved or who have failed therapy with amoxicillin.
2 1st line option if patient has a history of penicillin allergy (IgE mediated).
3 Options if unable to use any β-lactam (*S. pneumoniae* is increasingly becoming resistant to tetracyclines and macrolides).

8.3 APPENDIX C

Antibiotics Prescribed for Acute Sinusitis

Antibiotic	Number of Prescriptions	Percentage
amoxicillin	13597	37.48
amoxi/clav	5734	15.81
clarithromycin	3949	10.89
doxycycline	3388	9.34
azithromycin	3100	8.54
cefuroxime	2284	6.30
cefprozil	2139	5.90
moxifloxacin	442	1.22
sulfamethoxazole/trimethoprim	436	1.20
levofloxacin	260	0.72
cephalexin	233	0.64
ciprofloxacin	228	0.63
cefixime	218	0.60
clindamycin	99	0.27
erythromycin	57	0.16
penicillin	41	0.11
nitrofurantoin	25	0.07
ampicillin	16	0.04
tetracycline	10	0.03
cloxacillin	7	0.02
minocycline	7	0.02
fosfomycin	2	0.01
ceftriaxone	2	0.01
norfloxacin	2	0.01
cefazolin	1	0.00
tobramycin	1	0.00
cefadroxil	1	0.00

8.4 **APPENDIX D**

<u>Who to Target Calculations</u>
Mean provider prescribing rate: 62.3%

1. Reduce all prescriber's prescribing rates by 10 to 25%

Reduction in Rate	Prescribing Rate
10%	0.57
15%	0.53
20%	0.50
25%	0.47

2. Target the top X% gross prescribers with a Y% reduction

X	Y	Prescribing Rate
10%	10%	0.60
10%	25%	0.55
10%	40%	0.51
10%	50%	0.48
20%	10%	0.59
20%	25%	0.52
20%	40%	0.46
20%	50%	0.42
30%	10%	0.57
30%	25%	0.51
30%	40%	0.43
30%	50%	0.38

3. Target the top X% prescribing rates with a Y% reduction

X	Y	Prescribing Rate
10%	10%	0.62
10%	25%	0.60
10%	40%	0.58
10%	50%	0.57
20%	10%	0.61
20%	25%	0.57
20%	40%	0.54
20%	50%	0.52
30%	10%	0.60
30%	25%	0.55
30%	40%	0.50
30%	50%	0.47