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National and Local Antibiotic Prescribing Trends and Prescribing Appropriateness in Older Adults

Fawaz M. Alotaibi
Virginia Commonwealth University

NATIONAL AND LOCAL ANTIBIOTIC PRESCRIBING TRENDS AND PRESCRIBING APPROPRIATENESS IN OLDER ADULTS

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University

by

Fawaz Mutlaq Alotaibi

Pharm.D., College of Clinical Pharmacy, King Faisal University,

Kingdom of Saudi Arabia, 2011

Master of Pharmaceutical Sciences, Department of Pharmacotherapy and Outcomes Science, School of Pharmacy,

Virginia Commonwealth University, Richmond, VA, USA, 2015

Doctoral Candidate, Department of Pharmacotherapy and Outcomes Science,

School of Pharmacy, Virginia Commonwealth University, Richmond, VA, USA, 2019

Advisor:

Patricia W. Slattum, Pharm.D., Ph.D., BCGP

Director, Geriatric Pharmacotherapy Program

Victor A. Yanchick Professor of Pharmacotherapy and Outcomes Science

Virginia Commonwealth University, Richmond, VA
March, 2019

Dedications

This work is dedicated to the love of my life, my mother Munerah, and my father Mutlaq

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ABSTRACT

NATIONAL AND LOCAL ANTIBIOTIC PRESCRIBING TRENDS AND PRESCRIBING APPROPRIATENESS IN OLDER ADULTS

By Fawaz Alotaibi, Ph.D. Candidate., MS., Pharm.D.

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Background: Antibiotic overuse/misuse has been documented in several reports to increase the risk of *Clostridioides difficile* (*C.diff*) infection and antibiotic resistance. The older adult population is more prone to use antibiotic medications than any other age group due to decreased immune function, use of urinary catheters, ventilation during hospitalization and other factors. Antibiotic resistance and C.diff are major public health problems. However, studies examining the trends of antibiotic use and the association between the antibiotic use and negative health outcomes among older adults in the outpatient and emergency department settings are limited.

Objectives: The main objectives of this dissertation were to: 1) calculate the national antibiotic trends among community-dwelling older adults in the United State; 2) evaluate the antibiotic trends and antibiotic appropriateness among older adult patients visiting the geriatrics clinic and adult internal ambulatory care clinic at VCU Health; and 3)

examine the antibiotic trends and antibiotic appropriateness among older adult patients and middle-aged patients visiting the emergency department at VCU Health.

Methods: For the first objective, data were obtained from Medical Expenditure Panel survey (MEPS) a nationally representative dataset (2011-2015). Descriptive analyses were conducted and multiple logistic regression was performed to assess the association between the antibiotic use and demographic and sociodemographic characteristics. In the second objective, data were obtained from VCU Health outpatient clinics (geriatrics, and Internal medicine ambulatory care clinic only). Descriptive statistics were calculated and multiple logistic regression was performed to assess the association between antibiotic appropriateness and type of clinics and other demographic characteristics. In the third objective, the emergency department electronic medical records at VCU were used. Trend analysis was performed across the dissertation studies using the Cochran–Armitage test. All variables were considered statistically significant at an α level of 0.05. All the statistical analyses were conducted using the Statistical Analysis Software Version 9.4 (SAS v.9.4), (SAS Institute Inc, Cary, NC).

Results: There were 105,762,134 prescriptions dispensed to older adults in the outpatient setting in the US from 2011 to 2015. Antibiotic prescriptions were more common among women (18%) compared to men (12%). White participants received more antibiotics (27%) than African Americans (1.77%) and others (1.4%).

Among the 3,515 patients who visited either Geriatrics or Internal Medicine ambulatory clinic at VCU Health from 2012-2017, 1,534 antibiotics were prescribed. Potentially

inappropriate antibiotic prescriptions were similar between the two clinics (30% in Geriatrics clinic and 28% in Internal Medicine ambulatory clinic) with p-value of 0.08. In addition, 6,343 middle-aged or older adult patients were dispensed and prescribed an antibiotic in the ED at VCU Health from (2012 to 2017). Eighteen percent of the antibiotic prescriptions received by middle age group were considered potentially inappropriate, compared to 9% among the older adult patient ($p < 0.0001$).

Conclusions: The rate of antibiotic use overall remains unchanged despite the national and international efforts to reduce antibiotic prescriptions and eventually to reduce antibiotic resistance. The changes in the patterns of use in some of the antibiotic categories appear to be driven more by the safety concerns rather than reducing overall use. Future research is needed to strengthen antibiotic stewardship programs for older adults in outpatient settings.

CHAPTER ONE: INTRODUCTION

Antibiotic Therapy:

Antibiotics are one of the most significant discoveries in human history. Antibiotics are defined as a medication that inhibits the growth of or destroys microorganisms. Through serendipity, a Scottish bacteriologist, Alexander Fleming, left a culture of staphylococci uncovered in his lab and came back to discover that mold that grew there was attacking the bacteria. That observation marked the beginning of the penicillin revolution in 1925, the first antibiotic in history.[1,2] Following the introduction of penicillin, the leading causes of death shifted from communicable diseases to non-communicable diseases such as heart diseases and cancer. In the United States, the average life expectancy rose from 47 years to 78 years during the antibiotic era.[3] The percentage of older adults in the United States (U.S.) population increased from 4% to 13% as well.[4] Compared with other age groups, the older adult population has the highest antibiotic consumption rate. The antibiotic prescription rate in the U.S. decreased among children and adolescents from 2000 to 2010 and increased by 30% among the older adults over the same time period.[5]

A recent study conducted by Olesen, et al. using Medicare Part D data reported that 19.5 million antibiotic prescriptions were claimed to Medicare beneficiaries from 2011 to 2015.[6] The prescription rate was similar over the study period, with 1364.3 claims per 1000 beneficiaries. Of those claims, 552 per 1000 beneficiaries were considered potentially inappropriate. Another nationally representative study that captured 86% of all ambulatory outpatient prescriptions in the U.S. reported that 51.6 million antibiotic prescriptions were prescribed to older adult patients in 2014.[7] The rate of antibiotic prescribing (1115 prescriptions per 1000 persons) was lower than reported by Olesen, et al.,[6] but differences in the study population in terms of health insurance or patients' characteristics and diseases severity might explain this discrepancy. Fleming-Dutra et al.,[8] reported that 30% of outpatient antibiotic prescriptions among all ages were inappropriate in 2011. Older adults, in particular, received 617 prescriptions per 1000 persons and 18% of those prescriptions were deemed inappropriate. Table 1.1 presents the recent literature that examined the antibiotic prevalence among US adults population. There are still limited reports describing antibiotic use and antibiotic appropriateness among the older adult population in the U.S., a knowledge gap that we are hoping to address with this research.

Table 1.1 A summary of the recent studies that examine the antibiotics rate among the US population.

Author	Study Settings	Study Population	Sample Size	Conclusion
Lee, Grace C., et al.	MEPS data from 2000-2010	US civilian, non-institutionalized population	1.4 billion outpatients records	The antibiotic prescription rate in the U.S. decreased among children and adolescent from 2000 to 2010 and increased by 30% among older adults.
Fleming-Dutra, Katherine E., et al.	2010-2011 National Ambulatory Care Survey and National Hospital Ambulatory Medical Care Survey.	US population	184,032 sampled ambulatory care visits	12.6% of US Ambulatory care visits were associated with antibiotic prescriptions. 18% of the antibiotic prescriptions were considered inappropriate among the older adult population.
Kabbani, Sarah, et al.	2011-2014 of IQVIA Xponent database	US older adults visiting the outpatient settings	51.6 million prescriptions were dispensed in 2014	The rate of antibiotic prescriptions remains the same over the study period (1,115 prescriptions/1,000 persons)
Sanchez, Guillermo V., et al.	2008-2011 2010-2011 National Ambulatory Care Survey	US population related Macrolide visit	2399	Only 5% of macrolide prescribing is following the guidelines which macrolides are a first line therapy.
Roumie, Christianne L., et al.	1995-2002 National Ambulatory Care Survey and National Hospital Ambulatory Medical Care Survey.	US adults 18 year or older	Unknown	Overall antibiotic rate remains the same over the study period from 302.4 in 1996 to 304.1 in 2002.
Hicks, Lauri A., et al.	2011 IMS Health Xponent database	US population	Unknown	In 2011, health care providers prescribed over 260 million of antibiotics in the outpatient setting. The

				overall rate of antibiotic was 842 prescriptions per 1000 persons. Older adults received 1048 prescriptions per 1000 persons, which is the highest rate compared to other age groups.
Mundkur, Mallika L., et al.	2006-2015 Optum Clinformatics Datamart	US adult population	Unknown	The rate of antibiotic prescription decreased significantly (5%) among older adults from 991 to 943 prescriptions/1000 persons over the study period.
Olesen, Scott W., et al.	2011-2015 Medicare US national healthcare program database	US older adult population	4.5 million Medicare beneficiaries	The antibiotic use remains the same over the time period with 1364 prescriptions per 1000 beneficiaries during the study period. 40% of the US Medicare beneficiaries have received potentially inappropriate antibiotics.
Suda, Katie J., et al.	2006-2010 IMS Health Xponent	US adult population	Unknown	Overall, 1.34 billion antibiotic prescriptions were dispensed from 2006-2010. The antibiotic rate declined by 2.8% over the study period from 892.21 to 867.58/1000 population.

Antibiotic Complications:

Evidence shows that allergic reactions, antibiotic resistance, *C. difficile* infections and drug interactions and side effects are the most common complications associated with antibiotic use/overuse. Antibiotics are the second most common drug class associated with adverse drug events among older adults in the ambulatory setting (15%), after cardiovascular agents (26%), and carry double the risk associated with anticoagulant medications (7.9%).[9]

Antibiotic resistance is considered a global threat caused by antibiotic overuse or misuse. It happens when bacteria develop a way to overcome the medication that is intended to kill them.[10] The older adult population is at higher risk of antibiotic use, immune system impairment and multiple chronic health conditions which could lead to antibiotic resistance compared to other age groups.[11,12,13] The Centers for Disease Control and Prevention (CDC) reported that 2 million people each year are diagnosed with infections caused by antibiotic-resistant bacteria. In addition, 23,000 people die each year in the U.S. due to antibiotic resistance.[10] In 2015, the U.S. White House released a national action plan to defeat antibiotic resistance through developing innovative prevention strategies, enhancing surveillance, and implementing antimicrobial stewardship programs.[14]

Another complication due to antibiotic use/overuse is *Clostridioides difficile (C. diff)* Infection (CDI). *C. diff* is a gram-positive, anaerobic bacillus that is often associated with severe diarrhea and abdominal cramping. The CDC estimated in a recent report that each year there are 500,000 CDI cases in the U.S., with 15,000 deaths attributable to CDI annually.[15] CDI costs the U.S. health care system up to 4.8 billion each year. The rate of CDI has increased dramatically in recent years, specifically among the older adult population. Ninety-three percent of deaths attributable to CDI occur in older adults, making it the 18th leading cause of death in the United States among older adults.[16] Prior antibiotic use, recent hospitalization, proton pump inhibitors use and a weakened immune system are risk factors of CDI in older adults.[17,18,19] As with antibiotic resistance, the U.S. is working on a national plan to combat antibiotic resistant and reduce the rate by 50% by 2020. One major element of this program is antimicrobial stewardship programs.

Antibiotic Stewardship Programs (ASPs):

Antibiotic stewardship programs aim to improve antibiotic use and reduce the number of inappropriate antibiotic prescriptions, antibiotic resistance, side effects associated with antibiotic use, and CDI. The program should help health care providers and hospitals optimize antibiotic therapy. Progress in ASPs has primarily been in the acute care setting. Effective on January 2017, the Joint Commission approved and released the new antimicrobial stewardship standard, which requires all hospitals, critical access hospitals, nursing homes, ambulatory care organizations, and office-based surgery practices to implement ASP in their settings.[20] As a result, during the time frame when we conducted our studies, it was not mandatory for health systems to have an ASP for outpatient settings.

According to the CDC, a successful ASP is based on seven key elements including leadership commitment, accountability, medication expertise, action, tracking, reporting and education.[21] Table 1 shows the detail for each element.

Table 1.2. The CDC's essential core elements for antibiotic stewardship programs

Key Element	Explanation
Leadership commitment	Hospitals should invest money, clinicians, IT support, nurses, and pharmacists to implement ASP.
Accountability	Hospitals should appoint a single leader who will be responsible for program outcomes.
Medication expertise	Hospital should appoint a pharmacist to lead and support the appropriate antibiotic prescribing.
Action	Hospitals should design a systematic approach to evaluate patient's needs for antibiotic.
Tracking	Hospitals are responsible to track antibiotic prescriptions and antibiotic resistance.
Reporting	Hospitals should report the trend and the patterns of the negative outcomes related to antibiotic misuse.
Education	Hospitals should offer educational sessions to all health care providers regarding antibiotic use, side effect, resistance, and CDI.

Although many studies support the necessity of ASPs, other studies have shown little effect from implementing ASPs. The success of ASPs may depend on including all of the seven elements that we have mentioned in Table 1. ASPs have been projected to mitigate 619,000 infections associated with antibiotic resistance.[22] In addition, it is been estimated that implementing ASPs in acute care would save approximately $7.7 billion in direct medical costs. Although ASPs have been implemented in acute care for 30 years or more, they are still not required in most other health care settings including outpatient settings where most older patients receive care. The Centers for Medicare & Medicaid Services (CMS) announced that by November 2019, most long term care settings (nursing homes) will be required to implement ASPs.

The Older Adult Population:

Older adult is a term referring to a person who is 65 years or older. Today, there are almost 40 million persons aged 65 years and older living in the U.S., and this number is expected to increase to 89 million persons in the next 30 years.[23] This rapid change in population characteristics can lead to economic, social, and health care consequences, especially if the healthcare system does not prepare for this change. Many older adults have multiple comorbidities and receive more than one prescription medication, which may lead to difficulty in managing their health and maintaining their quality of life. Also, older adults experience physiologic changes associated with aging affecting their liver and kidney function and immune system which may necessitate more individualized dosing adjustment for antibiotics compared to other age groups.[24]

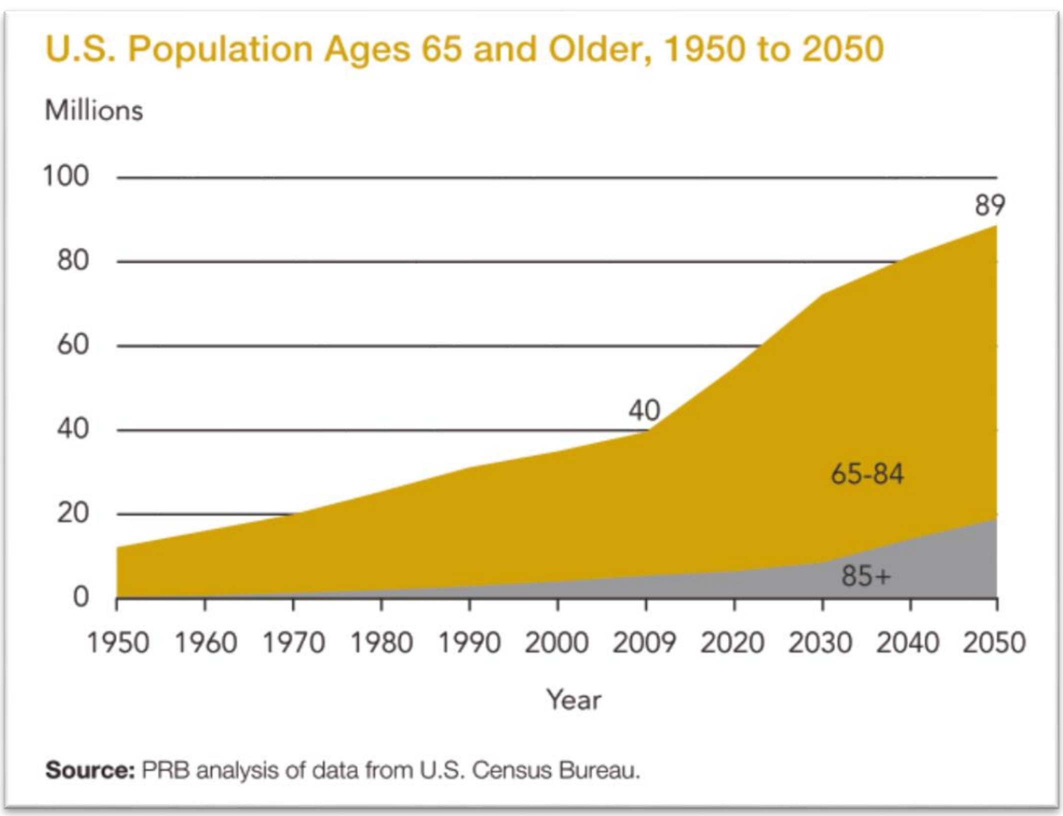

Figure 1.1. U.S. Population Ages 65 and Older, 1950 to 2050.[25]

Human beings experience normal changes during the aging process and these changes are categorized as biological, psychological, and sociological. The most critical changes contributing to an increased risk of infection in older age are the physiological changes in the immune system. It is well established that the immune system response to pathogens declines with age. In nonspecific immunity, the number of leukocytes decreases with age. In humoral immunity, the level of isoagglutinins in the blood declines in the older population. Also, the antibody response to the influenza vaccine decreases in the older population. Moreover, as we age the capacity for mounting a cell-mediated immune response declines.[25] In addition, there are several biological changes responsible for increasing the chance of infections in older adults including changes in skin and mucosal barriers as a first line defense in the immune system. During the aging process, skin becomes thinner and skin elasticity is weaker. Some observations showed that the atrophy and drying of the skin were responsible for endocarditis.[26] Also, blood flow to the skin decreases as we age, which increases the likelihood of chronic pressure ulcers. The rate of urinary tract infections (UTIs) is higher among older adults. The biological changes in the excretion system may play an essential role including decreased plasma flow through the kidney by 50% and decreased glomerular filtration rate by 30%, which likely contribute to the development of UTIs. Another physiological change as we age is the weakness of the muscles around the bladder, consequently the bladder accumulates urine and emptying the bladder becomes more difficult, which increases the risk of a urinary tract infection. Older adults are at higher risk of using urinary catheters, especially in long-term care facilities and this may also increase the risk of urinary tract infections in both genders.

Most nursing home residents are at higher risk of infections especially UTI and URI due to frailty, intubation, catheterization, physical dependence, cognitive impairment and altered host resistance.[27] However, the diagnosis of infection in older adult patients is not always obvious and simple. The symptoms of infections in the older patient is different than a younger patient and may not include fever that most of the health care providers rely on to make a clinical decision of infection.[11] This is because of the physiological changes in temperature regulation due to normal aging.[28] It is expected that older adult patients present with infection without having a fever as well.[28] On the other hand, taking patient history is an important element for an accurate diagnosis. This is an issue with cognitively impaired patients. In addition, the symptom of delirium may have many underlying causes including UTI which makes it difficult for the physician to reach on accurate diagnosis.[29,13] Physicians should be careful when initiating an antibiotic prescription to an older adult patient.

These physiological changes that occur during aging are not only contributing to an increased risk of infection, they also affect the response to antibiotics. As part of normal physiological changes as we age, several organ functions important for eliminating antibiotics from the body, including kidney function and liver function, decline.[30] Altered drug elimination may necessitate lower doses of antibiotics in older adults to avoid undesirable side effects or lower rate of clinical outcomes from the antibiotic.

Another common issues regarding antibiotic use among older adult population are adverse drug reactions and drug-drug interactions. Previous studies have demonstrated a positive relationship between adverse drug reactions and increasing age.[31] It has been reported to increase the odds of hospital admission and health care cost.[31] The common reported adverse drug reactions among older adults are anaphylaxis or allergic reaction, Q-T prolongation, nephrotoxicity, and ototoxicity.[32] On the other hand, older adult patients at increased risk of drug-drug interactions due to polypharmacy, comorbidities, and altered physiological functions due to aging.[33]

Geriatrics Clinic and Adult Internal Medicine Ambulatory Clinic at VCU Health:

The Geriatrics clinic (GC) at VCU Health, under the internal medicine clinics structure, has been active for more than 30 years when it was founded by Dr. Peter Boling. Dr. Boling had the passion and initiative to establish the GC to provide specialized care to complex and vulnerable older adult patients. Due to an increase in the number of complex patients being cared for at VCU Health, the Geriatrics clinic became a separate clinic from the Adult Internal Medicine Clinic starting in January 2012. All of the physicians serving the patients in the GC are geriatricians, and the nurse practitioners are either adult-gerontology or family medicine specialists. The overall goal of the GC is to provide comprehensive care for older adults (65 years or older) who have complex needs like polypharmacy and multiple chronic conditions. In comparison with older adult patients visiting the Adult Internal Medicine clinic, the GC patients are considered sicker and more complex patients regarding medications and the number of medical conditions according to Martha Purvis, an experienced nurse practitioner at the GC. A recent statistic shows that the GC provides care to over 500 patients per provider annually.

On the other hand, the Adult Internal Medicine clinic has been providing care for older adult patients at VCU Health since 1838. The Department of Internal Medicine at VCU Health consists of more than 180 clinicians, 124 residents under training, and over 80 fellows. There are ten divisions under the department of internal medicine, which includes Cardiology, Endocrinology, Gastroenterology, General Internal Medicine, Geriatrics, Hematology, Infectious Diseases, Nephrology, Pulmonary diseases, and Rheumatology.

In one of the studies presented in this dissertation (Study Two), we used data from 2012-2017 from the Geriatrics clinic, and the Adult Internal Medicine clinic.

Antibiotic Appropriateness:

Antibiotic inappropriateness could lead to increased risk of antibiotic resistance, C.diff infection and preventable adverse drug reactions. Antibiotic inappropriate is defined as "Use of antimicrobials in the setting of established infection to which the pathogen is resistant or use of antimicrobials not recommended in treatment guidelines."[34] There are different definitions of assessing antibiotic appropriateness in epidemiological studies. Most of them have used subjective measures based on expert opinion-based definitions. These opinions are usually based on treatment guidelines for specific infections, dosage adjustment, medication route, or duration of therapy. In our studies, we have used a validated method developed by Fleming-Dutra et al.[8] This study used a comprehensive methodology with a team of experts systematically reviewing the national guidelines for antibiotic use for common infectious diseases among the older adult population. The criteria for antibiotic appropriateness that we have used in our studies was based on diagnoses and treatment guidelines. This method was appropriate for our studies due to availability of the variables that we need to assess antibiotic appropriateness. For instance, we lack the medication dose, or duration of therapy variables, that is why we didn't evaluate the appropriateness based on either dose or duration of therapy. Despite the limitation of our method, expert opinion-based evaluations are commonly used in epidemiological studies.

Rational (Significance):

A nationally representative study in the U.S. demonstrated significant increases in broad-spectrum antibiotic use among the older adult population from 2000 to 2010.[5] In 2000, the antibiotic use was about 287 prescriptions per 1,000 persons, and this number doubled by 2010 to 482 prescriptions per 1,000 persons. The most commonly prescribed antibiotics vary and depend on the guidelines of the treatment in specific countries. For instance, in the U.S. and Canada, quinolones were the most commonly prescribed antibiotics for urinary tract infections (UTI),[35,36] while in Australia, doxycycline was the most widely prescribed antibiotic for UTI and respiratory infections.[37] The term "older adult" that was used in these studies referred to a person who was 65 years or older. Today, there are almost 40 million persons aged 65 years and older living in the U.S., and this number is expected to increase to 89 million persons in the next 40 years.[38] This rapid change in population characteristics can lead to economic, social, and health care consequences, especially if the healthcare system does not prepare for this change.

The two major threats of antibiotic overprescribing are antibiotic resistance and increased CDI incidence rate. These threats have received significant focus at the international level from organizations like the World Health Organization (WHO) and at the national level in the U.S. from organizations like the White House initiative to combat antibiotic resistance.[39] As a result of our studies, we seek to add valuable information to the literature in order to better understand antibiotic use among the older adult population. This information is currently limited in the literature, and comparing our results with the previous studies within the same scope would be helpful to understand antibiotic use among older adults. There is limited information regarding this issue within the older adult population due to lack of accessible data to facilitate this kind of study. We are aiming that the results of our studies will help to uncover needs that might be addressed through antibiotic stewardship programs and the consequences of antibiotic misuse among older adults.

Specific Aims:

This dissertation project is comprised of three different studies that are related to antibiotic use among the older adult population using national and local data sources. The objectives of each study are listed below.

Study 1: The Trend of Antibiotic Use Among Community-Dwelling Older Adults in The United States (Medical Expenditure Panel Survey MEPS 2011-2015).

The specific aims are:

1) To understand the patterns of antibiotic use among non-institutionalized community-dwelling older adults using Medical Expenditure Panel Survey MEPS from 2011-2015.
2) To describe the patterns of the most common infectious diseases among non-institutionalized community-dwelling older adults using Medical Expenditure Panel Survey MEPS from 2011-2015.
3) To understand the association between antibiotic use and demographic, socioeconomic characteristics and emergency department visits.

Study 2: A Comparison of Antibiotic Use and Infectious Diseases Among Older Adults between Geriatrics Clinic and Adult Internal Medicine Ambulatory Care Clinic in VCU Health.

The specific aims are:

1. To assess the trend of antibiotic use and infectious diseases among Geriatrics clinic patients at VCU Health from 2012-2017.

1A) To assess the most common antibiotics prescribed for the three most common infectious diseases: urinary tract infection (UTI), upper respiratory tract infection (URI), and skin infection.

2. To assess the trend of antibiotic use and infectious diseases among older adult patients visiting adult internal medicine ambulatory care clinic at VCU Health from 2012-2017.

    2A) To assess the most common antibiotics prescribed for the three most common infectious diseases: urinary tract infection (UTI), upper respiratory tract infection (URI), and skin infection.

3. To compare the antibiotic appropriateness between the Geriatrics clinic and Adult Internal Medicine Ambulatory clinic at VCU Health from 2012-2017.
4. To assess the relationship between the antibiotic appropriateness and demographic, socio-demographic characteristics, type of clinic, antibiotic negative outcomes like emergency department visit or hospitalization within 30 days after the initiation of antibiotics.

Study 3: Antibiotic Use Among Older Adults Visiting The Emergency Department (ED) at VCU Health 2012-2017.

The specific aims are:

1. To assess the trend of antibiotic use and infectious diseases among older adult patients (65 years or older) visiting the ED at VCU Health from 2012-2017.

1A) To assess the most common antibiotics prescribed for the three most common infectious diseases: urinary tract infection (UTI), upper respiratory tract infection (URI), and skin infection.

2. To assess the trend of antibiotic use and infectious diseases among middle-aged patients (55 to 64 years old) visiting the ED at VCU Health from 2012-2017.

    2A) To assess the most common antibiotics prescribed for the three most common infectious diseases: urinary tract infection (UTI), upper respiratory tract infection (URI), and skin infection.

3. To compare the antibiotic appropriateness between older adult patients and middle-aged patients visiting the ED at VCU Health from 2012-2017.
4. To assess the relationship between antibiotic appropriateness and demographic, socio-demographic characteristics, age group, antibiotic negative outcomes like ED visit or hospitalization within 30 days after the initiation of antibiotics.

Summary:

This dissertation contains five chapters. The first chapter is the introductory chapter, which provides an overview of antibiotic use, and its complications among older adults. In addition, the first chapter describes the aging population in the U.S. and the rational and specific aims for each study. The second chapter details the first study, which aims to answer questions related to antibiotic use among non-institutionalized older adults in the U.S. using nationally representative data. The third chapter describes a study examining the issue of antibiotic appropriateness and compares the patterns of antibiotic use and infectious diseases between Geriatrics clinic patients vs. adult Internal Medicine Ambulatory clinic at VCU Health from 2012-2017. The fourth chapter describes the results of the final study, which examined antibiotic appropriateness among older adults visiting the ED at VCU Health from 2012-2017. The final chapter is the discussion chapter, which describes the main findings, draws overarching conclusions and discussed the implications of the work and future directions.

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CHAPTER TWO

Study 1: The Trend of Antibiotic Use Among Community-Dwelling Older Adults in The United States (Medical Expenditure Panel Survey MEPS 2011-2015)

Background:

It has been well documented that antibiotic overuse/misuse increases the risk of *Clostridioides difficile* (*C.diff*) infection as well as antibiotic resistance.[1,2] The Centers for Disease Control and Prevention (CDC) has reported that 23,000 people die each year due to antibiotic resistant infections.[2] Older adult populations are growing globally and in the United State (US) specifically. It was estimated that the adult population aged 65 or older will grow to around 89 million people by 2050 in the US, more than double the number of older adults in 2010.[3] This specific population has unique characteristics that need more attention in terms of health care improvement. Older adult patients are more likely to have comorbidities, polypharmacy, and changes in kidney and liver function that could affect the pharmacokinetics and other responses to antibiotics.[4,5]

Antibiotic overuse leads to significant increase in the emergency department visits associated with adverse drug reactions.[6] Older adults aged 65 and older are at increased risk of adverse outcomes from antibiotics and other drug classes like anticoagulants and antidiabetic medications.[7] Despite the extensive efforts from the CDC, US government, and the health care system to reduce antibiotic prescribing through implementing antimicrobial stewardship programs[8] among all ages, antibiotic prescription rates increased 30% among older adults from 2000 to 2010, while the antibiotics rate decreased among children and adolescents.[9]

In addition, it is important to understand prescribing practices among older adults from a nationally representative perspective to inform health care initiatives to improve antibiotic use and reduce the negative outcomes related to antibiotic misuse like allergic reactions, drug-drug interactions, and *C.diff* infections. Therefore, the first objective of this study was to understand the patterns of antibiotic use among community-dwelling older adults in the US using the Medical Expenditure Panel Survey (MEPS), a nationally representative database from 2011-2015. The second objective was to document the most common infectious diseases in the same population. The third objective was to understand the association between antibiotic use and demographic characteristics, socioeconomic characteristics and emergency department utilization.

Methods:

Data Source:

A cross-sectional retrospective study was conducted to assess the patterns of antibiotic use among community-dwelling older adults using MEPS 2011-2015. The most recent MEPS database available was used in this study. MEPS is collected by the Agency for Healthcare Research and Quality (AHRQ).[10] MEPS is a publicly available nationally representative database that surveys non-institutional families and individuals, and their medical providers across the US. The data includes only de-identified patient characteristics and pharmacy claims. MEPS uses a complex stratified multistage cluster design technique during the survey collection, which allows researchers to calculate national weighted estimates. In addition, all the information in the patient full-year consolidated data files, medical conditions files, prescribed medicine files, and emergency room files were used in the analysis.

Study Sample:

Only individuals 65 years and older were included in this analysis. From the full-year consolidated file, we obtained age, gender, race, marital status, level of education, health status, flu vaccination status, annual family income, and health insurance status. We collected antibiotic prescriptions dispensed and prescribed proton pump inhibitor use from the prescriptions file. In MEPS data, participants reported the list of medications and were asked for permission to look at their pharmacy data as well. From the emergency file, we obtained the number of ER visits in the past 30 days. Infectious disease diagnoses were obtained from the medical conditions file and identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-

CM). Upper respiratory tract infections (URI) were included using the following ICD-9-Codes: 041, 460, 461, 462, 463, 464, 465, 466, 486, and 490. ICD-9-Code 599 was used for urinary tract infection (UTI). Skin and soft tissue infections were included using ICD-9-Codes 681, 682, 686, 690, 691, and 691. ICD-9-Codes 008 and 009 were used to define any intestinal infections, while 486 was used to define pneumonia cases. Any participants younger than 65 years of age or with incomplete information regarding antibiotic use were excluded.

Statistical Analysis:

Descriptive analysis was used to calculate the weighted frequency and percentage for the categorical variables in both antibiotic users and non-users. A chi-square test was used to test the association between the covariates and the outcome of interest (antibiotic use). Trend analysis was performed using the Cochran–Armitage test. U.S. Census data were used to calculate the rate of infectious diseases and antibiotic prescriptions per 10,000 population.[11] A multiple logistic regression model was used to test the association between antibiotic use and demographic characteristics, geographic region, socioeconomic characteristics and emergency department use. Any variable that maintained a p-value of 0.1 was included in the multiple logistic regression model. We have used the MEPS person weights, sampling variance estimation strata for each year in order to calculate a nationally weighted estimate. A p-value less than 0.05 was considered statistically significant. All the statistical analyses were conducted using SAS software version 9.4 (SAS Institute, Inc., Cary, NC).

Ethical Considerations:

This study was deemed as an exempt study by the Virginia Commonwealth University Institutional Review Board (VCU IRB #HM20013520).

Results:

In our study, there were 105,762,134 prescriptions dispensed to older adults in the outpatient settings in the US from 2011 to 2015. The overall rate of antibiotic prescriptions dispensed increased slightly, from 484 prescriptions per 1,000 persons in 2011 to 540 prescriptions per 1,000 persons in 2015. Prescribing rates decreased with age, the oldest-old participants (80 years or older) reported lower prescriptions than 65-69 year olds, 7% and 11% respectively (Table 2.1). Antibiotic prescriptions were more common among women (18%) compared to men (12%). White participants received more antibiotics (27%) than African Americans (1.77%) and others (1.4%). Eight percent of older adults who received antibiotic prescriptions reported that they visited the emergency department at least once in the study period (2011-2015).

Multiple logistic regression modeling shows that the 75-79 years age group are 41% more likely to receive antibiotics compared to the oldest-old group (80 or older) (Table 2.2). Females were significantly (52%) more likely to receive antibiotics compared to men. Moreover, ER visits were significantly associated with antibiotic prescriptions; older adults visiting the ER were two times more likely to receive and antibiotic compared to non-ER visitors. Proton-pump inhibitors PPI users were not associated with antibiotic dispensing compared to non-antibiotic users.

URI, UTI, and skin infections were the most common infectious diseases documented in our study population. The rate of URI increased over time from 135 infections per 1,000 persons in 2011 to 166 infections per 1,000 persons in 2015 (Figure 2.1). The same trend was observed in UTI infections which increased from 55 to 75 infections per 1,000 persons between 2011 and 2015. Macrolides, quinolones, and penicillins were the most common antibiotic categories prescribed to older adults from 2011 to 2015. The rate of use of penicillins increased over the study period from 169 prescriptions per 1,000 prescriptions to 256 prescriptions per 1,000 prescriptions, accounting for 21% of all antibiotic prescriptions. Quinolone prescription rates were stable while macrolide prescription rates dropped from 334 to 156 prescriptions per 1,000 prescriptions, accounting for 26% of all antibiotic prescriptions (Figure 2.2).

Table 2.1. The demographic characteristics of antibiotic users and non-users in MEPS from 2011-2015.

Variable	Antibiotic Use (Yes)		Antibiotic Use (No)	
	Sample persons	Weighted %, [95% CI]	Sample persons	Weighted %, [95% CI]
Age (years)				
65-69	1844	10.59 [9.77- 11.40]	4286	21.78 [20.80-22.77]
70-47	1182	7.40 [6.88-7.91]	3053	16.38 [15.51-17.26]
75-79	891	5.60 [5.10-6.09]	2317	12.41 [11.64-13.18]
80 or older	1110	6.99 [6.31-7.67]	3438	18.82 [17.59-20.05]
Sex				
Male	1927	12.17 [11.50-12.85]	5829	31.98 [30.96-33.00]
Female	3100	18.41 [17.64-19.17]	7265	37.42 [36.45-38.38]
Race				
White	3996	27.41 [26-24-28.58]	9004	58.00 [56.55-59.45]
African American	658	1.77 [1.51-2.02]	2730	6.90 [6.00-7.80]
Other	373	1.40 [1.09-1.71]	1360	4.49 [3.44-5.53]
Marital status				
Married	2598	17.31 [16.27-18.34]	6541	37.88 [36.45-39.30]
Other	2429	13.27 [12.52-14.02]	6553	31.53 [30.04-33.01]
Education				
No education	12	0.13 [0.01-0.25]	40	0.28 [0.14-0.41]
High school or less	1148	19.26 [17.66-20.86]	2997	40.86 [38.99-42.74]
College years	617	11.85 [10.69-13.01]	1589	27.59 [25.62-29.57]
Health status				
Excellent	649	4.79 [4.31-5.27]	1778	11.16 [10.37-11.95]
Very good	1380	9.04 [8.41-9.67]	3563	21.48 [20.67-22.30]
Good or fair	2585	14.90 [14.06-15.74]	6797	33.26 32.21-34.30]
Poor	347	1.87 1.60-2.13]	770	3.46 [3.09-3.84]
Flu vaccine				
Yes	890	24.20 [22.28-26.11]	2214	51.13 [48.58-53.68]
No	242	6.15 [5.09-7.20]	858	18.51 [16.72-20.30]
Family income				
Poor or near poor	1411	6.85 [6.28-7.43]	4084	17.25 [16.20-18.30]
Low income	1268	7.67 [7.10-8.24]	3381	18.56 [17.53-19.60]
Middle income	1071	7.19 [6.59-7.79]	2767	16.35 [15.40-17.30]
High income	1180	8.94 [8.12-9.76]	2513	17.14 [15.82-18.46]
Insurance				
Private	1740	12.11 [11.26-12.97]	3848	25.09 [23.92-26.26]
Medicaid	3207	18.49 [17.63-19.36]	8914	43.89 [42.64-45.14]
Medicare	26	0.06 [0.03-0.10]	103	0.32 [0.17-0.48]
ER visit				
No visit	3555	21.97 [21.09-22.85]	10800	57.55 [56.47-58.63]
1 to 3 visits	1389	8.18 [7.61-8.75]	2225	11.48 [10.81-12.15]
4 or more visits	83	0.43 [0.32-0.53]	69	0.36 [0.24-0.49]
PPI prescribed				
Yes	1285	7.77 [7.16-8.39]	2629	13.67 [12.86-14.47]
No	3742	22.80 [21.91-23.70]	10465	55.74 [54.57-56.91]

Table 2.2. Multiple logistic regression analysis predicting antibiotic users vs. non-users

Variable	Unadjusted or [95% CI]	Adjusted or [95% CI]
Age (years)		
80 or older	1 [Reference]	1 [Reference]
65-69	1.30 [1.13-1.50] *	1.19 [0.66-2.13]
70-47	1.21 [1.07-1.38] *	1.36 [0.80-2.29]
75-79	1.21 [1.04-1.40] *	1.41 [0.81-2.44]
Sex		
Male	1 [Reference]	1 [Reference]
Female	1.29 [1.18-1.40]*	1.52 [1.10-2.10] *
Race		
White	1 [Reference]	1 [Reference]
African American	0.54 [0.47-0.62] *	0.69 [0.43-1.10]
Other	0.66 [0.54-0.79] *	1.20 [0.70-2.08]
Marital status		
Other	1 [Reference]	1 [Reference]
Married	1.08 [0.98-1.19]	1.17 [0.86-1.59]
Education		
College years	1 [Reference]	1 [Reference]
No education	1.10[0.41-2.95]	0.73 [0.26-2.01]
High school or less	1.09[0.95-1.26]	1.43 [1.00-2.04] *
Health status		
Good or fair	1 [Reference]	1 [Reference]
Excellent	0.95 [0.84-1.09]	0.96[0.53-1.76]
Very good	0.93 [0.85-1.03]	0.93 [0.66-1.32]
Poor	1.20 [0.99-1.46]	1.23[0.72-2.09]
Flu vaccine		
No	1 [Reference]	1 [Reference]
Yes	1.42 [1.15-1.75] *	1.12 [0.79-1.59]
Family income		
High income	1 [Reference]	1 [Reference]
Poor or near poor	0.76 [0.68-0.85] *	0.49 [0.29-0.84] *
Low income	0.79 [0.70-0.88] *	0.60 [0.37-0.98] *
Middle income	0.84 [0.74-0.95] *	0.54 [0.33-0.89] *
Insurance		
Medicare	1 [Reference]	1 [Reference]
Private	1.14[1.04-1.25] *	1.09 [0.77-1.55]
Medicaid	0.50[0.28-0.90] *	1.01[0.27-3.80]
ER visit		
No Visit	1 [Reference]	1 [Reference]
1 to 3 visits	1.86 [1.69-2.05] *	2.03 [1.42-2.89] *
4 or more visits	3.06 [2.02-4.63] *	0.08 [0.00-1.04]
PPI prescribed		
No	1 [Reference]	1 [Reference]
Yes	1.39 [1.26-1.53] *	1.10 [0.76-1.58]

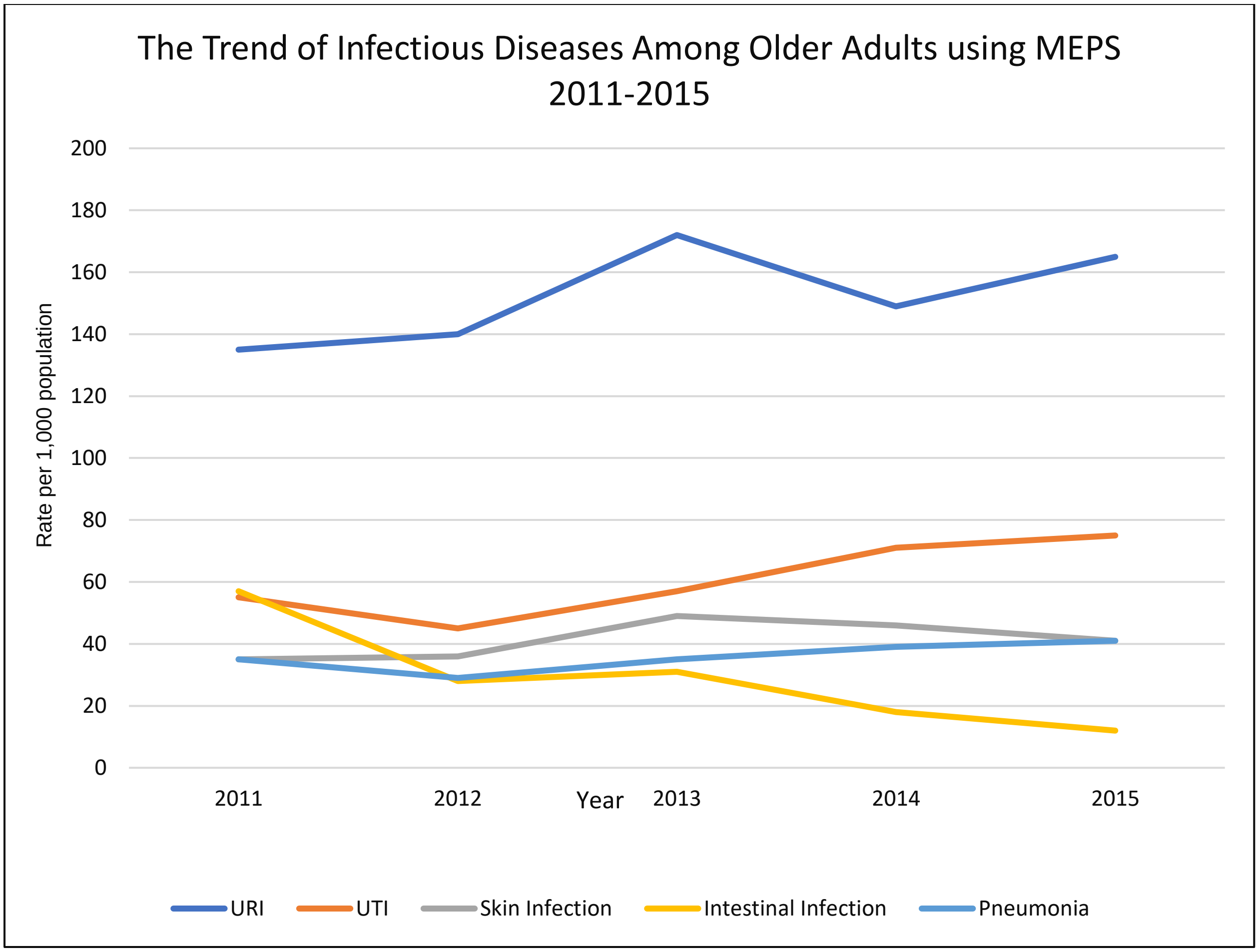

Figure 2.1. The trend of infectious diseases among older adults using MEPS 2011-2015.

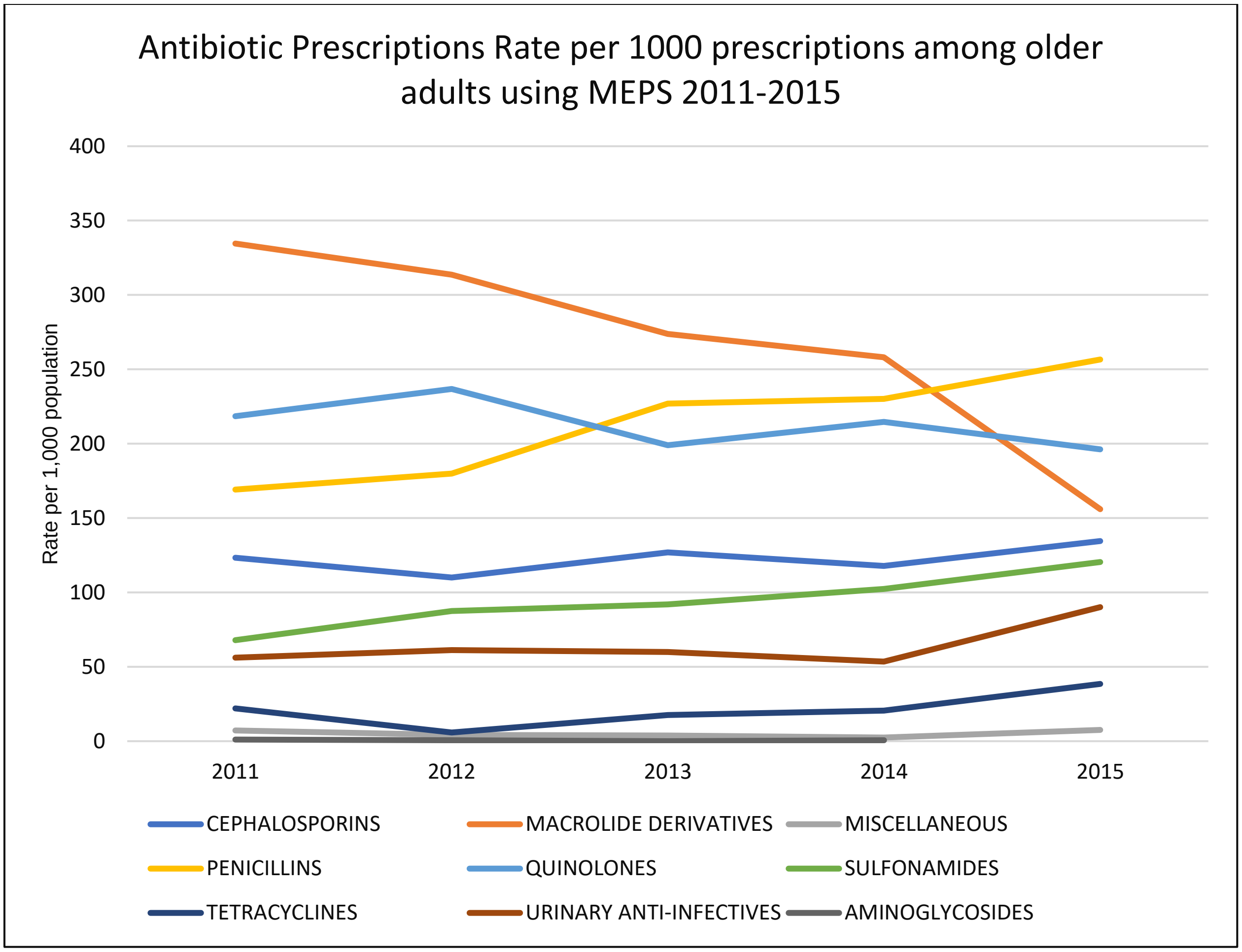

Figure 2.2. The rate of antibiotic prescriptions per 1000 prescriptions among older adults using MEPS 2011-2015.

Discussion:

This study assessed the prevalence of antibiotic prescriptions dispensed among community-dwelling older adults in the US using MEPS 2011-2015 data. In addition, this study assessed the rate of infectious diseases and the predictors of antibiotic users compared to non-users. Several studies have reported the rate antibiotic use in different time periods, age groups, and data sources, but this study specifically focused on the older adult population. Older adults are at high risk of polypharmacy, drug-drug interactions, adverse drug reactions, comorbidities as well as age-associated physiological and changes that affect the pharmacokinetics and pharmacodynamics of medications. Antibiotic use in this population has rarely been reported in the literature and antibiotic prescribing practices are not clear. Based on our results, 31% of the non-institutional older adults in the US were prescribed antibiotics, accounting for 105,762,134 prescriptions over the study period. We estimate that the antibiotic prescribing rate increased slightly from 483 to 540 prescriptions per 1,000 persons. A similar rate was observed in 2010 by Lee et al., using the early rounds of MEPS data suggesting that the rate has been relatively stable since 2010.[9] This unchanged rate since 2010 could be explained by several reasons. First, the effort of implementing antibiotic stewardship programs (ASPs) is not strong enough to cover a wide range of settings in the health care system, like ambulatory care clinics, assisted living facilities, and pharmacies. A study estimated that 30% of outpatient antibiotics were inappropriate among all ages.[12] Therefore it is crucial to implement ASPs in outpatient settings in addition to inpatient settings. Second, there could be a lack of knowledge among some health care providers about ASPs instituted by institutions where they practice. A study found that 25% of nurses at VCU-HS were not aware that ASPs existed at VCU Health.[13] Education is also important to family members who have a significant impact on antibiotic prescribing among older adult populations.[14,15,16]

We have found that in 2015, the antibiotic prescribing rate was 540 prescriptions per 1,000 persons, and this estimate is lower than the rate of antibiotic prescribing reported in a study conducted by Olesen et al., using data from Medicare beneficiaries enrolled Medicare Part D.[17] They found that the rate of antibiotic prescriptions in 2015 was 1,364.3 per 1,000 persons. This difference could be related to the differences in the data sources. MEPS does not include nursing home patients or any institutionalized patients, unlike Medicare Part D data. We found that older adults aged 65-69 years were more likely to be prescribed an antibiotic than the oldest-old participants. This observation could be related to increasing complexity with age resulting in health care providers avoiding adding extra medications that could lead to an emergency visit or hospitalization. Evaluating the antibiotic appropriateness among older adult populations is necessary for future research.

In addition, this study found that URI was on the most common infectious disease among older adults followed by urinary tract infections and skin and soft tissue infections. The rate for these diseases was relatively stable from 2011-2015. Similar results were found by Tan et al., when they conducted a similar study among older adults in Canada using The Ontario Drug Benefit Program database.[18] Although the two databases could be different in nature, the population of older adults studied shared common characteristics.

Macrolides, quinolones, and penicillins were the most common antibiotic classes dispensed to older adults in the US from 2011-2015. In the Olesen et al. study, quinolones were most commonly prescribed, followed by macrolides and penicillins.[17] In our study, we had a higher rate of URI treated by macrolides than rates observed in the other study. We observed that macrolide prescriptions deceased since 2013, while the rate of penicillins increased over the study period. This could be due to shifting practice from prescribing macrolides to pencillins due to reports of cases of severe toxicity and death related to macrolide use.[19]

This study has several limitations. First, although we have used nationally representative data, using MEPS specifically could raise a selection bias limitation. MEPS uses self-reported surveys among active members of the society which leads to selection bias. Also, using MEPS data could underestimate capturing the acute diseases like infectious diseases. Second, in order to assess the rate of infectious diseases, we used ICD-9-Codes for the primary diagnosis of each participant. This method could underestimate the antibiotic rate because not all antibiotic prescriptions were prescribed for the primary diagnosis. Third, some of the variables including emergency department visits, health status, and annual income were obtained through a survey methodology which is subject to potential recall bias. Fourth, in our analysis for the antibiotic indications, we have used ICD-9-Codes for the entire study period, while ICD-10-Codes came into use in mid-2015, so there a potential that we have underestimated some of the indications in 2015.

Conclusions:

In conclusion, the rate of antibiotic use overall remains unchanged despite antimicrobial stewardship efforts. The changes in the patterns of use in some of the antibiotic categories appear to be driven more by safety concerns rather than reducing overall use. Future research is needed to strengthen antibiotic stewardship programs for older adults in outpatient settings.

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CHAPTER THREE

Study 2: A Comparison of Antibiotic Use and Infectious Diseases Among Older Adult Patients of VCU Health's Geriatrics and Internal Medicine Ambulatory Care Clinics

Background:

Antibiotic resistance is a global threat following antibiotic use.[1,2,3,4] Several reports have documented that the mortality rate due to antibiotic resistant infections is projected to reach 10 million per year by the year 2050 with an estimated health care cost burden of 100 trillion dollars per year by 2050.[1] Studies suggest that antibiotic overprescribing and misuse increases antibiotic resistance and *Clostridioides difficile (C.diff)* infection. 51.6 million prescriptions (1,115 prescriptions/1,000 persons) were written in 2014 for older adult outpatients in the United States according to a recent report.[5] A nationally representative study demonstrated significant increases in broad-spectrum antibiotic use among the older adult population from 2000 to 2010. In 2000, antibiotic use was about 287 prescriptions per 1,000 persons, and this number doubled by 2010 to 482 prescriptions per 1,000 persons. In the same study, the rate of antibiotic prescriptions decreased from 2000-2010 among children and adolescence and increased about 30% among older adults.[6]

The older adult population in the United States is projected to increase by 20% by 2030 according to a recent Centers for Disease Control and Prevention (CDC) report.[7] This population is more prone to use antibiotic medications than any other age group due to decreased immune function, use of urinary catheters, ventilation during hospitalization and other factors.[8,9,10] In 2010 study, older adults reported the highest antibiotic use rate compare to younger adults in the US.[11] In addition, older adults are more susceptible to adverse drug reactions including *C.diff* infections and drug-drug interaction due to polypharmacy, comorbidities, and normal physiological changes like changes in the liver and kidney functions.[12,13,14] In 2015, The White House published the National Action Plan For Combating Antibiotic-Resistant Bacteria, which aspires to achieve a major reduction in *C.diff* infections and Methicillin-Resistant *Staphylococcus aureus* (MRSA) infections by 2020 by reducing inappropriate antibiotic prescriptions by 50%.[3] It is crucial to understand antibiotic use patterns in different settings in the healthcare system and among the older adult population in particular in order to meet the White House goals.

The Geriatrics clinic at Virginia Commonwealth University (VCU) Health was established to support the specific care needs of older adults in the outpatient setting, but the pattern of antibiotic prescribing in this clinic compared to an adult Internal Medicine clinic serving adults of all ages at VCU Health is unknown. Therefore, the specific aims for this study were to:

1. Assess the trends of infectious diseases and antibiotic prescribing among Geriatrics clinic patients at VCU Health from 2012-2017.
2. Assess the trends of infectious diseases and antibiotic prescribing among older adult patients visiting adult Internal Medicine ambulatory care clinic at VCU Health from 2012-2017.
3. Compare the antibiotic appropriateness between the Geriatrics clinic and the adult Internal Medicine ambulatory care clinic at VCU Health from 2012-2017.
4. Assess the relationship between the antibiotic appropriateness and socio-demographic characteristics, type of clinic and negative outcomes associated with antibiotic use including an emergency department visit hospitalization during the 30 days after the initiation of antibiotics**.**

Methods:

Data Source:

We used electronic medical records data from the VCU Health Ambulatory Care Center (ACC) for the geriatric clinic and the internal medicine clinic from 2012-2017. The 2012 year was selected to start data collection because this was the founding year for the geriatric clinic at VCU Health. The year 2017 was the most recent complete data available at the time of data retrieval. VCU Health is an urban academic medical center in central Virginia. The data was retrieved from the electronic medical records and billing records by the Bioinformatics core of the VCU Center for Clinical and Translational Research (CCTR).

Study Design and Sample Selection:

This is a cross-sectional retrospective cohort study of electronic medical records of Geriatrics clinic and adult Internal Medicine ambulatory care clinic from 2012-2017.

Inclusion and Exclusion Criteria:

Only patients 65 years or older who received an antibiotic prescription during an outpatient visit to either the Geriatrics clinic or adult Internal Medicine clinic at VCU Health from 2012-2017 were included in this study. Only oral antibiotic prescriptions were included in the study to avoid any inpatient antibiotic prescriptions. All patients who received an antibiotic prescription within 2 days of hospital discharge were excluded from the study to avoid any hospital related infections. All patients who received an antibiotic prescription that was not prescribed on the day of clinic visit were excluded from the study. Finally, any patient with missing information in the medication file or diagnosis file were excluded from the study.

Study Measures:

Demographic Characteristics:

Age, race, gender, marital status, and clinic visited were collected from VCU Health electronic medical records from 2012-2017. Age was treated as categorical variable in this study and categorized into 5 year intervals for the analysis (65-69, 70-74, 75-79, and 80 years and older). Patients older than 80 years were censored in the oldest group to preserve patient confidentiality as required for an exempt study with the VCU Institutional Review Board (IRB). The race variable was categorized as White, African American, and other. The 'other' category in the race variable includes American Indian/Alaskan, Asian, Native Hawaiian, and other. The gender variable was categorized as male or female. Marital status was categorized as married, single, or other (divorced, separated, or widowed). Type of clinic was a dichotomous variable defined as Internal Medicine or Geriatrics clinic.

Outcomes Measures:

Infectious Disease Diagnoses:

The infectious disease diagnoses were identified by the International Classification of Diseases ICD-9-CM code assigned to each patient during the outpatient visit. VCU Health shifted to ICD-10-CM codes by end of 2015, so in our analysis, we have used both ICD-9-CM and ICD-10-CM codes. In our study, we included the most common infectious diseases among older adult patients visiting VCU Health outpatient clinics, which included urinary tract infection, upper respiratory tract infection, skin infection, pneumonia, *C. diff.* infection and otitis media. Table 3.1 details the ICD-9-CM and ICD-10-CM codes for each infectious diseases included in our analyses.

Antibiotic Prescribing Patterns:

The trends of antibiotic prescribing over time was derived from the 'anti-infective' medication category in the medication files. The medication file was abstracted from the electronic medical record and contains the medication name, category name, dosage form, and medication dose. The medication file includes all of the antibiotic prescriptions that every patient at VCU Health received over the study period in the two clinics that we studied, so a patient could have multiple antibiotic prescriptions over the study period. Our data has eleven antibiotic categories including macrolides (azithromycin, erythromycin), quinolones (ciprofloxacin, levofloxacin), sulfonamides (sulfamethoxazole-trimethoprim), urinary anti-infectives (nitrofurantoin), penicillins/beta-lactamase inhibitors (amoxicillin-clavulanate), miscellaneous antibiotics (metronidazole, rifaximin), tetracyclines (tetracycline, doxycycline), first generation cephalosporins (cephalexin), second generation cephalosporins (cefuroxime), third generation cephalosporins (cefdinir, cefpodoxime), and aminopenicillins (amoxicillin). The antibiotic prescribing trend was tested across all indications in each clinic and individually among the three most common infectious diseases (urinary tract infection (UTI), upper respiratory tract infection (URI) and skin infection) in the older adult population.

Antibiotic Appropriateness:

To assess oral antibiotic appropriateness, we used a validated method that was conducted by Fleming-Dutra et al.[15] Fleming-Dutra et al, has developed this tool with the help of a team of experts to review national guidelines for antibiotic use for the common infectious diseases among outpatient clinics. The criteria categorized antibiotic appropriateness into three different tiers based on the clinical diagnosis as follows:

1. **Tier 1: Antibiotics almost always indicated:** including UTI, *C.diff.* Infection and pneumonia.
2. **Tier 2: Antibiotics may be indicated:** such as acute sinusitis, suppurative otitis media, and some types of skin infections.
3. **Tier 3: Antibiotics not indicated:** including acute and chronic bronchitis, influenza, some type of skin infection, and URI.

Table 3.2 lists the ICD-9-CM and ICD-10-CM codes for each tier in this analysis.

Statistical Analysis:

The demographic characteristics were summarized using descriptive statistics (frequency/percentage). Chi-square tests were used to test the relationship between the outcomes variables and the categorical demographic variables. To adjust for the clinic visit variabilities, we calculated the antibiotic rate normalizing each year by the total number of visits for each clinic separately. Trend analysis was performed using the Cochran–Armitage test. Logistic regression modeling was performed after checking the assumptions, and odds ratio and ninety-five percent confidence intervals were reported for all estimates. Variables were included in the model if α equal to 0.1 and all variables were considered statistically significant at an α level of 0.05. All the statistical analyses were conducted using the Statistical Analysis Software Version 9.4 (SAS v.9.4), (SAS Institute Inc, Cary, NC).

Ethical Considerations:

The VCU IRB reviewed and approved this study as exempt (VCU IRB #: HM20013584).

Table 3.1. The ICD-9-CM and ICD-10-CM codes for each infectious diseases included in the study.

Type of infection	ICD-9-CM or ICD-10-CM
Urinary tract infection	'599' 'N39.0'
Upper respiratory tract infection	'478.9' '465.9' 'J06.9' '490' '491.21' '466' 'J20.9' 'J40' '491.9' '461.9' 'J01.90' '473.9' 'J32.9' 'J01.00' '477.9' 'J30.9'
Pneumonia	'486' 'Z87.01' 'J18.9' 'J18.8' '516.3' 'B96.1'
Skin infection	'682.6' '682.9' '682.6' '528.3' 'L03.90' 'L03.116' 'L03.115' 'H60.12'
Otitis media	'380.1' '381.1' 'H66.93' 'H66.92' 'H66.91' 'H66.90' '382.9' '381.4'
Clostridioides difficile infection	'A04.7' '8.45'

Table 3.2. Antibiotics appropriateness criteria according to Fleming-Dutra et al.[15]

Diagnosis	Corresponding ICD-9-CM or ICD-10-CM
Tier 1: Antibiotics almost always indicated:	
Urinary tract infection (UTI)	'599' 'N39.0'
Bacterial pneumonia	'486' 'Z87.01' 'J18.9' 'J18.8' '516.3' 'B96.1'
Clostridioides difficile infection	'A04.7' '8.45'
Tier 2: Antibiotics may be indicated:	
Acute sinusitis	'461.9' 'J01.90' '473.9' 'J32.9' 'J01.00'
Skin, cutaneous and mucosal infections	'382.9' 'H66.90' 'L03.115' 'L03.116' 'L03.90' '528.3' '682.6' '682.9' '682.6'
Suppurative otitis media	'H66.91' '380.1' '381.1' 'H66.93' 'H66.92'
Tier 3: Antibiotics not indicated:	
Acute and chronic bronchitis, bronchiolitis, allergic rhinitis	'490' '491.21' '466' 'J20.9' 'J40' '491.9' '477.9' 'J30.9'
Non-suppurative otitis media	'381.4'
Viral upper respiratory infection (URI)	'478.9' '465.9' 'J06.9'

Results:

Among the 3,515 patients who visited either Geriatrics or Internal Medicine ambulatory clinic from 2012-2017, 1,534 antibiotics were prescribed. Most of the prescriptions (69%) were prescribed in the Internal Medicine ambulatory clinic compared to. 31% of prescriptions initiated from the Geriatrics clinic. A majority of Geriatrics clinic antibiotic recipients were 80 years and older (45%), female (77%), and white or black (51% and 45%) respectively. In contrast, Internal Medicine ambulatory clinic antibiotic recipients were more evenly distributed among the older adult age categories. Demographic characteristics are presented in Table 3.3.

Antibiotic Appropriateness:

In our study, 43% of antibiotic prescriptions from the Geriatrics clinic were considered potentially appropriate, while 50% were considered potentially appropriate in the Internal Medicine ambulatory clinic. Potentially inappropriate antibiotic prescriptions were similar between the two clinics (30% in Geriatrics clinic and 28% in Internal Medicine ambulatory clinic) with p-value 0.08. Appropriateness of antibiotic prescribing is presented in Table 3.4.

Infectious Diseases Trends:

Most of the antibiotics in our study were prescribed for six indications: UTI, URI, pneumonia, skin infection, *C. diff* infection and otitis media. Among Internal Medicine ambulatory clinic patients, the rate of UTI decreased from 32 diagnoses per 10,000 visits in 2012 to 23 diagnoses per 10,000 in 2017 compared to Geriatrics clinic patients where the UTI rate dropped only slightly from 60 cases per 10,000 visits in 2012 to 56 diagnoses per 10,000 visits. Skin infections were the most common infectious diseases in 2017 in the Geriatrics clinic. The rate of skin infection in the Internal Medicine ambulatory clinic dropped by half from 2012 to 2017 (10 vs. 5 diagnoses per 10,000 visits) respectively. On the other hand, the rate of skin infection increased in Geriatrics clinic from 44 diagnosis per 10,000 visits to 76 diagnosis per 10,000 visits. Figure 3.1 presents the trend of infectious disease diagnoses from 2012 to 2017 in both clinics.

Antibiotic Prescribing Trends in Geriatrics Clinic Compared to Internal Medicine a Ambulatory Clinic:

Quinolones, macrolides, and first generation cephalosporins were the most common antibiotics prescribed in both clinics over the study period. The directionality of the antibiotic rate between the two clinics remained the same from 2012 to 2017 in most of the antibiotic categories. For instance, quinolone prescribing in the Geriatrics clinic dropped from 179 prescriptions per 10,000 visits in 2012 to 106 prescriptions per 10,000 visits in 2017. The same pattern was seen in the Internal Medicine ambulatory clinic where the quinolone prescribing dropped from 63 prescriptions per 10,000 visits in 2012 to 30 prescriptions per 10,000 visits in 2017. Likewise, first generation cephalosporin prescribing in the Geriatrics clinic increased from 49 prescriptions per 10,000 visits in 2012 to 126 prescriptions per 10,000 visits in 2017. In the Internal Medicine ambulatory clinic, first generation cephalosporin prescribing increased only slightly from 15 to 20 prescriptions per 10,000 visits over the 5 year study period. Moreover, third generation cephalosporin prescribing increased from 0 to 45 prescriptions per 10,000 visits among Geriatrics clinic patients, and the same rate was observed among Internal Medicine ambulatory clinic patients (3 to 11 prescriptions per

10,000 visits over the study period). The rates of prescribing for the eleven antibiotic categories are shown in Figure 3.2.

Predictors of Receiving Potentially Inappropriate Antibiotics among Geriatrics Clinic Compared to Internal Medicine Ambulatory Clinic:

Table 3.5 shows the results of multiple logistic regression modeling predicting potentially inappropriate antibiotic prescriptions. This analysis showed that Internal Medicine clinic providers are significantly (p-value <0.05) less likely to prescribe potentially inappropriate antibiotics compared to the Geriatricians in the geriatric clinics (OR=0.70 95% CI [0.54-0.90]. Age, gender, race, marital status, hospitalization within 30 days after an antibiotic prescription, emergency department visit within 30 days after an antibiotic prescription were not significant predictors of receiving potentially inappropriate antibiotics or potentially appropriate antibiotics.

Antibiotic Treatment for UTI, URI, and skin infections:

Among UTI patients in both clinics, quinolones and first generation cephalosporins were the most common antibiotics prescribed over the study period (Figure 3.3). In both clinics, the use of quinolones to treat UTI dropped over time from 81 to 18 prescriptions per 100 UTI patients in the Geriatric clinic, and from 66 to 36 prescriptions per 100 UTI patients in the Internal Medicine ambulatory clinic from 2012 to 2017. The rate of first generation cephalosporin prescribing remained the same over time in the Geriatrics clinic, but increased from 15 to 33 prescriptions per 100 UTI patients in the Internal Medicine ambulatory clinic.

Macrolides, penicillins and quinolones were the most common antibiotic categories prescribed to treat URI in both clinics in our study. The rate of macrolide prescriptions increased in the Geriatrics clinic while the rate of quinolones and penicillins slightly decreased or remained the same (Figure 3.4).

Finally, tetracyclines, first generation cephalosporins and penicillins were the most common antibiotic categories prescribed to treat skin infection for patients in both clinics. The rate of tetracycline prescribing dropped from 62 to 26 prescriptions per 100 skin infection diagnoses from 2012 to 2017 in the Geriatrics clinic. The same trend was observed in the Internal Medicine ambulatory clinic where the rate of tetracycline prescribing dropped from 58 to 50 prescriptions per 100 skin infections diagnosed. In addition, the rate of first generation cephalosporin prescribing increased in the Geriatrics clinic and the Internal Medicine ambulatory clinic from (50 to 66 and from 21 to 37 prescriptions per 100 skin infection diagnosis over the study period respectively) (Figure 3.5).

Table 3.3. Demographic characteristics among those who were prescribed antibiotics in both ambulatory care clinics from 2012 to 2017

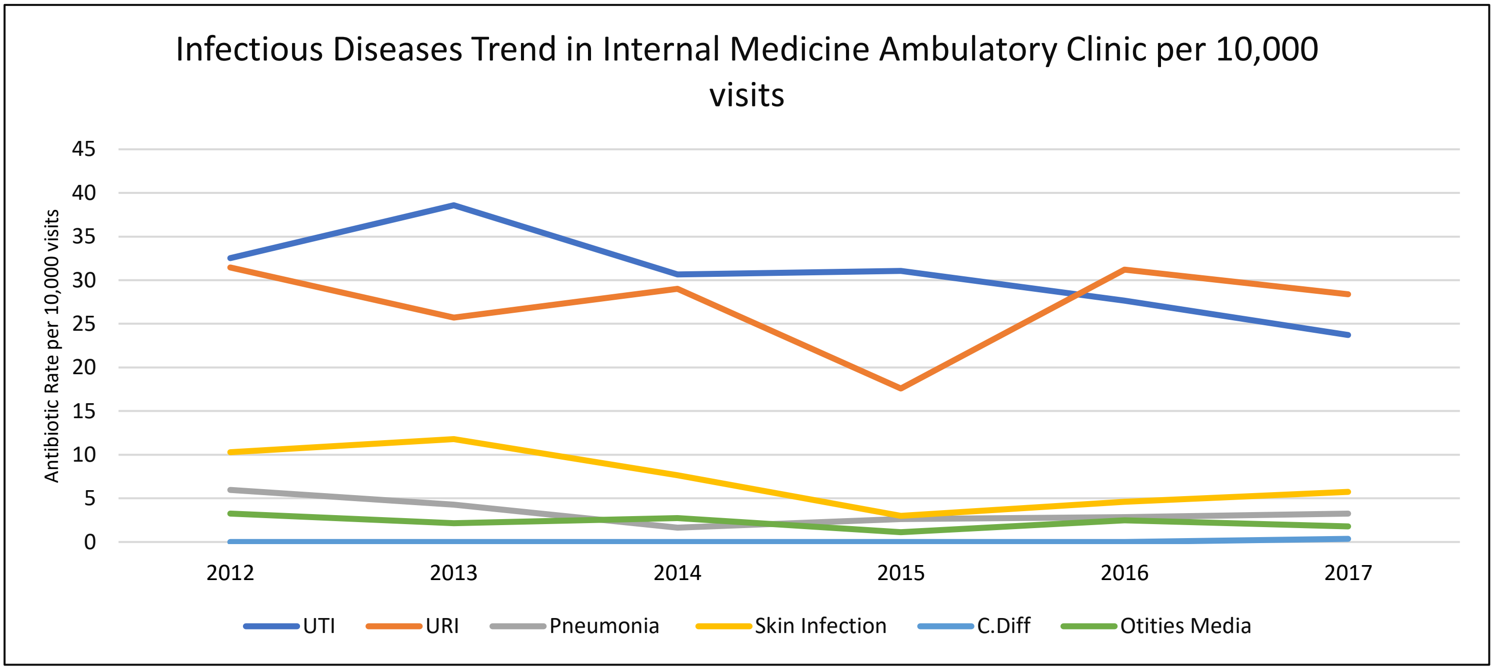
Factor (n=1534)	Geriatrics Clinic (Freq/%)	Internal Medicine Clinic (Freq/%)	P-Value
Age (years)			<0.0001
65-69	94 (20.13)	384 (35.99)	
70-74	96 (20.56)	245 (22.96)	
75-79	67 (14.35)	229 (21.46)	
80 and over	210 (44.94)	209 (19.59)	
Gender			0.6100
Male	106 (22.70)	255 (23.90)	
Female	361 (77.30)	812 (76.10)	
Race			0.8582
White	242 (51.82)	556 (52.11)	
African American	212 (45.40)	476 (44.61)	
Other	13 (2.78)	35 (3.28)	
Marital Status			<0.0001
Married	113 (24.20)	364 (34.11)	
Single	59 (12.63)	527 (49.39)	
Other	295 (63.17)	176 (16.49)	
Hospitalization Within 30 days after an Antibiotic prescription			0.8158
Yes	29 (6.21)	63 (5.90)	
No	438 (93.79)	1004 (94.10)	
ER visit Within 30 days after an Antibiotic prescription			0.0176
Yes	45 (9.64)	65 (6.09)	
No	422 (90.64)	1002 (93.91)	

Table 3.4. Antibiotic appropriateness between Geriatrics clinic and Internal Medicine ambulatory clinic.

Antibiotic appropriateness (n=1534)	Geriatric Clinic (Freq/%)	Internal Medicine Clinic (Freq/%)	P-Value
Antibiotics Almost always indicated	203 (43.47)	527 (49.39)	0.0830
Antibiotics maybe indicated	125 (26.77)	243 (22.77)	
Antibiotics not indicated	139 (29.76)	297 (27.84)	

Table 3.5. Multiple logistic regression modeling assessing predictors of antibiotic appropriateness among older adults visiting Geriatrics clinic and Internal Medicine ambulatory clinic from 2012-2017.

Factor (n=1534)	Adjusted Odds Ratio [95% CI])	Unadjusted Odds Ratio [95% CI])
Age (years)		
65-69	1 [Reference]	1 [Reference]
70-74	0.83 [0.55-1.26]	0.81 [0.60-1.09]
75-79	0.61 [0.31-1.19]	0.58 [0.42-0.80] [¶]
80 and above	0.37 [0.12-1.11]	0.37 [0.27-0.50] [¶]
Gender		
Female	1 [Reference]	1 [Reference]
Male	1.28 [0.97-1.69]	1.28 [0.99-1.66]
Race		
White	1 [Reference]	1 [Reference]
African American	1.21 [0.95-1.54]	1.20 [0.95-1.50]
Other	0.68 [0.33-1.37]	0.77 [0.39-1.54]
Marital Status		
Married	1 [Reference]	1 [Reference]
Single	1.28 [0.90-1.82]	1.32 [0.95-1.84]
Other	1.00 [0.75-1.33]	0.81 [0.63-1.04]
Hospitalization Within 30 days after an Antibiotic Prescription	1 [Reference]	1 [Reference]
No	0.51 [0.26-1.02]	0.50 [0.29-0.87] [¶]
Yes		
ER visit Within 30 days of after Antibiotic prescription		
No	1 [Reference]	1 [Reference]
Yes	1.03 [0.57-1.85]	0.72 [0.45-1.14]
Clinic		
Geriatrics	1 [Reference]	1 [Reference]
Internal Medicine	0.73 [0.56-0.94] [¶]	0.90 [0.71-1.15]



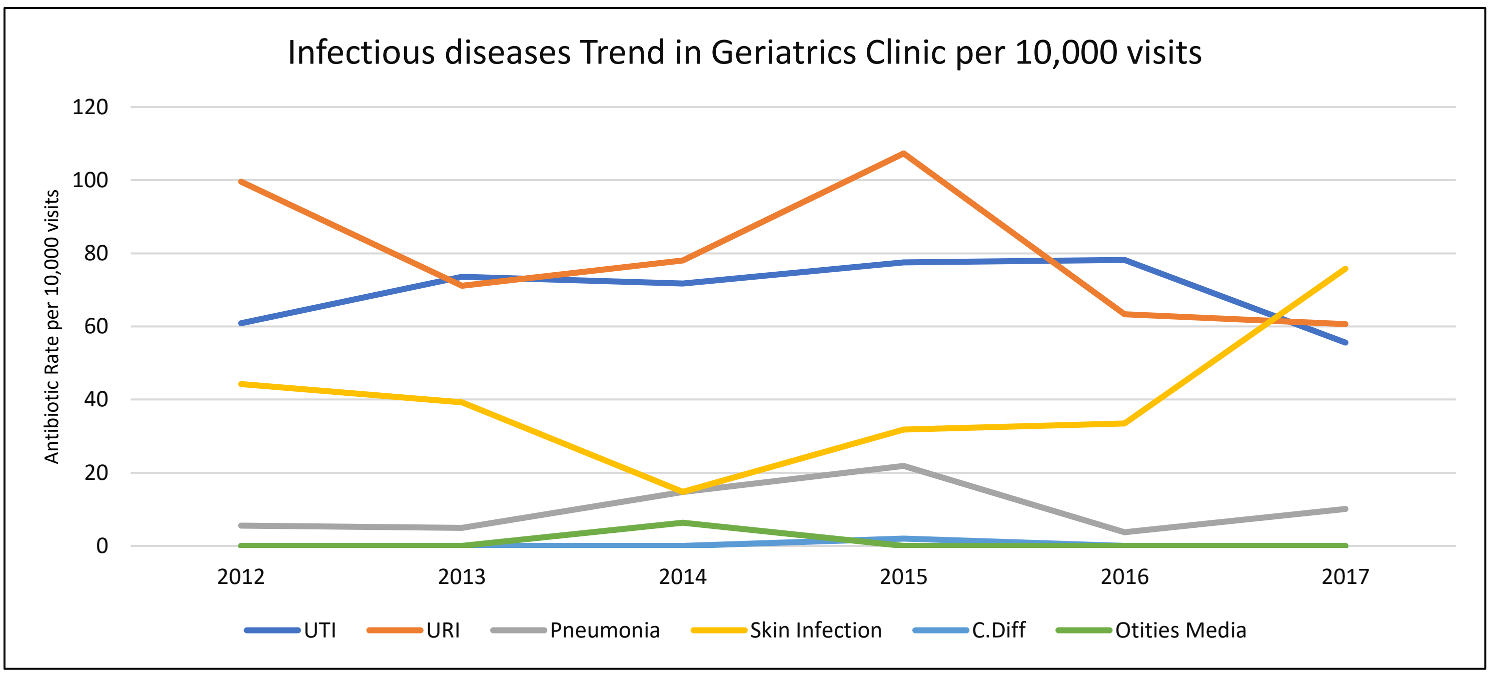
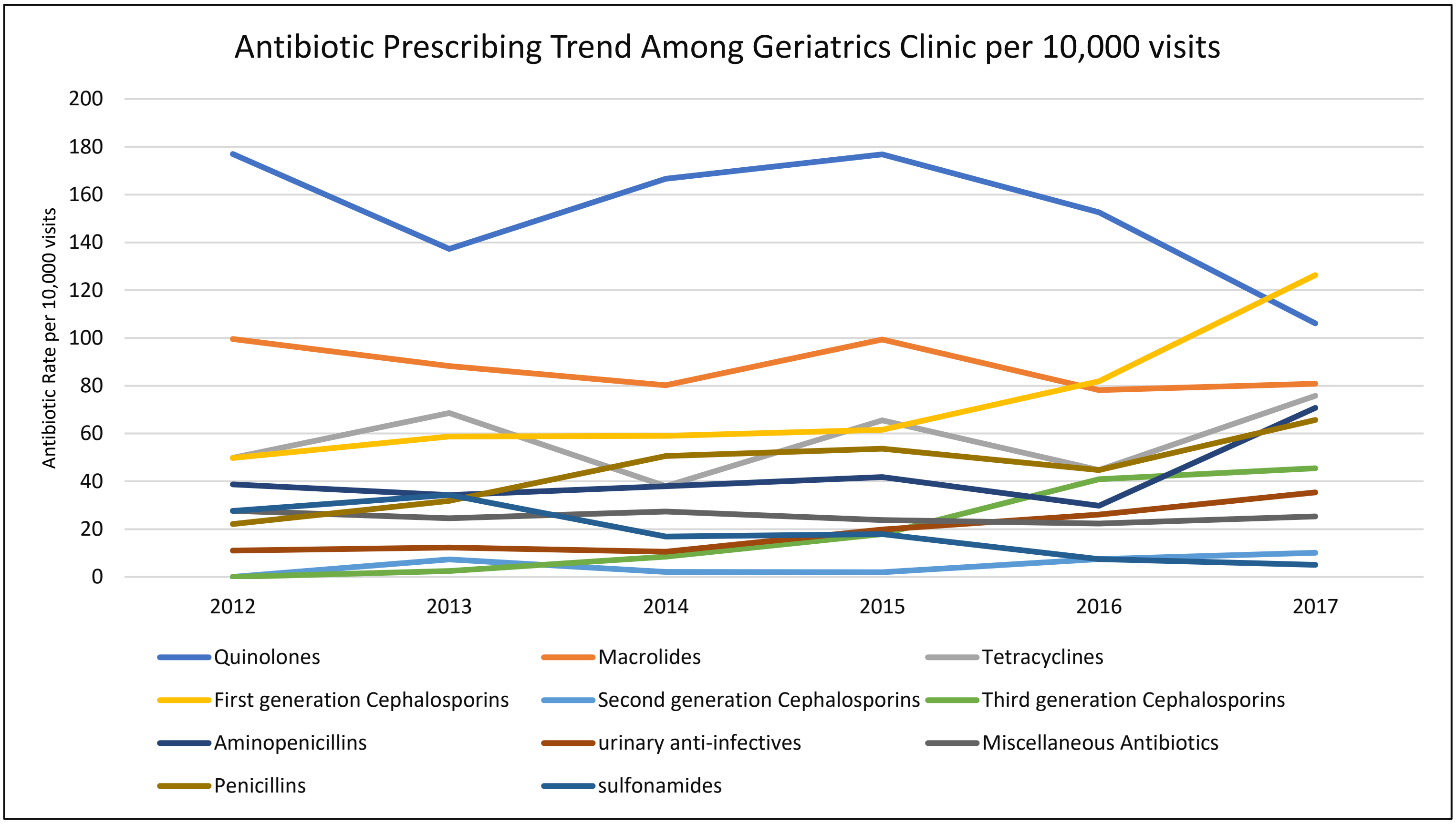


Figure 3.1. The trend of infectious diseases diagnosed among older adults (65 years and older) in Internal Medicine and Geriatrics clinic per 10,000 visits at VCU Health from 2012-2017



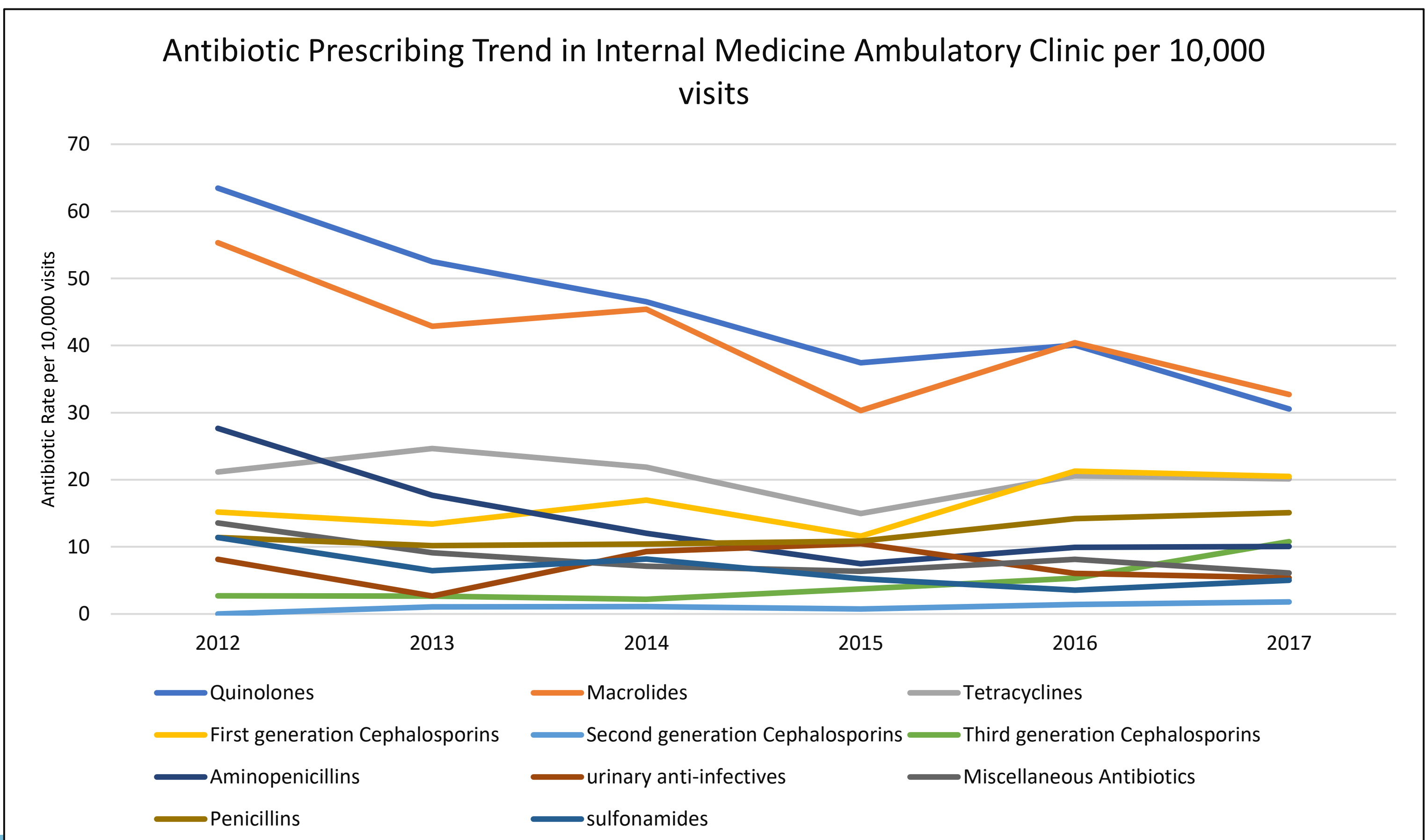
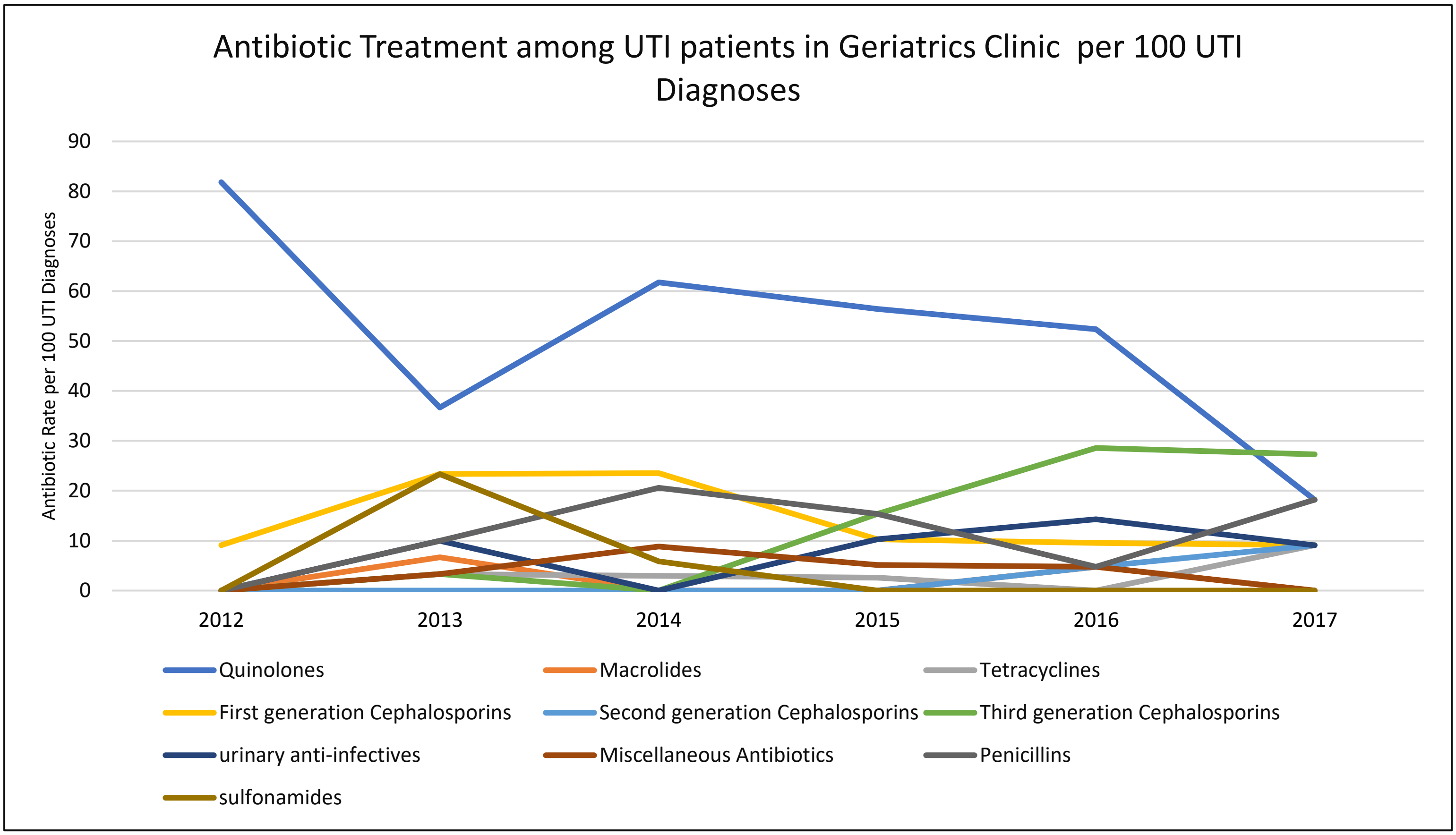


Figure 3.2. The trend of antibiotic prescribing among older adults (65 years and older) in Internal Medicine and Geriatrics clinic per 10,000 visits at VCU Health from 2012-2017



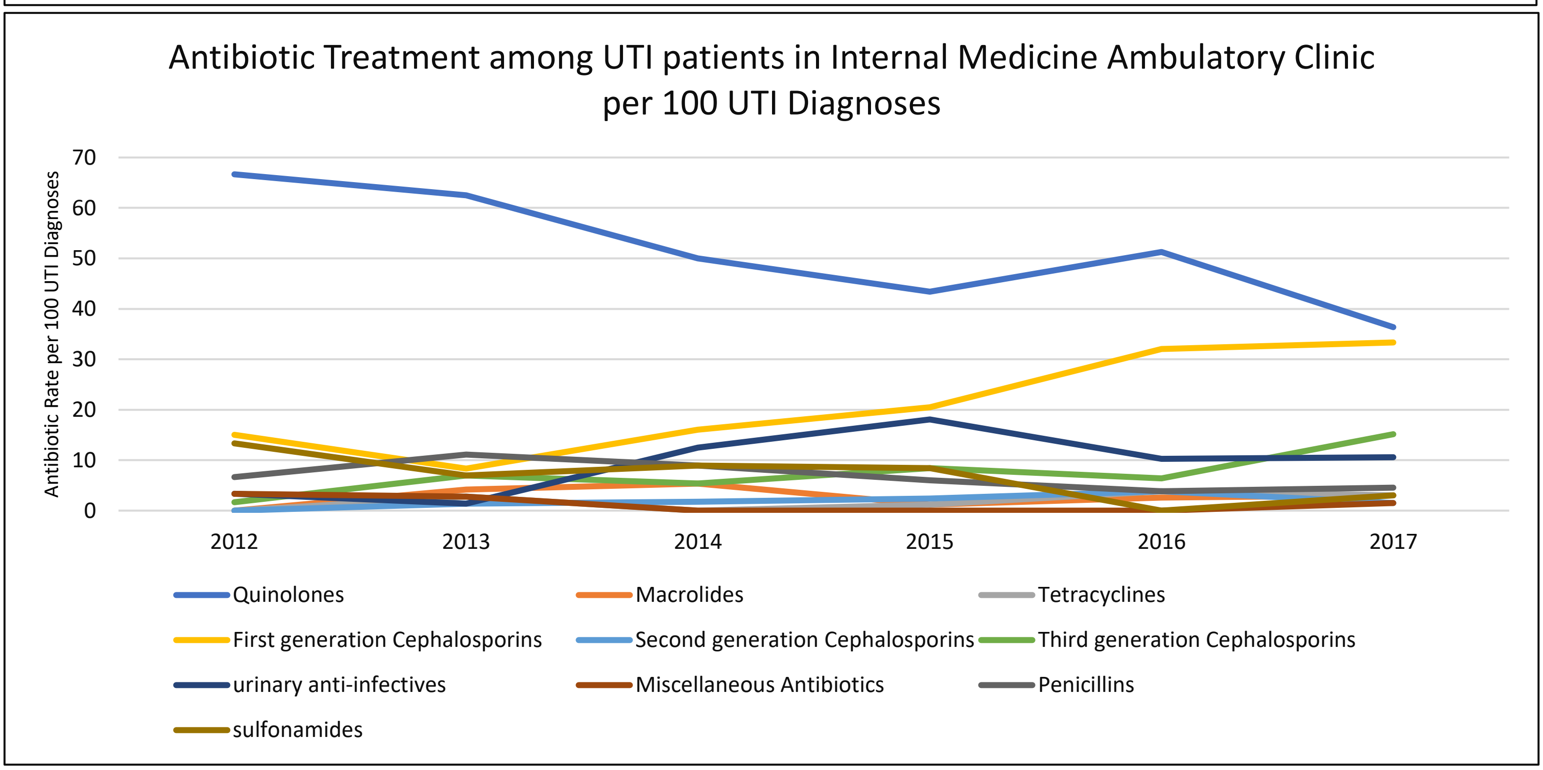
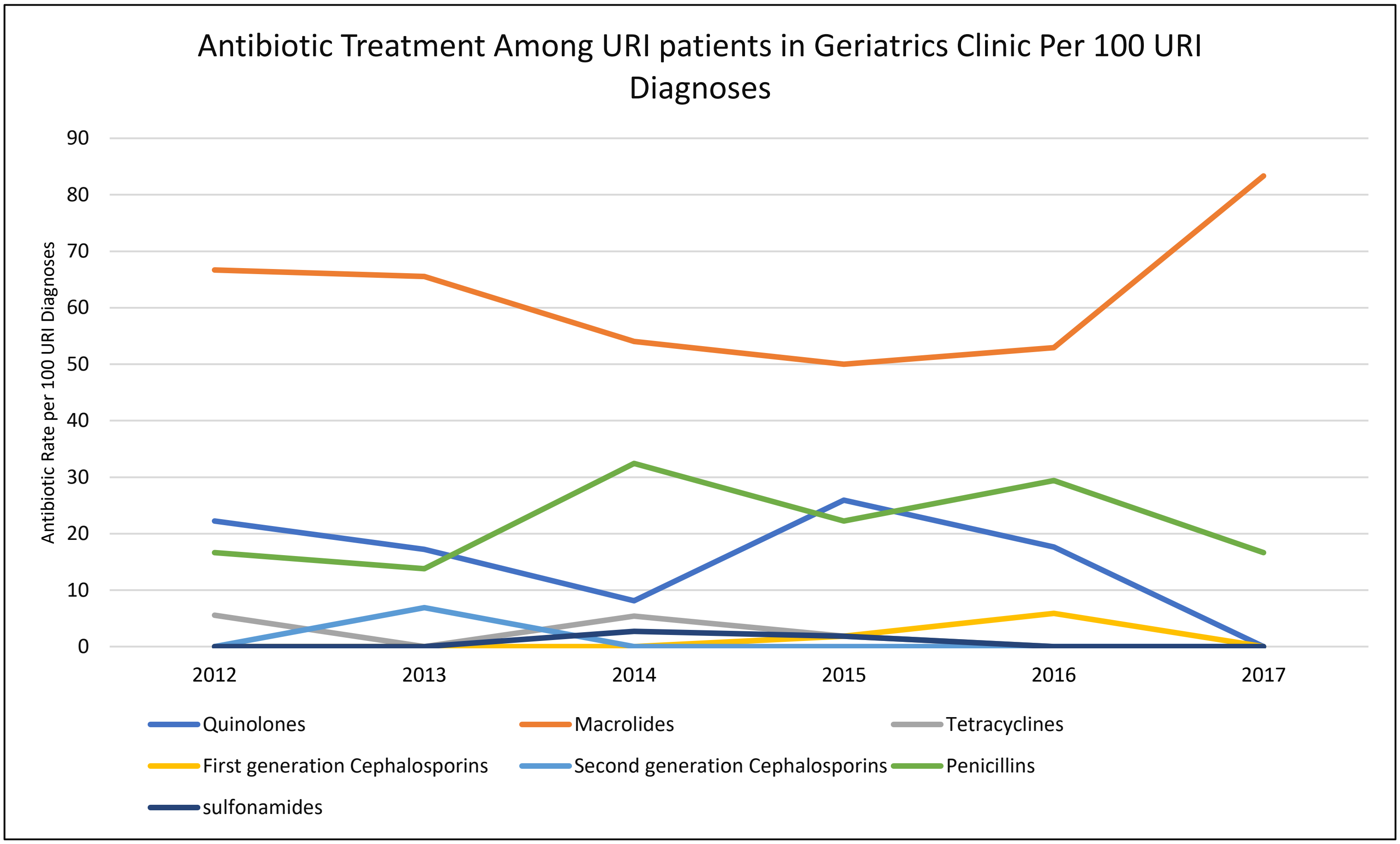


Figure 3.3. The trend of antibiotic treatment for UTI among older adults (65 years and older) in Internal Medicine and Geriatrics clinic per 10,000 visits at VCU Health from 2012-2017



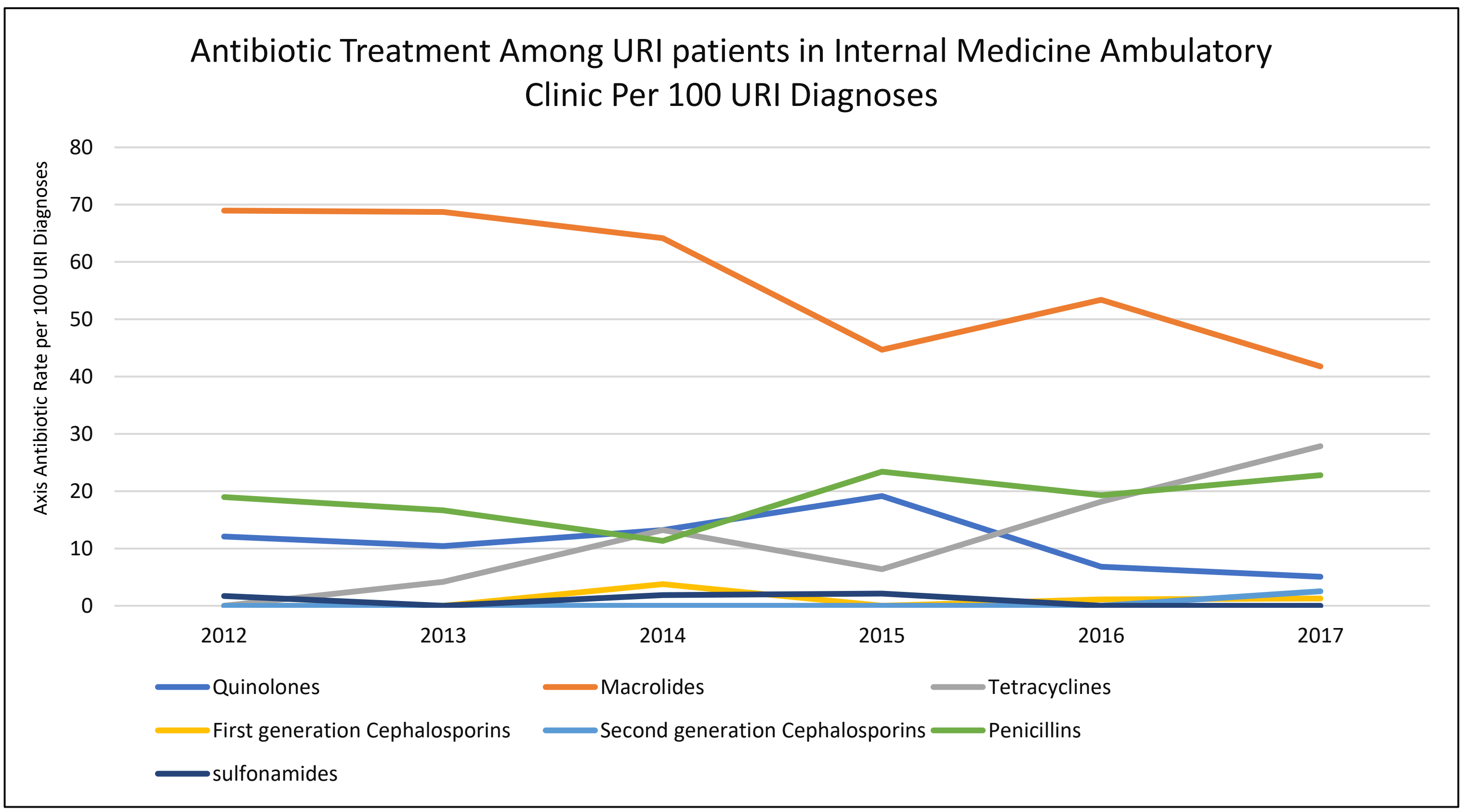
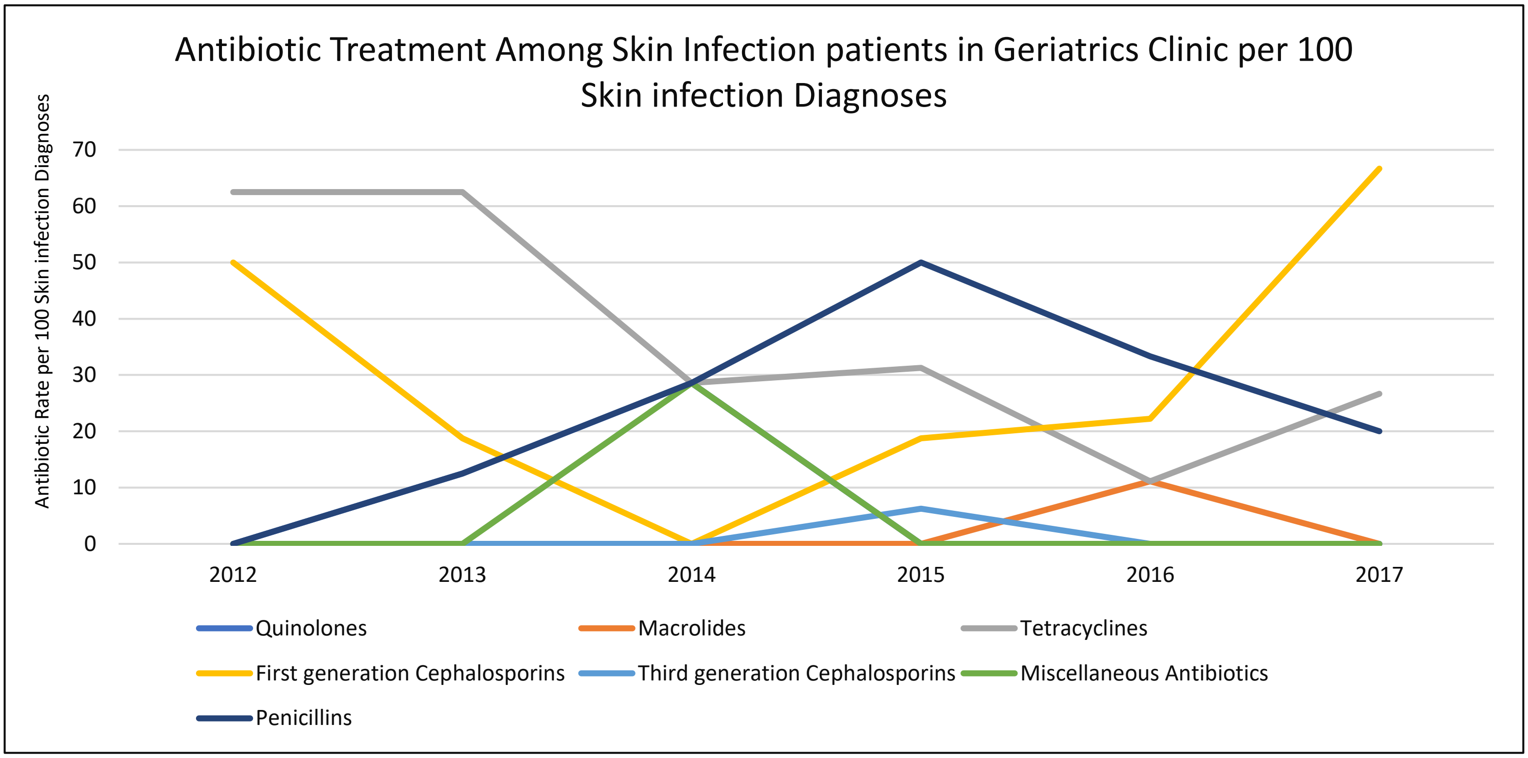


Figure 3.4. The trend of antibiotic treatment for URI among older adults (65 years and older) in Internal Medicine and Geriatrics clinic per 10,000 visits at VCU Health from 2012-2017



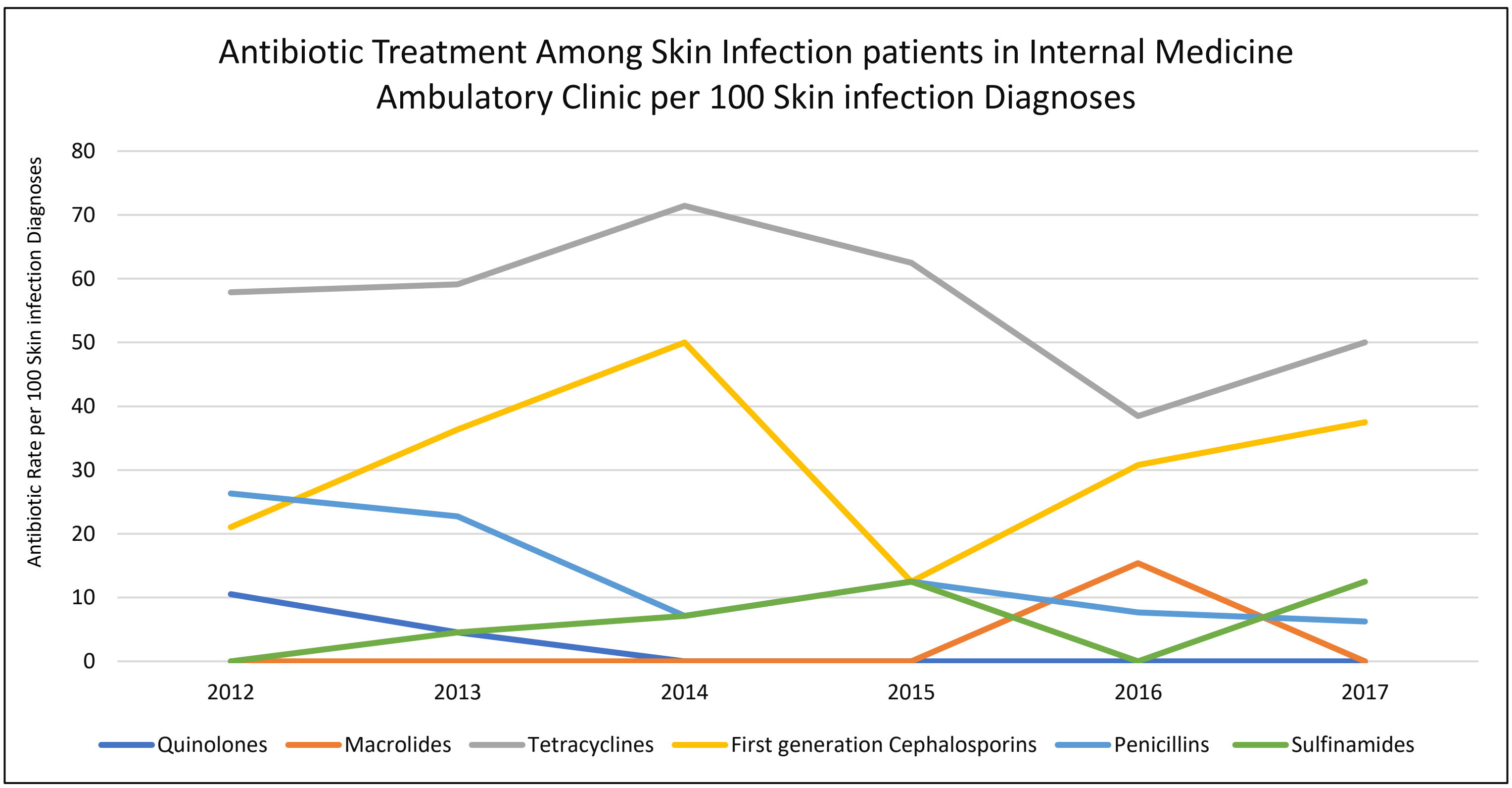


Figure 3.5. The trend of antibiotic treatment for skin infections among older adults (65 years and older) in Internal Medicine and Geriatrics clinic per 10,000 visits at VCU Health from 2012-2017

Discussion:

This study tested the trends of infectious diseases and antibiotic prescribing among the older adult population visiting VCU Health over the past five years (2012-2017) in two ambulatory care clinics (Internal Medicine and Geriatrics clinic). To our knowledge, this is the first study to evaluate and compare the antibiotic prescribing practices between internal medicine physicians and geriatricians who specialize in the care of older adult patients in an academic medical center.

Overall, the estimate of the rate of potentially inappropriate antibiotic prescriptions was 30% in the Geriatrics clinic and 28% in the Internal Medicine clinic. Our estimate is higher than previously reported (18% among older adults from National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) data).[15] Another study conducted among the Medicare population by Olesen, et al.[16] reported that the estimate of antibiotic potentially inappropriate prescriptions was 40%, which is slightly higher than we observed. Although we have used the same methodological approach to define antibiotic appropriateness as in the previous studies, the differences we have noted could be related to the nature of our data regarding linking and coding the diseases with each antibiotic. Also, the differences could be related to regional or institutional practice differences. Moreover, in our study uses two years more recent data than Olesen's study, which could explain also the differences in prescribing over time.

Moreover, we found that UTI, URI, and skin infections are the most common infectious diseases among the older adult outpatient population and this is consistent with previous reports. [15,11,17,18] Among all infectious diseases the trend over time remained the same or only slightly increased/decreased and was not statistically significant except for skin infections. Hersh et al., reported that skin and soft infections nearly doubled among adults 45 years or older from 1997 to 2005.[19] The patterns of infectious diseases were the same among both clinics over the study period. This could be due to consistency of following diagnostic guidelines within the institution between the two clinics. We were unable to test the trend of *C.diff* infection due to the low number of cases documented in our data (C.diff infections= 5 cases overall).

The most common antibiotic classes prescribed in both clinics were quinolones, macrolides, and 1st generation cephalosporins, which is consistent with Olsen et al. and other studies.[16, 5, 20, 21] We observed that the use of macrolides dropped in 2013 and following years in both clinics (Figure 3.2). This behavior could have resulted from a safety concern due to the announcement issued in 2013 by the US Food and Drug Administration (FDA) warning that azithromycin could cause serious cardiovascular side effects and death.[22] In addition, the US FDA warned prescribers to restrict the use of quinolones as first line therapy to treat certain infections such as acute bacterial sinusitis and uncomplicated UTI due to potentially permanent side effects affecting muscles, joints, nerves, and central nervous system.[23] Likely due to this safety concern, we observed a significant reduction in quinolone prescriptions since 2016 (Figures 3.2 & Figure 3.4). These findings support that despite efforts to reduce antibiotic prescribing (nationally and within VCU Health) safety concerns with specific antibiotics are more likely to reduce use than overall concerns about antibiotic resistance.

We found that geriatricians prescribed more potentially inappropriate antibiotics than internal medicine providers. Many factors may contribute to this observation. One factor may be differences in family/caregiver/patient pressure on geriatricians to prescribe an antibiotic compared to internal medicine providers.[24] Another possible factor is that some of the patients in the geriatrics clinic may live in an assisted living facility where the facility care adds pressure to prescribe antibiotics.[9] Patients' characteristics, severity of the illness and frailty could be higher in the geriatrics clinic which could affect the prescriber's decision to be more willing to prescribe antibiotics assuming that the older adult has a weaker immune system.[25,26]

This study has several limitations. First, we used medical record data at VCU Health, an academic medical center, which limits the generalizability of our results. Second, we have used a validated methodology to evaluate antibiotic appropriateness, but that method assumes that the diagnoses are accurate. This is not always the case in real world patient care, especially among the older adult population. For example, confusion often arises in distinguishing UTI and asymptomatic bacteriuria.[27] Third, only a few cases of *C.diff* infection were documented in the VCU Health outpatient medical records, limiting our ability to test for the trend and the predictors of this disease in the logistic regression models. Finally, we have tested for ER visit and hospitalization within 30 days after antibiotic prescribing, and this assumes that the ER visit and hospitalization are due to antibiotic use and not any other cause.

Conclusion:

In conclusion, antibiotic inappropriateness is an important issue among older adult patients in both Geriatrics and Internal Medicine clinic. Despite the efforts to reduce antibiotic prescribing (nationally and within VCU Health) safety concerns with specific antibiotics are more likely to reduce use than overall concerns about antibiotic resistance. Future studies are needed to evaluate the antibiotic appropriateness in a larger level to include more diverse patient population.

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CHAPTER FOUR

Study 3: Antibiotic Use Among Older Adults Visiting The Emergency Department at VCU Health from 2012-2017

Background:

Antibiotic resistance is a serious problem in the United States and worldwide that is associated with significant impact on mortality and morbidity among all age groups.[1, 2, 3] According to the World Health Organization (WHO), inappropriate antibiotic use or overuse and lack of infection control were associated with increased antibiotic resistance.[4] A recent nationally representative study reported that antibiotics were one of the top ten drug classes highly associated with emergency department (ED) visits for adverse events in the United States.[5] Several studies have reported that inappropriate antibiotic utilization is prevalent among acute respiratory tract infected (ARTI) patients visiting the ED.[6,7] Sixty-one percent of ARTI patients received antimicrobial therapy and older adults had the highest overall rate of antibiotic use compared to other age groups (676 per 1,000 visits).

The ED is an important component of the health care system that provides care for vulnerable populations including older adults. In 2015, there were an estimated 21 million visits by older adult patients to the ED in the US, accounting for 15.6% of all ED visits.[8] Among all ED patient visits, infectious diseases were one of the top twenty primary diagnoses. In 2012, there were an estimated 3,123,909 ED visits due to infectious diseases among older adults.[9] Moreover, the geriatric population is the most common age group visiting the ED due to adverse drug reactions.[10]

Many Americans rely on the ED for health care due to difficulties accessing primary care offices and several other barriers reported previously.[11] Although there are national and global initiatives to combat antibiotic resistance by improving antibiotic prescribing practices in all settings, there is little known about antibiotic use among geriatric populations in the ED. Therefore, the specific aims for this study are to:

1. Assess the trend of antibiotic use and infectious diseases among older adult patients aged 65 years or older visiting the ED at VCU Health from 2012-2017.
2. Assess the trend of antibiotic use and infectious diseases among middle aged patients aged 54 to 64 years visiting the ED at VCU Health from 2012-2017.
3. Compare the antibiotic appropriateness between older adult patients and middle-aged patients visiting the ED at VCU Health from 2012-2017.
4. Assess the relationship between antibiotic appropriateness and socio-demographic characteristics, age group and antibiotic negative outcomes including ED visits within 30 days after the initiation of antibiotics and hospitalization within 30 days after the initiation of antibiotics.

Methods:

Data Source:

The ED electronic medical records at VCU Health from 2012-2017 were used in this study. The complete data was available through Cerner (Kansas City, Missouri, U.S.) by the beginning of 2012, so we abstracted the data starting from that date. The year 2017 was the most recent complete data available at the time of data retrieval. VCU Health is an urban academic medical center in central Virginia. The data was retrieved from the electronic medical records and billing records by the Bioinformatics core of the VCU Center for Clinical and Translational Research (CCTR).

Study Design and sample selection:

A cross-sectional retrospective cohort study design was used to conduct this study using the electronic medical records at VCU Health from 2012-2017.

Inclusion and Exclusion Criteria:

Only older adult patients (65 years or older) and middle-aged patients (54-64 years of age) who received antibiotic prescriptions during their ED visit at VCU Health from 2012-2017 were included in this study. Oral and intravenous antibiotic prescriptions were included in the study. All patients who received an antibiotic prescription within 2 days of hospital discharge were excluded from the study to avoid including hospital-related infections. Patients who received an antibiotic prescription that was not prescribed on the day of the ED visit were excluded from the study. Any patients diagnosed with a viral infection were excluded as well. Finally, any patient with missing information in the medication file or diagnosis file was excluded from the study.

Study Measures:

Demographic Characteristics:

Age, race, gender and marital status were collected from VCU Health's ED electronic medical records. Age was treated as categorical variable and categorized into 2 groups: older adults (65 years or older) and middle-aged adults (54-64 years of age). Age was censored as patients 80 years or older were grouped together and their actual age was not included in the dataset to protect patient confidentiality. The race variable was categorized as white, African American, and other. The 'other' category in the race variable includes American Indian/Alaskan, Asian, Native Hawaiian, and other. The gender variable was categorized as male or female. Marital status was categorized as married, single, and other. The 'other' category included divorced, separated, and widowed.

Outcomes Measures:

Antibiotic Use Patterns:

Antibiotic use determination included only the medications classified as 'anti-infective' in the prescription files. The medication file was abstracted from the ED electronic medical records (Cerner, Kansas City, Missouri, U.S.) and included the medication name, category name, and strength. The medication file contains all of the antibiotic prescriptions that each patient received over the study period, so a patient could have multiple antibiotic prescriptions over the study period related to multiple ED visits. Our dataset comprises eleven antibiotic categories including macrolides (azithromycin, erythromycin), quinolones (ciprofloxacin, levofloxacin), sulfonamides (sulfamethoxazole-trimethoprim), urinary anti-infectives (nitrofurantoin), penicillins/beta-lactamase inhibitors (amoxicillin-clavulanate), miscellaneous antibiotics (metronidazole, rifaximin), tetracyclines (tetracycline, doxycycline), first generation cephalosporins (cephalexin), second generation cephalosporins (cefuroxime), third generation cephalosporins (cefdinir, cefpodoxime), Lincomycin derivatives (clindamycin) and aminopenicillins (amoxicillin). The trend of antibiotic prescribing over time was tested across all indications in each age group and also separately for the three most common infectious diseases in the older adult population (urinary tract infection (UTI), upper respiratory tract infection (URI) and skin and soft tissue infection).

Infectious Disease Diagnoses:

The infectious disease diagnoses in the VCU Health data were identified using the International Classification of Diseases ICD-9-CM codes assigned to each patient during the ED visit. VCU Health converted to ICD-10-CM coding by the end of 2015, so in our analysis, we have used both ICD-9-CM and ICD-10-CM codes. We included the most common infectious diseases among older and middle-aged patients visiting the VCU Health ED, which include UTI, URI, skin and soft tissue infections, pneumonia, *Clostridioides difficile* (*C. diff*) infection and otitis media. Table 4.1 details the ICD-9-CM and ICD-10-CM codes used to identify each infectious disease.

Antibiotic Appropriateness:

To estimate oral antibiotic appropriateness we used a validated method developed by Fleming-Dutra et al.[12] This study used a comprehensive methodology with a team of experts systematically reviewing the national guidelines for antibiotic use for common infectious diseases among the older adult population. The criteria for antibiotic appropriateness categorized antibiotic use into three tiers based on the clinical diagnosis as follows:

1. **Tier 1: Antibiotics almost always indicated:** includes UTI, *C.diff*. infection and pneumonia.
2. **Tier 2: Antibiotics may be indicated:** includes acute sinusitis, suppurative otitis media, and some type of skin and soft tissue infections.
3. **Tier 3: Antibiotics not indicated:** Acute and chronic bronchitis, influenza, some types of skin and soft tissue infection, and URI.

All the ICD-9-CM and ICD-10-CM codes included in each category are listed in Table 4.2**.**

Statistical Analyses:

Demographic characteristics were summarized by descriptive analyses (frequency/percentage). Chi-square tests were used to assess the relationship between the outcomes variables and the categorical demographic variables. To adjust for the ED visit variability between age groups, we calculated the antibiotic rate normalizing each year by the total ED visits for each age group separately. Trend analysis was performed using the Cochran–Armitage test. A logistic regression model was developed after checking that the assumptions of the model were met, and odds ratios and ninety-five percent confidence intervals were reported for all estimates. All variables with α equal to 0.1 or less were included in the model and all variables were considered statistically significant at α level of 0.05 or less. Statistical analyses were conducted using the Statistical Analysis Software Version 9.4 (SAS v.9.4 (SAS Institute Inc, Cary, NC)).

Ethical Considerations:

The Virginia Commonwealth University Institutional Review Board (VCU IRB) reviewed and approved this study as exempt (VCU IRB NO: HM20013606).

Table 4.1. ICD-9-CM and ICD-10-CM codes for each infectious disease included in the study.

Type of infection	ICD-9-CM or ICD-10-CM
Urinary tract infection	'599' 'N39.0'
Upper respiratory tract infection	'478.9' '465.9' 'J06.9' '490' '491.21' '466' 'J20.9' 'J40' '491.9' '461.9' 'J01.90' '473.9' 'J32.9' 'J01.00' '477.9' 'J30.9'
Pneumonia	'486' 'Z87.01' 'J18.9' 'J18.8' '516.3' 'B96.1'
Skin and soft tissue infection	'682.6' '682.9' '682.6' '528.3' 'L03.90' 'L03.116' 'L03.115' 'H60.12'
Otitis media	'380.1' '381.1' 'H66.93' 'H66.92' 'H66.91' 'H66.90' '382.9' '381.4'
Clostridioides difficile infection	'A04.7' '8.45'

Table 4.2. Antibiotic appropriateness criteria according to Fleming-Dutra, et al.[12]

Diagnosis	Corresponding ICD-9-CM or ICD-10-CM
Tier 1: Antibiotics almost always indicated:	
Urinary tract Infection	'599' 'N39.0'
Bacterial pneumonia	'486' 'Z87.01' 'J18.9' 'J18.8' '516.3' 'B96.1'
Clostridioides difficile infection	'A04.7' '8.45'
Tier 2: Antibiotics may be indicated:	
Acute sinusitis	'461.9' 'J01.90' '473.9' 'J32.9' 'J01.00'
Skin, cutaneous and mucosal infections	'382.9' 'H66.90' 'L03.115' 'L03.116' 'L03.90' '528.3' '682.6' '682.9' '682.6'
Suppurative otitis media	'H66.91' '380.1' '381.1' 'H66.93' 'H66.92'
Tier 3: Antibiotics not indicated:	
Acute and chronic bronchitis, bronchiolitis, allergic rhinitis	'490' '491.21' '466' 'J20.9' 'J40' '491.9' '477.9' 'J30.9'
non-suppurative otitis media	'381.4'
viral upper respiratory infection (URI)	'478.9' '465.9' 'J06.9'

Results:

Demographic Characteristics:

The sample size of this study is 6,343 middle-aged or older adult patients who received an antibiotic dispensed and prescribed in the ED at VCU Health from 2012 to 2017. The proportion of antibiotic prescriptions was evenly distributed across both genders and age groups. A higher proportion of whites and African Americans received antibiotic prescriptions compared to other races. Moreover, 14% of middle-aged patients who were prescribed antibiotics in the ED visited the ED again within 30 days following that prescription compared to 11% among older adult patients. Table 4.3 details the demographic characteristics of antibiotic users in the ED at VCU Health from 2012-2017 in both age groups.

Antibiotic Appropriateness:

Among all of the antibiotic prescriptions that older adults received in the ED, 90% were considered potentially appropriate, compared to 81% among middle-aged patients. Eighteen percent of the antibiotic prescriptions received by the middle age group were considered potentially inappropriate, compared to 9% among the older adult patient. Antibiotic appropriateness practices were statistically different between different antibiotic appropriateness tiers ($p < 0.0001$) (Table 4.4).

Infectious disease trends among older adult patients compared to middle- aged patients:

In our study, most of the antibiotic indications were limited to six infectious diseases including UTI, URI, pneumonia, skin and soft tissue infection, *C. diff* infection, and otitis media. In both age groups, the trend of infectious diseases seemed to be stable from 2012-2017 except for three diseases: UTI, URI, and pneumonia. The three most common infectious diseases among the middle-aged group were UTI, URI, and pneumonia. Among middle-aged patients, URI dropped from 180 diagnoses per 10,000 ED visits in 2012 to 76 diagnoses in 2017. The same trend was observed in the UTI diagnoses which declined from 136 diagnoses per 10,000 ED visits in 2012 to 122 diagnoses in 2017. The opposite trend was seen with pneumonia, where the cases increased from 83 cases per 10,000 ED visits in 2012 to 102 cases in 2017. Among older adults, UTI, pneumonia, URI and skin and soft tissue infections were the most common diagnoses seen in the ED visits over the study period. UTI rates were stable over the study period, while URI rates dropped from 98 to 54 cases per 10,000 ED visits among older adults from 2012 to 2017. *C.diff* infection rates were stable over the study period in both age groups. Figure 4.1 shows the trends over time from 2012-2017 in both age groups at the ED at VCU Health.

Antibiotic trends among older adult patients compared to middle-aged patients:

Interestingly, we observed similar trends in terms of antibiotic prescriptions by category between middle-aged and older adult patients visiting the ED at VCU Health from 2012-2017 (Figure 4.2). Quinolones, penicillins, first generation and third generation cephalosporins were the most common antibiotic classes prescribed in both age groups. The rate of quinolone prescriptions dropped slightly over time in middle-aged and older adults (from 215 to 206 and 400 to 372 per 10,000 ED visits, respectively). On the other hand, the rate of penicillins almost doubled in middle-aged and older adults (from 179 to 334 and from 288 to 541 per 10,000 ED visits, respectively). Third generation cephalosporin prescriptions were stable most of the study period and increased from 2016 to 2017 in both age groups. The same observations were seen with the remaining antibiotic categories.

Predictors of Receiving Potentially Inappropriate Antibiotics Among Older Adult Patients Compared to Middle-Aged Patients:

Table 4.5 presents the results of multiple logistic regression model analysis predicting potentially appropriate versus potentially inappropriate antibiotic prescriptions with demographic characteristics and outcomes of interest as predictors. Multiple logistic regression modelling found that middle-aged patients were 70% significantly more likely to be prescribed potentially inappropriate antibiotics compared to older adult patients adjusting for other predictors (95% CI [1.38-2.06]. African Americans, single adults, and non-insured patients were significantly more likely to be prescribed potentially inappropriate antibiotics in the ED at VCU Health adjusting for other covariates. Gender and hospitalization or ED visits within 30 days after an antibiotic prescription were not associated with antibiotic potentially inappropriateness practices in the ED at VCU Health.

Antibiotic Prescribing for UTI, URI, and Skin and soft tissue Infections:

Among patients diagnosed with UTI in both age groups, third generation cephalosporins, quinolinones, penicillins, and first generation cephalosporins were the most common antibiotic categories prescribed over the study period (Figure 4.3). The rate of quinolone prescriptions to treat UTIs in the ED dropped in older and middle-aged patients from 22 prescriptions per 100 UTI diagnosis to 14, and from 19 to 7 respectively from 2012-2017. In contrast, the rate of penicillin prescribing almost doubled over the study period from 6 prescriptions per 100 UTI diagnosis in 2012 to 15 in 2017 among older adult patients. A similar trend was observed in the middle-aged group, with penicillin prescribing increasing from 7 to 16 prescriptions per 100 UTI diagnoses from 2012-2017.

Figure 4.4 shows the antibiotic prescribing rate over time for the treatment of patients with URI in both age groups. Macrolides, quinolones, tetracyclines and penicillins were the most common antibiotic categories prescribed to treat URI in both age groups. Among older adults who were treated for URI, the rate of macrolide, quinolone, and penicillin prescriptions more than doubled over the study period. In contrast, the rate of prescribing of all antibiotic categories dropped from 2012-2017 among middle-aged patients except for penicillins.

In our study, the treatment options for skin and soft tissue infections were limited to clindamycin, penicillins, 1st generation cephalosporins, and tetracyclines. The rate of penicillin prescribing increased significantly among older adults and middle-aged patients, from 32 prescriptions to 46 per 100 skin and soft tissue infection diagnoses, and from 18 to 45 prescriptions per 100 skin and soft tissue infection diagnoses respectively. Figure 4.5 presents the treatment of patients diagnosed with skin infected by antibiotic category from 2012-2017.

Table 4.3. Demographic characteristics of those who received antibiotics in the emergency department at VCU Health by age group from 2012 to 2017.

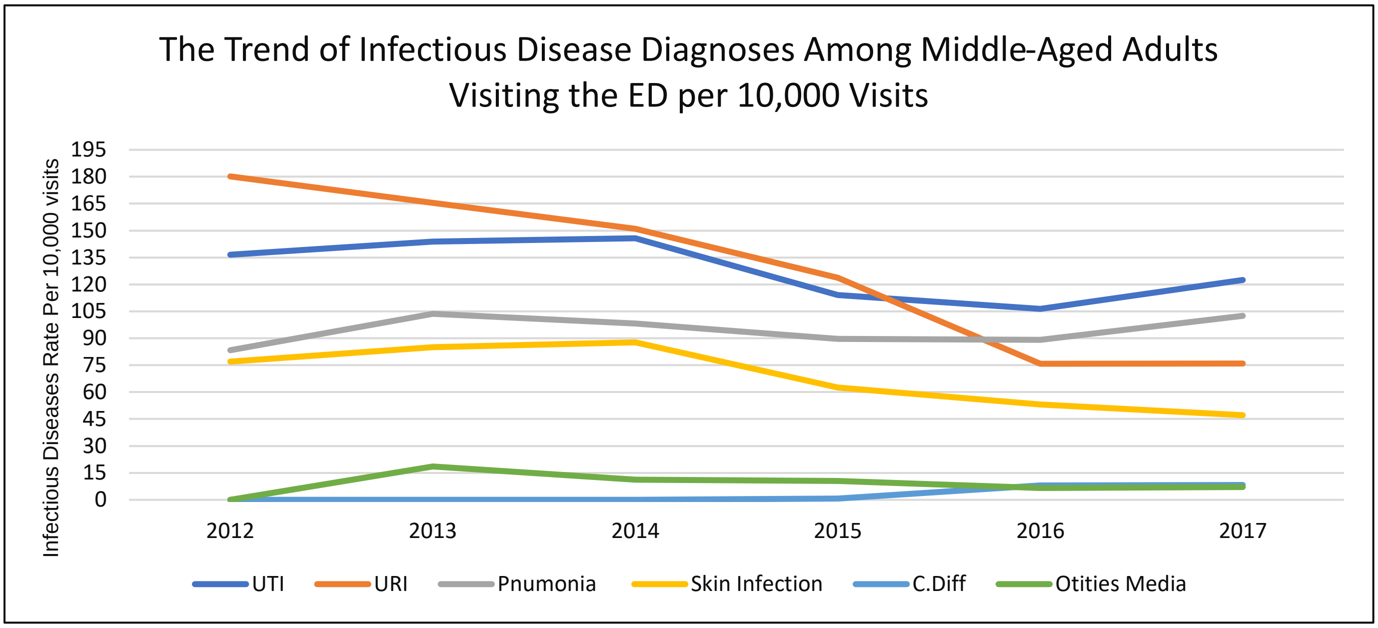
Factors (n=6343)	Aged 54-64 years (Freq/%)	Aged 65 years and older (Freq/%)	P-Value
Gender			0.0002
Male	1725 (54.83)	1421 (45.17)	
Female	1605 (50.20)	1592 (49.80)	
Race			<0.0001
White	1337 (47.34)	1487 (52.66)	
African American	1821 (56.96)	1376 (43.04)	
Other	169 (55.23)	137 (44.77)	
Marital Status			<0.0001
Married	969 (46.52)	1114 (53.48)	
Single	1181 (65.68)	617 (34.32)	
Other	1163 (48.38)	1241 (51.62)	
Hospitalization within 30 days of an antibiotic prescription			0.4765
Yes	301 (9.04)	288 (9.56)	
No	3029 (90.96)	2725 (90.44)	
ED visit within 30 days of an antibiotic prescription			0.0012
Yes	472 (14.17)	345 (11.45)	
No	2858 (85.83)	2668 (88.55)	

Table 4.4. Antibiotic prescribing appropriateness by age group at the emergency department, VCU Health from 2012-2017.

Antibiotic appropriateness (n=6343)	54-64 years old (Freq/%)	65 and older (Freq/%)	P-Value
Antibiotics Almost always indicated	2700 (81.08)	2722 (90.34)	<.0001
Antibiotics maybe indicated	26 (0.78)	17 (0.56)	
Antibiotics not indicated	604 (18.14)	274 (9.09)	

Table 4.5. Multiple logistic regression model assessing predictors of antibiotic appropriateness among older adults and middle-aged patients visiting the emergency department at VCU Health from 2012-2017.

Factors (n=6343)	Adjusted Odds Ratio [95% CI])	Unadjusted Odds Ratio [95% CI])
Age (years)		
65 and older	1 [Reference]	1 [Reference]
54-64	2.14 [1.82-2.50]¶	2.30 [1.97-2.68]¶
Gender		
Female	1 [Reference]	1 [Reference]
Male	0.98 [0.84-1.13]	0.95 [0.82-1.10]
Race		
White	1 [Reference]	1 [Reference]
African American	1.46 [1.24-1.71]¶	1.73 [1.49-2.02]¶
Other	1.25 [0.87-1.81]	1.23 [0.85-1.76]
Marital Status		
Married	1 [Reference]	1 [Reference]
Single	1.58 [1.29-1.93]¶	2.06 [1.70-2.49]¶
Other	1.53 [1.26-1.86]¶	1.70 [1.41-2.04]¶
Hospitalization within 30 days of an antibiotic prescription		
No	1 [Reference]	1 [Reference]
Yes	0.65 [0.47-0.90]	0.71 [0.54-0.93]
ED visit within 30 days of an antibiotic prescription		
No	1 [Reference]	1 [Reference]
Yes	1.30 [1.02-1.65]¶	1.21 [0.98-1.48]



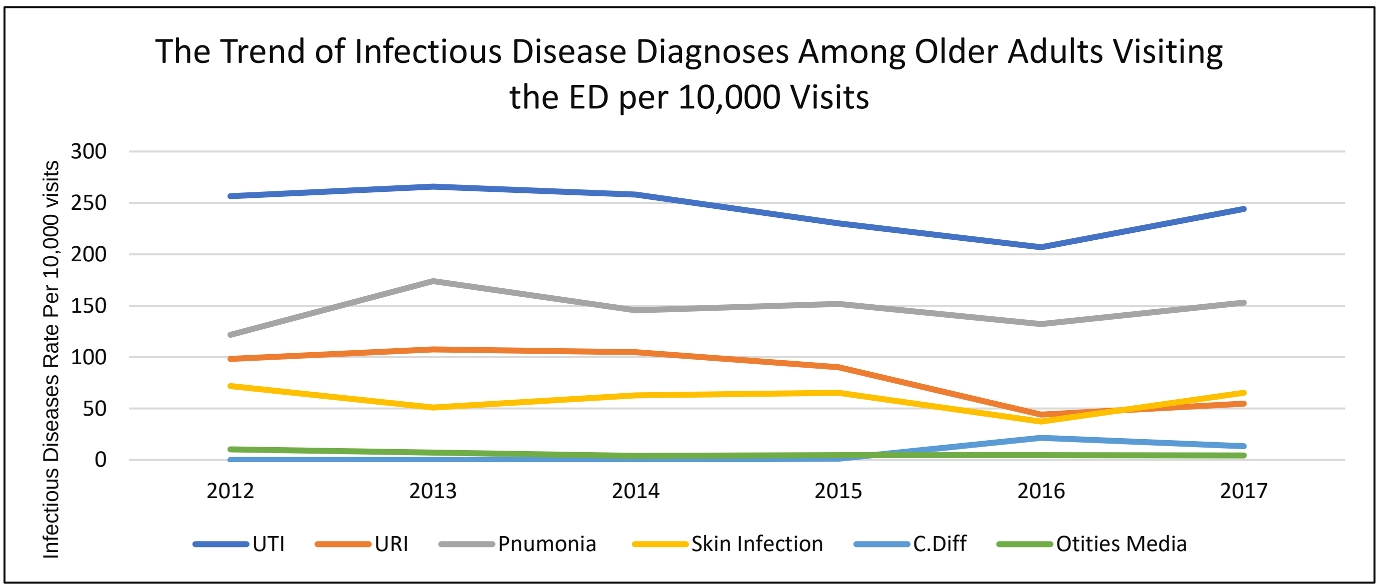
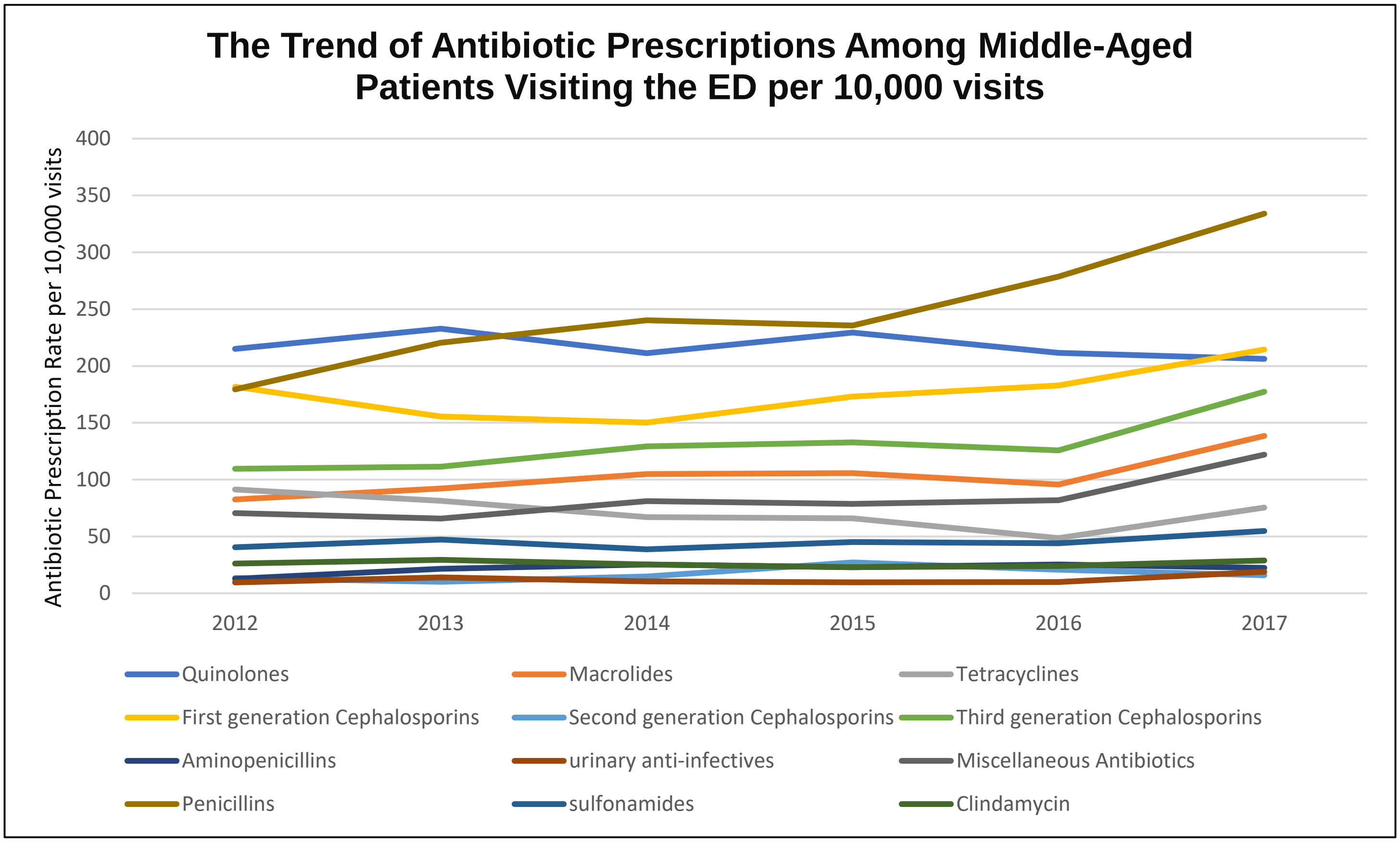


Figure 4.1. The trend of infectious disease diagnoses per 10,000 visits among older adults (65 years and older) and middle- aged adults (54-64 years) in the emergency department at VCU Health from 2012-2017



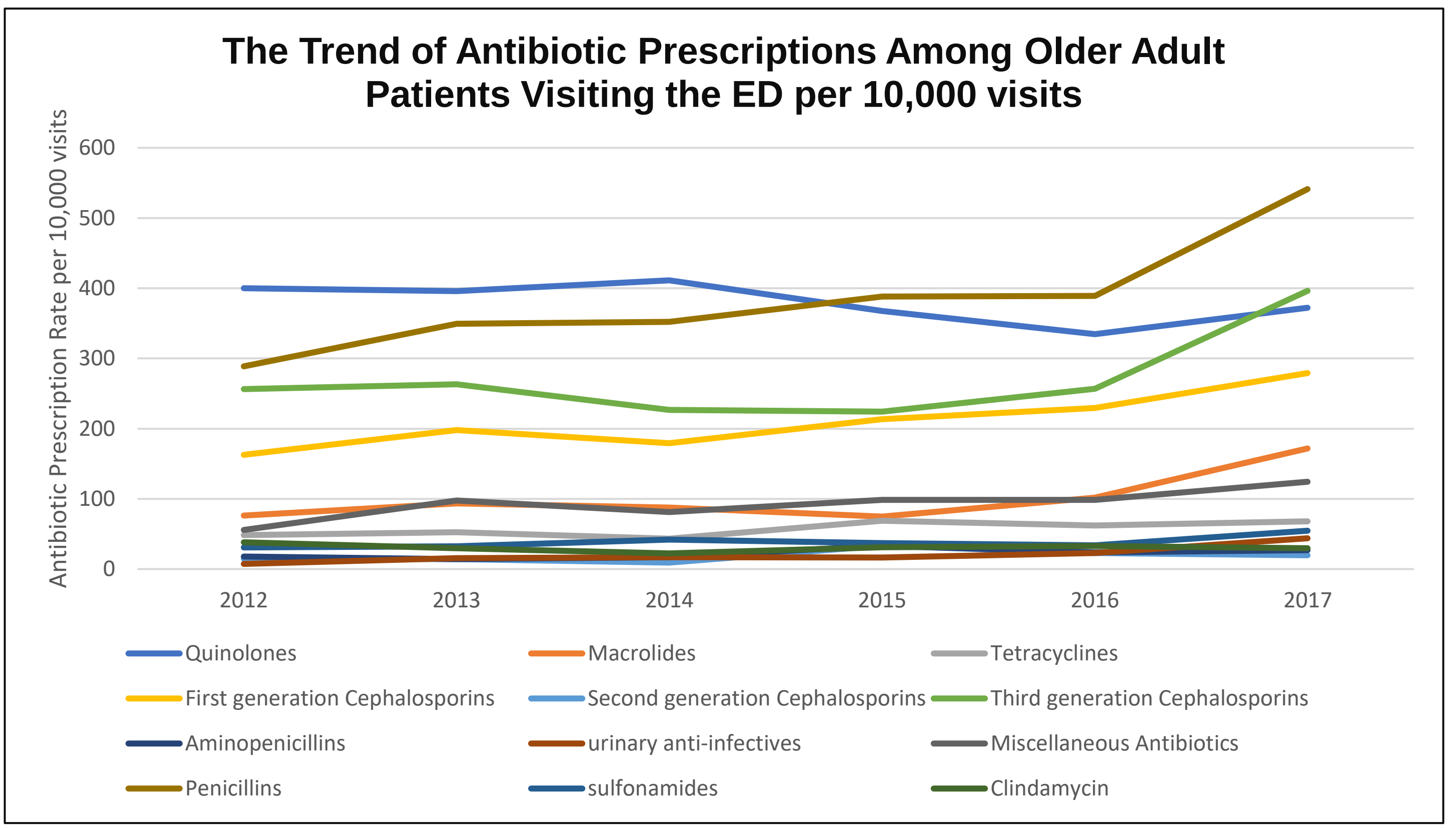
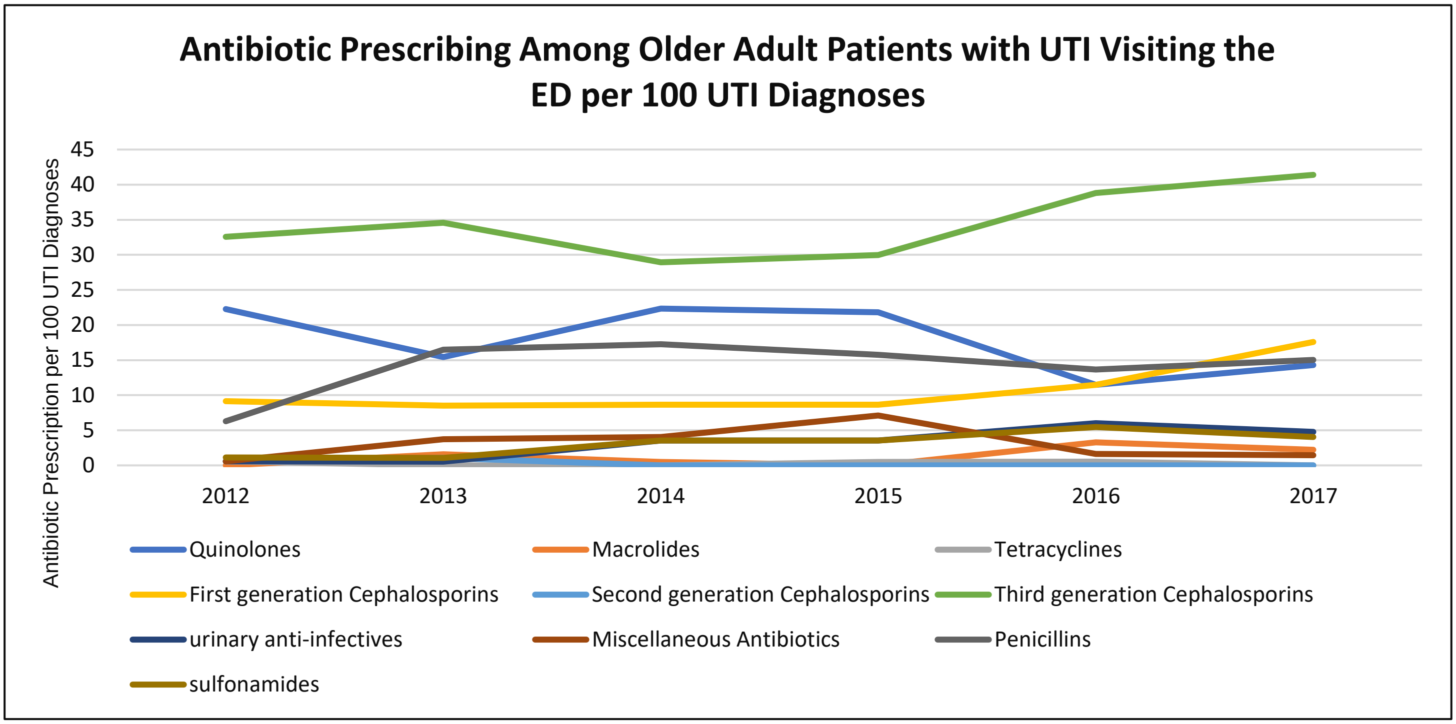


Figure 4.2. The trend of antibiotic prescriptions per 10,000 visits among older adults (65 years and older) and middle-aged adults (54-64 years) in the emergency department at VCU Health from 2012-2017



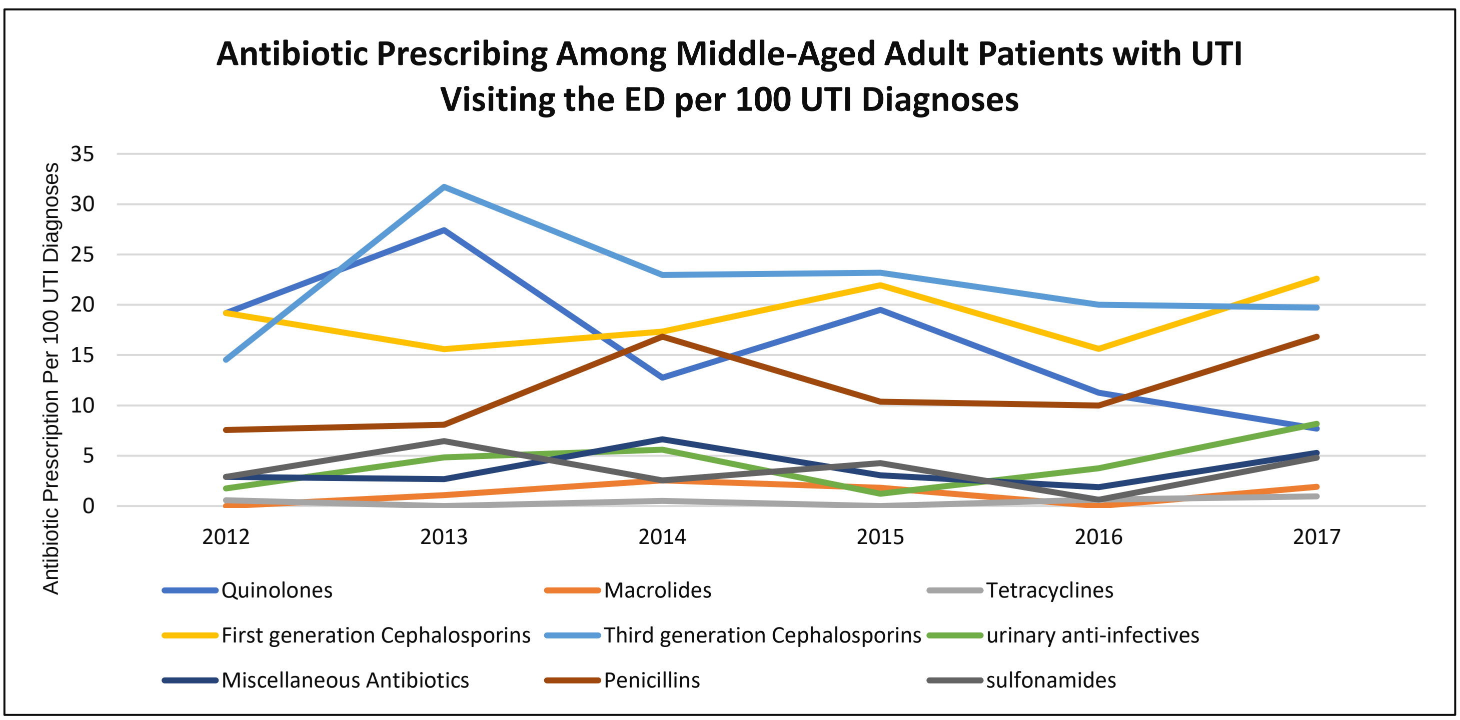
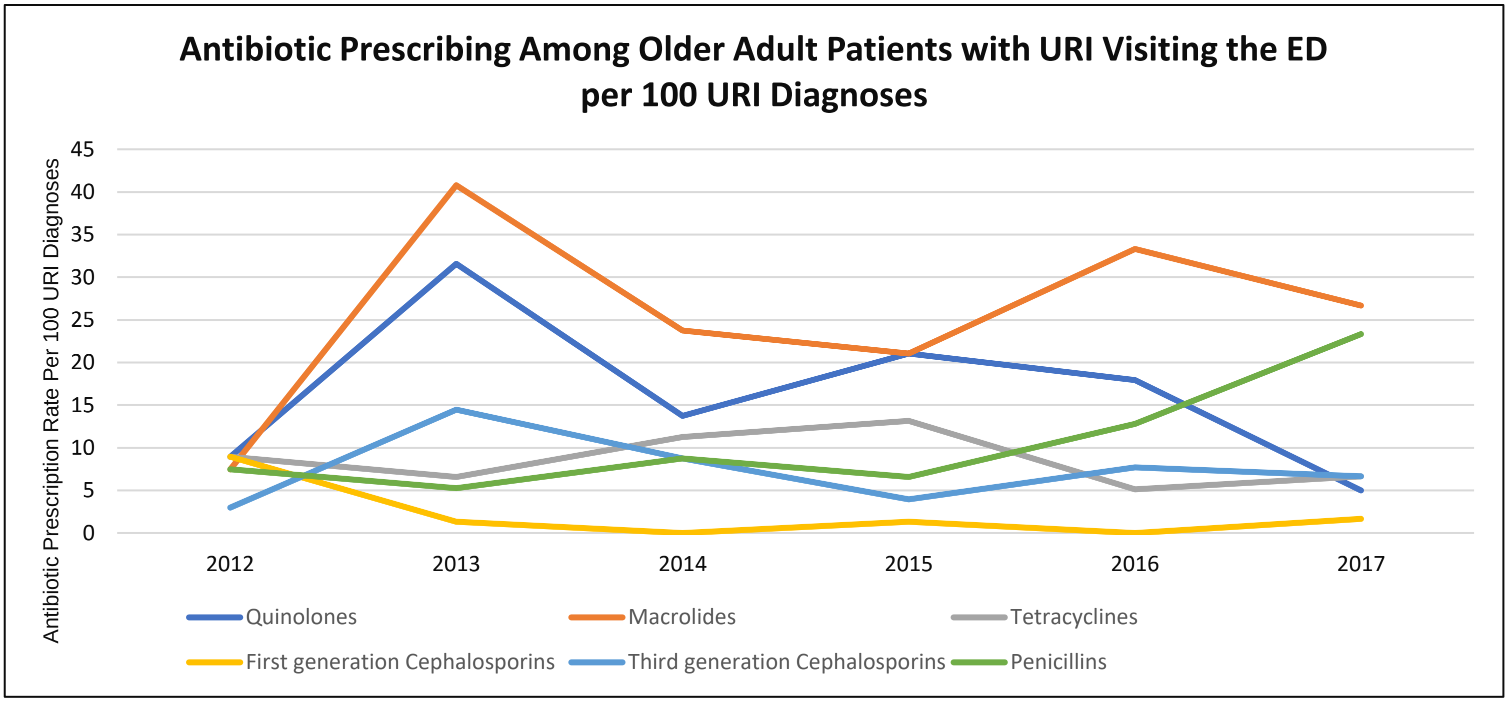


Figure 4.3. The trend of antibiotic prescribing for UTI per 100 UTI diagnoses among older adult patients (65 years and older) and middle-aged adults (54-64 years) in the emergency department at VCU Health from 2012-2017



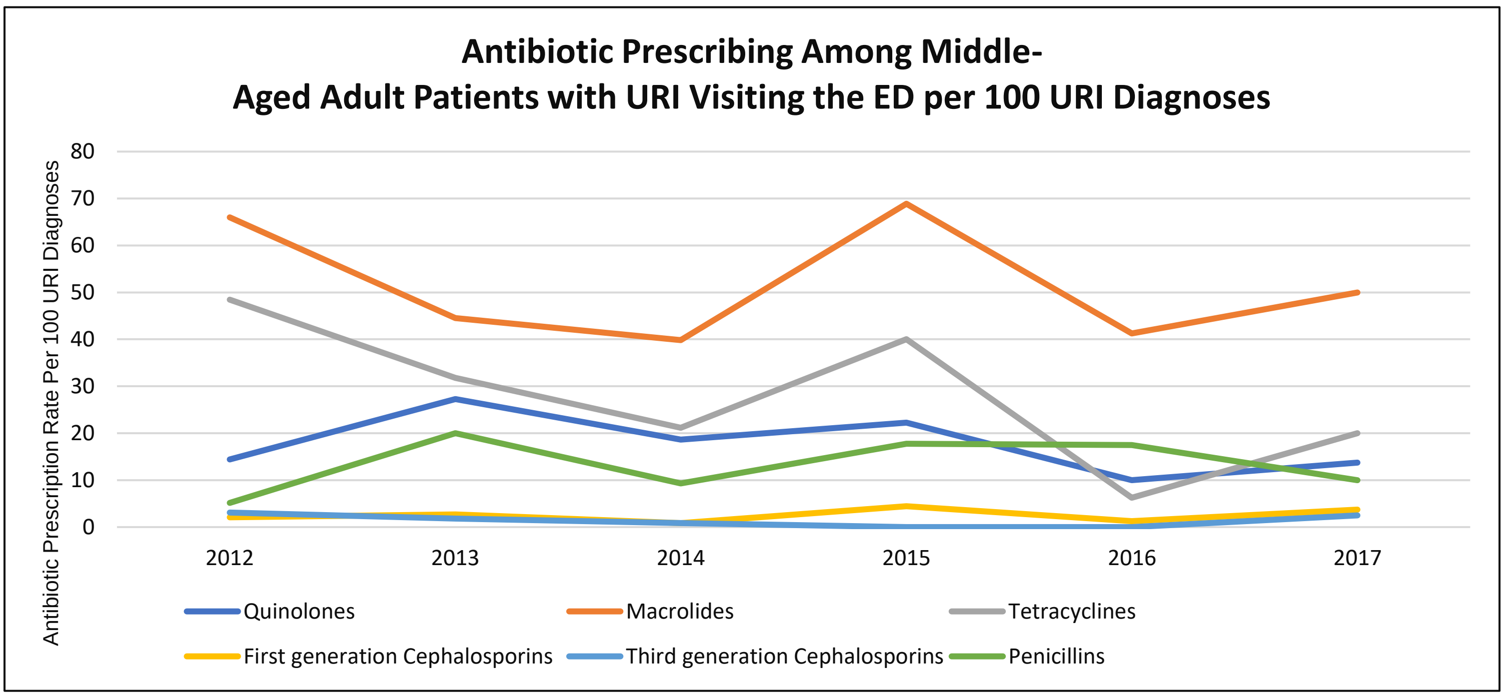


Figure 4.4. The trend of antibiotic prescribing for URI per 100 URI diagnoses among older adult patients (65 years and older) and middle-aged adults (54-64 years) in the emergency department at VCU Health from 2012-2017.

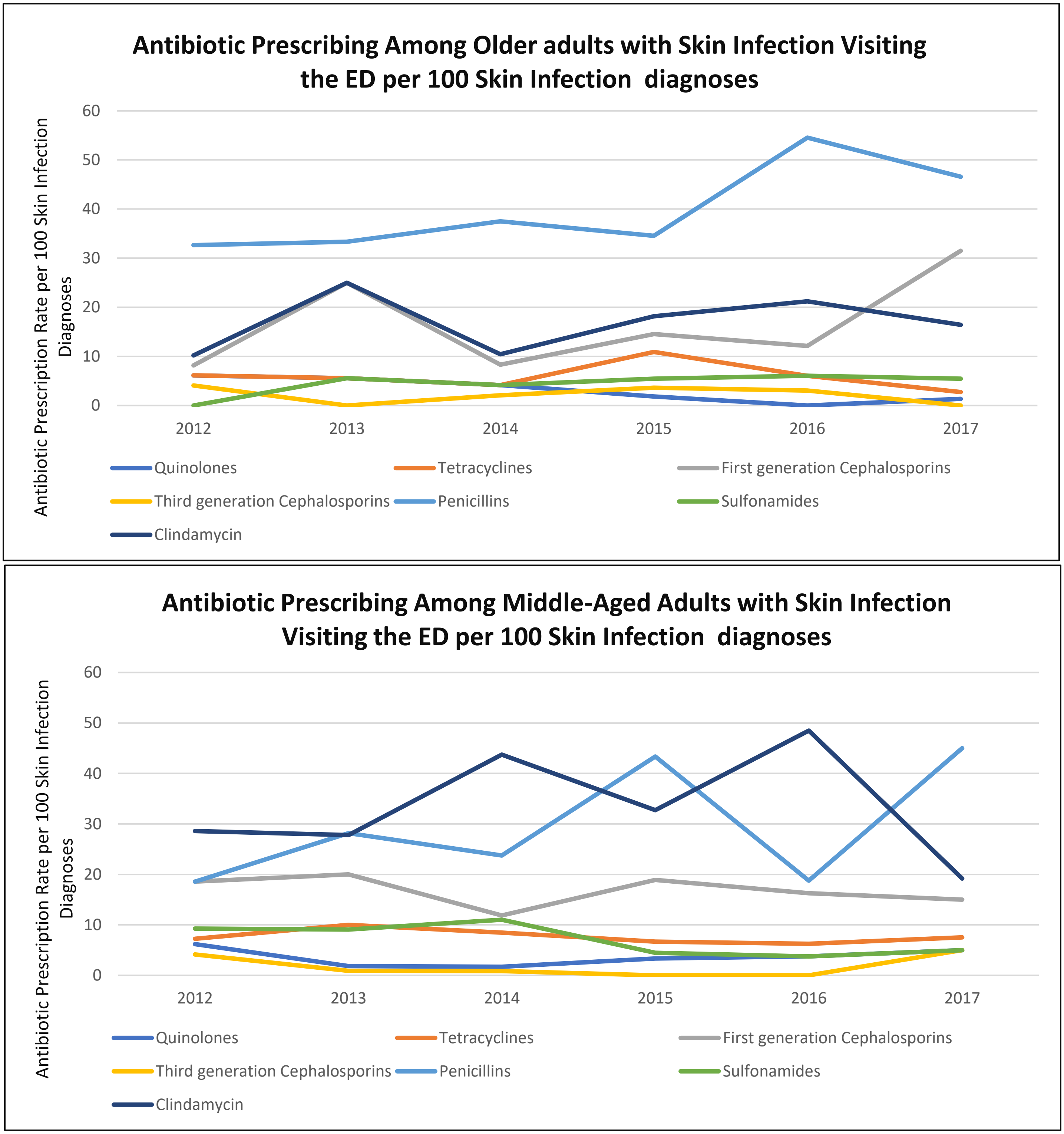


Figure 4.5. The trend of antibiotic prescribing for skin infections per 100 skin infection diagnoses among older adult patients (65 years and older) and middle-aged adults (54-64 years) in the emergency department at VCU Health from 2012-2017

Discussion:

Our study evaluated the trend of infectious disease diagnoses and antibiotic prescribing practices among older and middle-aged patients visiting the ED at VCU Health from 2012-2017. This study presents the most common infectious diseases diagnosed in the ED, and the most common antibiotics prescribed in the same setting. In addition, we have evaluated the antibiotic prescribing practices for the most common infectious diseases among older adult patients including, UTI, URI, and skin and soft tissue infections. To the best of our knowledge, the trend of infectious diseases and antibiotic appropriateness presenting at the ED in academic medical centers is still unclear among older adult populations. This is the first study to compare antibiotic appropriateness between older adults and middle age patients at the ED.

Inappropriate antibiotic use has been documented as a risk factor for antibiotic resistance.[13,14,15] The overall estimate of potentially inappropriate antibiotic prescriptions in our study was 27%, similar to previous reports of 24% in the ED[16] and 18% based on data from the National Ambulatory Medical Care Survey (NAMCS) which included an ED patients,[12] but lower than the 40% reported by Olesen, et al.[17] in the Medicare population. The Olesen, et al. study was not limited to ED patients, but included outpatients as well.[17] Nine percent of older adults' antibiotic prescriptions were deemed potentially inappropriate, which was lower than the 18% observed in middle-aged patients, but this percentage may still be an important contributor to unnecessary hospital admissions, preventable adverse drug reactions or unnecessary health care costs.

Goto, et al.[9] found in a recent study conducted using nationally representative data that lower respiratory infection, UTI, and pneumonia were among the five most common infectious diseases among older adults visiting the ED, similar to what we observed among older adult patients. The same pattern was found by Stone et al among ED patients.[7] except that skin and soft tissue infections were the most common indications for antibiotic prescribing in the ED among all age groups.

Our results suggested that ED providers prescribed broad-spectrum antibiotics more than narrow-spectrum antibiotics and that could be due to the nature of the ED diagnosis process. For instance, quinolones and penicillins were the most commonly prescribed antibiotics in the ED. Although the Food and Drug Administration (FDA) released in 2016 a warning regarding the use of quinolones as a first-line therapy due to serious adverse events, we observed an increase in quinolone prescribing.[18] This behavior could be due to the antimicrobial susceptibility patterns in our study suggested empiric treatment with quinolones rather than other antibiotic classes. In addition, a possible explanation of the increased use of all antibiotic categories since 2016 was due to the fact of CMS requiring all hospitals to implement the sepsis core measures.[19]

This study has several limitations. First, while we examined six years of data and our sample size was large, our study was limited to one large academic medical center and we cannot generalize our findings to other academic medical centers in the US. Second, although we have used a validated definition of antibiotic appropriateness, the definition relies only on the indication of each antibiotic prescription and assumes that the diagnosis is accurate. For instance, all of the UTI diagnoses were considered accurate, while in real world scenarios they can sometimes be inaccurate due to the confusion between UTI, which should be treated with antibiotics, and asymptomatic bacteriuria, which should not be treated with antibiotics. Third, we have evaluated ED visits and hospitalization within 30 days following antibiotic prescribing as negative outcomes related to antibiotic consumption while in reality there are other potential causes for the ED visits and hospitalizations we observed. Finally, our findings derive from secondary analysis of data from electronic health records, and our results could be underestimated or overestimated due to possibly inaccurate ICD-9/10 coding in the medical records.

Conclusion:

In conclusion, Geriatric patients received fewer potentially inappropriate antibiotic prescriptions compared to middle-aged patients. This study provides trend analysis regarding the most common antibiotics prescribed for both older adults and middle-aged patients, and this analysis could help to improve antibiotic prescribing practices in the future among all ages and especially older adults who are at high risk of medication complexity. This analysis can serve as a baseline to understand the impact of interventions to improve antimicrobial use in the ED in the future. It can also be benchmarked against prescribing in the ED in other academic medical centers to inform development of best practices for antimicrobial stewardship in the ED in safety net hospitals.

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CHAPTER FIVE

DISCUSSION

Summary of Findings:

This dissertation consists of three investigations of issues related to antibiotic use and associated complications among older adult patients visiting different health care settings from the emergency department (ED) to outpatient clinics. The first study examined the trend of antibiotic use among community-dwelling older adults using a nationally representative dataset, the Medical Expenditure Panel Survey (MEPS), from 2011-2015. In this study, we evaluated the trend of common infectious diseases and the association between antibiotic use and demographic characteristics, sociodemographic characteristics, and the negative outcomes of antibiotic use such as ED visits. The second study calculated the trend of antibiotic use and common infectious diseases among older adult patients visiting VCU Health in two different outpatient clinics, Geriatrics clinic and adult Internal Medicine clinic, from 2012-2017. We evaluated and compared the antibiotic prescribing appropriateness practices between the two clinics. The third study described the trend of antibiotic prescriptions among older adult patients and compared it with middle-aged patients visiting the ED at VCU Health from 2012-2017. This study evaluated antibiotic use predictors and the prescribing appropriateness practices between older adult patients and middle-aged patients. This chapter presents the highlights of the main findings, implications of the studies' results, and possible future research.

Thirty-one percent of community-dwelling U.S. older adults reported using antibiotics, accounting for 105,762,134 prescriptions from 2011-2015. In addition, the overall rate of antibiotic prescriptions increased slightly over the study period from 484 prescriptions per 1,000 persons in 2011 to 540 prescriptions per 1,000 persons in 2015.

This rate is higher than the rate of antibiotic use among a younger adult population in 2010 where a study reported that the rate was 354 prescriptions per 1,000 persons.[1] Several previous studies have reported mixed results regarding the antibiotic rate among younger adults compared to an older adult population. These differences in the overall antibiotic rate are possibly due to the nature of the dataset, and the methodological approach for assessing antibiotic prescriptions. For those reasons it is difficult to directly compare the antibiotic trends between populations using different datasets. To the best of our knowledge, this study uses the most recently available data to evaluate antibiotic use among older adult patients using nationally representative data. Our analysis found that the rate of antibiotic prescribing varied by age group. Younger older adults (65-69) received more antibiotic prescriptions compared to the oldest-old group (80 years of age or older). Interestingly, antibiotic users were more likely to visit the ED compared to non-users. Our analysis estimated that upper respiratory tract infections were the most common antibiotic indications from 2011-2015, and most of these indications do not require antibacterial therapy. Among antibiotic users, macrolides, quinolones, and penicillins were the most common antibiotic categories prescribed in the U.S. The rate of macrolide prescribing significantly decreased while penicillins prescribing rates increased over the study period. These findings support the hypothesis that health care professionals may not be reducing their prescribing of antibiotics in response to calls to reduce use to avoid antibiotic resistance, but rather they are changing prescribing from one antibiotic category to another perhaps in response to drug safety concerns.

Among VCU Health patients visiting adult ambulatory care clinics, Internal Medicine clinic providers prescribed more antibiotic prescriptions compared to the Geriatrics clinic (69% vs. 31%) respectively. In addition, we found that Geriatrics clinic providers prescribed more potentially inappropriate antibiotic prescriptions compared to Internal Medicine clinic providers. We may expect that the geriatrics patients are more likely to have compromised immune response and that the geriatricians are erring on the side of caution. In addition, patients visiting the geriatrics clinics are considered complex patients, which means they are sicker than the Internal Medicine patients and older as well. The rate of common infectious diseases among VCU Health patients was similar to the national findings where UTI, URI, and skin infections were observed to be the most common antibiotic indications. In addition, we observed similar patterns of antibiotic categories prescribed between Internal Medicine clinic and the Geriatrics clinic with quinolone and macrolide use decreasing over time and penicillins increasing slightly along with first-generation cephalosporins. We found that the patterns of antibiotic categories prescribed varied by the indication and were consistent with national guidelines.[2,3,4]

Among the VCU Health ED patients, we found that older adult patients were significantly less likely to receive potentially inappropriate antibiotic prescriptions compared to middle-aged patients. In both age groups, UTI, URI, and pneumonia were the three most common indications for antibiotic prescriptions. Similar to the previous studies' findings, broad-spectrum antibiotic prescribing was common in the ED patients, irrespective of the age of the patients. Penicillins and quinolones were the most common antibiotics prescribed for ED patients from 2012-2017 at VCU Health.

Moreover, we found differences in the antibiotic categories prescribed based on the indications in both age groups. Our findings from the studies at VCU Health are limited in their generalizability to other academic medicine centers or other care settings. The choice of the antibiotic prescribed depends in part on the formulary system and this is likely to vary from one hospital to another.

Implications:

Most of the previous studies of antibiotic use in the U.S. were not focused on the older adult population specifically, a population that could be affected negatively by antibiotic overuse or misuse due to several factors such as polypharmacy, comorbidities, and normal biological and physiological changes with age that could affect antibiotic pharmacokinetics/pharmacodynamics. Our nationally representative findings could be used to evaluate the impact of national antimicrobial stewardship programs and the National Action Plan for Combating Antibiotic-Resistant Bacteria for decreasing the antibiotic resistance in 2020 as the programs are implemented by establishing a baseline for comparison. These findings could also be used to compare antibiotic prescribing and infectious diseases trends to those observed in different datasets such as Medicare claims data. The findings from the VCU Health System could be used to improve health care provider treatment practices in the care of older adults, including practices in the Geriatrics clinic. Comparing our results with the hospital antibiogram would be useful for the hospital administration to evaluate the antibiotic stewardship program in the hospital. In addition, our findings could help other health care providers like nurse practitioners and pharmacists to evaluate their knowledge, practices towards antibiotic use among vulnerable population like older adults and identify opportunities to improve care for this population and reduce the risk of outcomes such as antibiotic resistance.

Future Research:

In our retrospective cohort studies, we have assessed the antibiotic prescribing trends on a national level and local level. In addition, we have evaluated antibiotic appropriateness based on the ICD-codes, assuming the diagnosis is correct. Future studies could test antibiotic prescription appropriateness through a more robust definition taking into consideration the antibiotic susceptibility of each patient, accurate diagnosis and lab culture, age-appropriate dosing and choice of antibiotic, and risk of drug interactions. Moreover, antibiotic inappropriateness could be defined in different ways, such as a patient receiving an antibiotic from a friend or family member or an individual not following the correct directions for use. Taking all these factors into consideration when defining antibiotic appropriateness measures will strengthen the definition and the study's findings.

In the three studies that we have conducted, we examined antibiotic use among non-institutionalized older adults. Previous studies have shown that antibiotic prescribing rates among older adult patients in the nursing home is high. The same study objectives need to be replicated among nursing home residents using the most recent nationally representative data. On the other hand, assisted living residents share common characteristics with both community-dwelling older adults and nursing home residents such as age, polypharmacy, and comorbidities that could affect the medication prescription practices. There is a lack of research evaluating prescribing practices in assisted living facilities. Unlike inpatient or nursing home settings, assisted living facilities are a social model, not a medical model. For that reason, it is very difficult to collect medical information regarding assisted living residents. Also, it is expensive and time and resource exhausting. A study that would compare and evaluate antibiotic prescription practices among outpatient community older adults, nursing home residents, and assisted living facilities residents would be ideal research questions for future researchers.

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Appendix For Study 2

Appendix: 3.1 Infectious Diseases Trend in Internal Medicine Ambulatory Clinic per 10,000 visits

Type of Infection	2012	2013	2014	2015	2016	2017	P-value
UTI	32.54149	38.58728	30.64295	31.05939	27.66742	23.72053	0.4745
URI	31.45677	25.72485	29.00137	17.58785	31.21453	28.39275	0.1286
Pneumonia	5.96594	4.287475	1.641587	2.619466	2.837684	3.234618	0.305
Skin Infection	10.30481	11.79056	7.660739	2.993676	4.611237	5.750431	0.0021
C.Diff	0	0	0	0	0	0.359402	0.0514
Otitis Media	3.254149	2.143738	2.735978	1.122628	2.482974	1.79701	0.809

Appendix 3.2 Infectious Diseases Trend in Geriatrics Clinic per 10,000 visits

Type of Infection	2012	2013	2014	2015	2016	2017	p-value
UTI	60.84071	73.52941	71.71483	77.50397	78.18317	55.58363	0.9833
URI	99.55752	71.07843	78.04261	107.3132	63.29114	60.63669	0.2798
Pneumonia	5.530973	4.901961	14.76482	21.8601	3.723008	10.10611	0.4479
Skin Infection	44.24779	39.21569	14.76482	31.7965	33.50707	75.79586	0.3321
C.Diff	0	0	0	1.987281	0	0	0.705
Otitis Media	0	0	6.327779	0	0	0	0.5651

Appendix 3.3 Antibiotic Prescriptions Trend among Geriatrics Clinic per 10,000 visits

	2012	2013	2014	2015	2016	2017	
Quinolones	176.9912	137.2549	166.6315	176.868	152.6433	106.1142	
Macrolides	99.55752	88.23529	80.15187	99.36407	78.18317	80.84891	
Tetracyclines	49.77876	68.62745	37.96667	65.58029	44.6761	75.79586	
First generation Cephalosporins	49.77876	58.82353	59.05927	61.60572	81.90618	126.3264	
Second generation Cephalosporins	0	7.352941	2.10926	1.987281	7.446016	10.10611	
Third generation Cephalosporins	0	2.45098	8.437039	17.88553	40.95309	45.47751	
Aminopenicillins	38.71681	34.31373	37.96667	41.73291	29.78407	70.7428	
urinary anti-infectives	11.06195	12.2549	10.5463	19.87281	26.06106	35.3714	
Miscellaneous Antibiotics	27.65487	24.5098	27.42038	23.84738	22.33805	25.26529	
Penicillins	22.12389	31.86275	50.62223	53.6566	44.6761	65.68974	
Sulfinamides	27.65487	34.31373	16.87408	17.88553	7.446016	5.053057	

Appendix 3.4 Antibiotic Prescriptions trend among Internal Medicine Ambulatory Care Clinic per 10,000 visits

Antibiotic Category	2012	2013	2014	2015	2016	2017	p-value
Quinolones	63.45591	52.52157	46.51163	37.42095	40.08229	30.54917	0.0035
Macrolides	55.32053	42.87475	45.41724	30.31097	40.437	32.70558	0.333
Tetracyclines	21.15197	24.65298	21.88782	14.96838	20.57321	20.12651	0.26
First generation Cephalosporins	15.18603	13.39836	16.96306	11.60049	21.28263	20.48591	<.0001
Second generation Cephalosporins	0	1.071869	1.094391	0.748419	1.418842	1.79701	0.0403
Third generation Cephalosporins	2.711791	2.679672	2.188782	3.742095	5.320658	10.78206	<.0001
Aminopenicillins	27.66027	17.68584	12.0383	7.48419	9.931896	10.06325	0.0002
urinary anti-infectives	8.135373	2.679672	9.302326	10.47787	6.030079	5.391029	0.4684
Miscellaneous Antibiotics	13.55895	9.110885	7.113543	6.361561	8.158343	6.109833	0.2539
Penicillins	11.38952	10.18275	10.39672	10.85207	14.18842	15.09488	0.0013
sulfonamides	11.38952	6.431213	8.207934	5.238933	3.547106	5.031627	0.061

Appendix 3.4 Antibiotic Treatment Among UTI patients in Geriatrics Clinic Per 100 UTI Diagnoses

Antibiotic Category	2012	2013	2014	2015	2016	2017	P-value
Quinolones	81.81818	36.66667	61.76471	56.41026	52.38095	18.18182	0.096
Macrolides	0	6.666667	0	0	4.761905	0	0.5408
Tetracyclines	0	3.333333	2.941176	2.564103	0	9.090909	0.6706
First generation Cephalosporins	9.090909	23.33333	23.52941	10.25641	9.52381	9.090909	0.1424
Second generation Cephalosporins	0	0	0	0	4.761905	9.090909	0.0309
Third generation Cephalosporins	0	3.333333	0	15.38462	28.57143	27.27273	0.0003
urinary anti-infectives	0	10	0	10.25641	14.28571	9.090909	0.2595
Miscellaneous Antibiotics	0	3.333333	8.823529	5.128205	4.761905	0	0.9621
Penicillins	0	10	20.58824	15.38462	4.761905	18.18182	0.7034
sulfonamides	0	23.33333	5.882353	0	0	0	0.0041

Appendix 3.5 Antibiotic Treatment Among UTI Patients in Internal Medicine Ambulatory Care Clinic Per 100 UTI Diagnoses

Antibiotic Category	2012	2013	2014	2015	2016	2017	P-value
Quinolones	66.66667	62.5	50	43.37349	51.28205	36.36364	<.0001
Macrolides	0	4.166667	5.357143	1.204819	2.564103	3.030303	0.8719
Tetracyclines	0	2.777778	0	1.204819	3.846154	3.030303	0.2159
First generation Cephalosporins	15	8.333333	16.07143	20.48193	32.05128	33.33333	0.0003
Second generation Cephalosporins	0	1.388889	1.785714	2.409639	3.846154	1.515152	0.3053
Third generation Cephalosporins	1.666667	6.944444	5.357143	8.433735	6.410256	15.15152	0.0273
urinary anti-infectives	3.333333	1.388889	12.5	18.07229	10.25641	10.60606	0.0376
Miscellaneous Antibiotics	3.333333	2.777778	0	0	0	1.515152	0.0951
Penicillins	6.666667	11.11111	8.928571	6.024096	3.846154	4.545455	0.1019
sulfonamides	13.33333	6.944444	8.928571	8.433735	0	3.030303	0.0027

Appendix 3.6 Antibiotic Treatment Among URI patients in Geriatrics Clinic Per 100 URI Diagnoses

Antibiotic Category	2012	2013	2014	2015	2016	2017	P-value
Quinolones	22.22222	17.24138	8.108108	25.92593	17.64706	0	0.562
Macrolides	66.66667	65.51724	54.05405	50	52.94118	83.33333	0.6156
Tetracyclines	5.555556	0	5.405405	1.851852	0	0	0.3586
First generation Cephalosporins	0	0	0	1.851852	5.882353	0	0.2485
Second generation Cephalosporins	0	6.896552	0	0	0	0	0.1566
Penicillins	16.66667	13.7931	32.43243	22.22222	29.41176	16.66667	0.6303
sulfonamides	0	0	2.702703	1.851852	0	0	0.9

Appendix 3.7 Antibiotic Treatment Among URI patients in Internal Medicine Ambulatory Care Clinic Per 100 URI Diagnoses

Antibiotic Category	2012	2013	2014	2015	2016	2017	P-value
Quinolones	12.06897	10.41667	13.20755	19.14894	6.818182	5.063291	0.2113
Macrolides	68.96552	68.75	64.15094	44.68085	53.40909	41.77215	0.0083
Tetracyclines	0	4.166667	13.20755	6.382979	18.18182	27.8481	<.0001
First generation Cephalosporins	0	0	3.773585	0	1.136364	1.265823	0.5386
Second generation Cephalosporins	0	0	0	0	0	2.531646	0.0661
Penicillins	18.96552	16.66667	11.32075	23.40426	19.31818	22.78481	0.1674
sulfonamides	1.724138	0	1.886792	2.12766	0	0	0.3051

Appendix 3.8 Antibiotic Treatment Among Skin & Soft Tissue patients in Geriatrics Clinic Per 100 Skin & Soft Tissue Diagnoses

Antibiotic Category	2012	2013	2014	2015	2016	2017	p-value
Quinolones	0	12.5	28.57143	0	0	0	0.1818
Macrolides	0	0	0	0	11.11111	0	0.4082
Tetracyclines	62.5	62.5	28.57143	31.25	11.11111	26.66667	0.0161
First generation Cephalosporins	50	18.75	0	18.75	22.22222	66.66667	0.0618
Third generation Cephalosporins	0	0	0	6.25	0	0	0.8148
Miscellaneous Antibiotics	0	0	28.57143	0	0	0	0.6098
Penicillins	0	12.5	28.57143	50	33.33333	20	0.1114

Appendix 3.9 Antibiotic Treatment Among Skin & Soft Tissue patients in Internal Medicine Ambulatory Care Clinic Per 100 Skin & Soft Tissue Diagnoses

Antibiotic Category	2012	2013	2014	2015	2016	2017	p-value
Quinolones	10.52632	4.545455	0	0	0	0	0.0738
Macrolides	0	0	0	0	15.38462	0	0.126
Tetracyclines	57.89474	59.09091	71.42857	62.5	38.46154	50	0.8098
First generation Cephalosporins	21.05263	36.36364	50	12.5	30.76923	37.5	0.3642
Penicillins	26.31579	22.72727	7.142857	12.5	7.692308	6.25	0.0158
Sulfonamides	0	4.545455	7.142857	12.5	0	12.5	0.1585

Appendix For Study 3

Appendix 4.10 The Trend of Infectious Disease Diagnoses Among Middle-Aged Adults visiting the ED per 10,000 visits

Type of Infection	2012	2013	2014	2015	2016	2017	P-value
UTI	136.5188	143.8404	145.7249	113.9997	106.3759	122.5476	0.0102
URI	180.173	165.4938	150.9294	123.7314	75.79283	76.00306	<.0001
Pneumonia	83.33995	103.6269	98.14126	89.67051	89.08982	102.5158	<.0001
Skin Infection	76.99024	85.06689	87.73234	62.56082	53.18795	47.13368	0.1377
C.Diff	0	0	0	0.69512	7.978193	8.248395	<.0001
Otitis Media	0	18.56005	11.15242	10.4268	6.648494	7.070052	0.0433

Appendix 4.11 The Trend of Infectious Disease Diagnoses Among Older Adults visiting the ED per 10,000 visits

Type of Infection	2012	2013	2014	2015	2016	2017	P-value
UTI	256.523	265.8371	258.0223	230.1578	206.8732	244.2297	0.8107
URI	98.21167	107.4661	104.7806	90.16491	44.08772	54.57148	<.0001
Pneumonia	121.6652	173.9253	145.3831	151.8567	132.2632	152.9791	0.0381
Skin Infection	71.82644	50.90498	62.86837	65.25092	37.305	65.30685	0.8792
C.Diff	0	0	0	1.18638	21.47863	13.41922	<.0001
Otitis Media	10.26092	7.070136	3.929273	4.745521	4.521818	4.473072	0.2189

Appendix 4.12 The Trend of Antibiotic Prescriptions Among Older Adult patients Visiting the ED per 10,000 visits

	2012	2013	2014	2015	2016	2017	P-value
Quinolones	400.1759	395.9276	411.2639	367.7779	334.6145	372.1596	<.0001
Macrolides	76.22398	93.32579	87.75377	74.74196	101.7409	171.766	0.0043
Tetracyclines	48.37291	52.319	43.222	68.81006	62.17499	67.9907	0.8911
First generation Cephalosporins	162.7089	197.9638	179.4368	213.5485	229.4823	279.1197	0.2708
Second generation Cephalosporins	14.65846	14.14027	9.168304	33.21865	22.60909	19.68152	0.7515
Third generation Cephalosporins	256.523	263.009	226.5881	224.2259	256.6132	396.3142	0.7441
Aminopenicillins	17.59015	14.14027	17.02685	33.21865	23.73954	26.83843	0.5824
urinary anti-infectives	7.329229	15.5543	17.02685	16.60932	22.60909	43.83611	0.0003
Miscellaneous Antibiotics	55.70214	97.56787	81.20498	98.46957	98.34954	124.3514	0.2425
Penicillins	288.7716	349.2647	352.3248	387.9464	388.8763	541.2417	0.0142
sulfonamides	30.78276	32.52262	41.91225	36.77779	33.91363	54.57148	0.7505
Clindamycin	38.11199	29.69457	22.26588	30.84589	32.78318	29.52228	0.0338

Appendix 4.13 The Trend of Antibiotic Prescriptions Among Middle-Aged patients Visiting the ED per 10,000 visit

Antibiotic Category	2012	2013	2014	2015	2016	2017	P-value
Quinolones	215.0964	232.774	211.1524	229.3897	211.4221	206.2099	<.0001
Macrolides	82.54623	92.02691	104.8327	105.6583	95.73832	138.4552	0.1265
Tetracyclines	91.27709	81.20022	66.9145	66.03642	48.53401	75.41389	<.0001
First generation Cephalosporins	181.7605	155.4404	150.1859	173.0849	182.8336	214.4583	0.6478
Second generation Cephalosporins	13.49313	10.05336	14.86989	27.10969	20.61033	15.90762	0.53
Third generation Cephalosporins	109.5325	111.3603	129.368	132.768	125.6565	177.3405	0.0482
Aminopenicillins	12.69942	21.65339	25.27881	22.93897	25.26428	22.3885	0.7358
urinary anti-infectives	9.524565	13.92004	10.40892	9.731684	9.972741	18.85347	0.5361
Miscellaneous Antibiotics	70.64053	65.73351	81.04089	78.54859	81.77648	121.9584	0.0107
Penicillins	179.3793	220.4006	240.1487	235.6458	278.5719	334.06	<.0001
sulfonamides	40.4794	47.17346	38.66171	45.18282	43.88006	54.79291	0.7932
Clindamycin	26.19255	29.38675	25.27881	22.93897	23.93458	28.86938	0.1383

Appendix 4.14 Antibiotic Treatment Among UTI Older Adult Patients Visiting the ED per 100 UTI Diagnoses

Antibiotic Category	2012	2013	2014	2015	2016	2017	P-value
Quinolones	22.28571	15.42553	22.33503	21.82741	11.47541	14.28571	<.0001
Macrolides	0	1.595745	0.507614	0	3.278689	2.197802	0.0505
Tetracyclines	0.571429	0	0	0.507614	0.546448	0	0.5952
First generation Cephalosporins	9.142857	8.510638	8.629442	8.629442	11.47541	17.58242	0.0357
Second generation Cephalosporins	0.571429	1.06383	0	0	0	0	0.0263
Third generation Cephalosporins	32.57143	34.57447	28.93401	29.94924	38.79781	41.39194	0.9783
urinary anti-infectives	0.571429	0.531915	3.553299	3.553299	6.010929	4.761905	0.0039
Miscellaneous Antibiotics	0.571429	3.723404	4.060914	7.106599	1.639344	1.465201	0.3944
Penicillins	6.285714	16.48936	17.25888	15.73604	13.6612	15.01832	0.8968
sulfonamides	1.142857	1.06383	3.553299	3.553299	5.464481	4.029304	0.0502

Appendix 4.15 Antibiotic Treatment Among UTI Middle-Aged Patients Visiting the ED per 100 UTI Diagnoses

Antibiotic Category	2012	2013	2014	2015	2016	2017	P-value
Quinolones	19.18605	27.41935	12.7551	19.5122	11.25	7.692308	<.0001
Macrolides	0	1.075269	2.55102	1.829268	0	1.923077	0.3902
Tetracyclines	0.581395	0	0.510204	0	0.625	0.961538	0.384
First generation Cephalosporins	19.18605	15.5914	17.34694	21.95122	15.625	22.59615	0.3194
Third generation Cephalosporins	14.53488	31.72043	22.95918	23.17073	20	19.71154	0.5293
urinary anti-infectives	1.744186	4.83871	5.612245	1.219512	3.75	8.173077	0.036
Miscellaneous Antibiotics	2.906977	2.688172	6.632653	3.04878	1.875	5.288462	0.5626
Penicillins	7.55814	8.064516	16.83673	10.36585	10	16.82692	0.0161
sulfonamides	2.906977	6.451613	2.55102	4.268293	0.625	4.807692	0.6533

Appendix 4.16 Antibiotic Treatment Among URI Older Adult Patients Visiting the ED per 100 URI Diagnoses

Antibiotic Category	2012	2013	2014	2015	2016	2017	P-value
Quinolones	8.955224	31.57895	13.75	21.05263	17.94872	5	0.0526
Macrolides	7.462687	40.78947	23.75	21.05263	33.33333	26.66667	0.3746
Tetracyclines	8.955224	6.578947	11.25	13.15789	5.128205	6.666667	0.6133
First generation Cephalosporins	8.955224	1.315789	0	1.315789	0	1.666667	0.0084
Third generation Cephalosporins	2.985075	14.47368	8.75	3.947368	7.692308	6.666667	0.5236
Penicillins	7.462687	5.263158	8.75	6.578947	12.82051	23.33333	0.0027

Appendix 4.17 Antibiotic Treatment Among URI Middle-Aged Patients Visiting the ED per 100 URI Diagnoses

Antibiotic Category	2012	2013	2014	2015	2016	2017	P-value
Quinolones	14.43299	27.27273	18.64407	22.22222	10	13.75	0.8052
Macrolides	65.97938	44.54545	39.83051	68.88889	41.25	50	0.1673
Tetracyclines	48.45361	31.81818	21.18644	40	6.25	20	0.0015
First generation Cephalosporins	2.061856	2.727273	0.847458	4.444444	1.25	3.75	0.3195
Third generation Cephalosporins	3.092784	1.818182	0.847458	0	0	2.5	0.4961
Penicillins	5.154639	20	9.322034	17.77778	17.5	10	0.06

Appendix 4.18 Antibiotic Treatment Among Skin & Soft Tissue Older Adult Patients Visiting the ED per 100 Skin & Soft Tissue Diagnoses

Antibiotic Category	2012	2013	2014	2015	2016	2017	p-value
Quinolones	6.122449	5.555556	4.166667	1.818182	0	1.369863	0.0171
Tetracyclines	6.122449	5.555556	4.166667	10.90909	6.060606	2.739726	0.273
First generation Cephalosporins	8.163265	25	8.333333	14.54545	12.12121	31.50685	0.0676
Third generation Cephalosporins	4.081633	0	2.083333	3.636364	3.030303	0	0.1924
Penicillins	32.65306	33.33333	37.5	34.54545	54.54545	46.57534	0.6719
Sulfonamides	0	5.555556	4.166667	5.454545	6.060606	5.479452	0.4076
Clindamycin	10.20408	25	10.41667	18.18182	21.21212	16.43836	0.912

Appendix 4.19 Antibiotic Treatment Among Skin & Soft Tissue Middle-Aged Patients Visiting the ED per 100 Skin & Soft Tissue Diagnoses

Antibiotic Category	2012	2013	2014	2015	2016	2017	p-value
Quinolones	6.185567	1.818182	1.694915	3.333333	3.75	5	0.9462
Tetracyclines	7.216495	10	8.474576	6.666667	6.25	7.5	0.4686
First generation Cephalosporins	18.5567	20	11.86441	18.88889	16.25	15	0.3092
Third generation Cephalosporins	4.123711	0.909091	0.847458	0	0	5	0.8884
Penicillins	18.5567	28.18182	23.72881	43.33333	18.75	45	0.006
Sulfonamides	9.278351	9.090909	11.01695	4.444444	3.75	5	0.0379
Clindamycin	28.57143	27.77778	43.75	32.72727	48.48485	19.17808	0.1167

Appendix 5.1. Detailed of antibiotic categories that we included in the analyses of study two and study three.

Antibiotic Category	Medication Name
008 Carbapenems	Doripenem, Doripenem, Ertapenem, Imipenem, Meropenem.
009 Cephalosporin	All first generation cephalosporins, All second generation cephalosporins, All third generation cephalosporins, All fourth generation cephalosporins, All fifth generation cephalosporins.
011 Macrolide	Azithromycin, Clarithromycin, Dirithromycin, Erythromycin
012 Miscellaneous antibiotics	Aztreonam, Bacitacin, Chloramphenicol, Colistimethate, Fosfomycine, Metronidazole,
013 Penicillins	All penicillinase resistant penicillins, Antipsudomonal penicellins, Aminopenicillins, Beta-lactamse inhibitors, Natural penicillins.
014 Quinolones	Ciprofloxacin, Levofloxacin, Ofloxacin,
015 Sulfonamides	Sulfadiazine, Sulfamethoxazole, Sulfamethoxazole-Trimethoprim, Sulfasalazine
016 Tetracyclines	Doxycycline, Tetracycline,
017 Urinary anti-infective	Fosfomycin, Nitrofurantoin, Trimethoprim
240 Lincomycin	Clindamycin

VITA

Fawaz M. Alotaibi was born on March 9th, in Al-Ahsa, Kingdom of Saudi Arabia (KSA). He earned his Pharm.D. from King Faisal University, College of Clinical Pharmacy, KSA, in 2011. In early 2012, he was hired as a teaching assistant in College of Clinical Pharmacy in Dammam University, which he awarded a full scholarship to pursue a master and doctoral degrees in the United State starting from August, 2012. Fawaz enrolled in the master program in the Department of Pharmacotherapy and Outcomes Science in Virginia Commonwealth University in the fall of 2013 and he graduated in the spring 2015. In fall 2015, he joined the same department as a doctoral student and graduated in spring 2019. In addition, Fawaz enrolled in the certificate of aging program in the department of Gerontology in school of Allied health at VCU in fall 2015 and graduated in fall 2018. During the doctoral program, Fawaz completed several certificates related to teaching in higher education, which includes Preparing Future Faculty program from Graduate School at VCU (Completed in fall 2017) and Faculty Development Program from Virginia Geriatrics Center at VCU (completed in Summer 2018). At VCU, Fawaz participated in several national conferences and presented his research at the annual meeting of Gerontology Society of America GSA in 2015, 2016, and 2018 respectively.