2022

Impact of Poverty on Antibiotic Prescribing Rates in the United States Through Mediation Effects of Underlying Health Conditions

Nato Tarkhashvili
Walden University

<u>Walden University</u>

College of Health Sciences and Public Policy

This is to certify that the doctoral dissertation by

Nato Tarkhashvili

has been found to be complete and satisfactory in all respects,
and that any and all revisions required by
the review committee have been made.

Review Committee
Dr. Adebowale Awosika-Olumo, Committee Chairperson, Public Health Faculty
Dr. Nancy Rea, Committee Member, Public Health Faculty
Dr. Thomas O'Grady, University Reviewer, Public Health Faculty

Chief Academic Officer and Provost
Sue Subocz, Ph.D.

Walden University
2022

Abstract

Impact of Poverty on Antibiotic Prescribing Rates in the United States Through

Mediation Effects of Underlying Health Conditions

by

Nato Tarkhashvili

MD, Tbilisi State Medical University, Georgia, 1999

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health

Walden University

November 2022

Abstract

Resistance to antibiotics among bacteria develops largely due to frequent use of antibiotics in human and animal medicine. Little is known about how patients' socioeconomic factors, in conjunction with chronic health conditions, impact antibiotic prescribing rates in the United States. The research questions aimed to explore the relationship between poverty and antibiotic prescribing rates while also adjusting for confounders such as population aged ≥ 65, physician density, prevalence of obesity, diabetes, and chronic obstructive pulmonary disease (COPD). The relationships were evaluated using a quantitative, ecological study design using the ecosocial theory and mediation analysis of 2020 survey results provided by the Centers for Disease Control and Prevention (Behavioral Risk Factor Surveillance System, Antibiotic Resistance & Patient Safety Portal) and the Association of American Medical Colleges. Results showed a strong, linear relationship between prevalence of poverty and antibiotic prescribing rates. For every percent increase in prevalence of poverty in each state, the antibiotic prescribing rate increased by 17.4 courses (95% Confidence Intervals of 9.2, 24.9) of outpatient antibiotics per 1,000 population by indirect effects of poverty through mediators (COPD, obesity, and diabetes). Findings may impact positive social change by stimulating further studies leading to efforts directed at the quality improvement in measuring and tracking antibiotic use in clinical settings. Moreover, the results could encourage public health professionals to design and implement effective antibiotic stewardship programs by addressing clinical and social services needed to reduce prescribing rates.

Impact of Poverty on Antibiotic Prescribing Rates in the United States Through

Mediation Effects of Underlying Health Conditions

by

Nato Tarkhashvili

MD, Tbilisi State Medical University, Georgia, 1999

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health

Walden University

November 2022

Dedication

This study is dedicated to my school teachers in school No 1, Tbilisi, who did a great job in preparing me for PhD journey at Walden.

Acknowledgments

I would like to acknowledge Angela Cascio – a person who works tirelessly on antibiotic stewardship issues at South Dakota Department of Health, who also inspired me to conduct research on antibiotic use.

Table of Contents

List of Tables

List of Figures

Chapter 1: Introduction to the Study

Antibiotic resistance is a pressing public health issue across the globe (Centers for Disease Control and Prevention [CDC], 2019a). In clinical terms that means that currently circulating bacterial strains are no longer killed by therapeutic doses of antibiotics which makes infectious diseases caused by those bacteria essentially untreatable (CDC, 2019a). Resistance to one particular antibiotic would be more or less tolerable from a clinical perspective if other antibiotics were effective against bacteria (CDC, 2019a). However, this option becomes more and more elusive with the development of so called multidrug-resistant strains – the organisms that are resistant to several antibiotics simultaneously and some of them resistant to all antibiotics currently used in clinical practice (Suay-García & Pérez-Gracia, 2019). For example, Carbapenemase-producing organisms are reported to be resistant to several drugs simultaneously and most notably to carbapenems - a group of antibiotics that are considered as the drugs of last resort to treat infections caused by *Enterobacterales* (Suay-García & Pérez-Gracia, 2019). Carbapenemases are a group of enzymes capable of destroying powerful drugs called carbapenems (van Duin & Doi, 2017). This is one of the resistance mechanisms that is considered particularly dangerous from epidemiologic perspective because it is mediated by plasmids capable of transferring resistance genes horizontally and thus affecting strains of different species (van Duin & Doi, 2017). Once developed, resistant strains spread quickly and easily in communities and clinical settings (Yi & Kim, 2021). Suboptimal hand hygiene, frequent interaction among populations, and international travel propagate the spread of multidrug-resistant strains globally (Tängdén et al., 2010).

According to a CDC (2019a) report, every year 2.8 million patients get infected with multidrug-resistant strains and 35,000 succumb due to infections caused by them. In addition to that, 223,900 patients in 2017 alone experienced hospitalizations due to *C. difficile* infection (as a result of antibiotic therapy) and 12,800 died from it (CDC, 2019a). Financial burden caused by multidrug-resistant strains is also substantial in the United States and is estimated as $2.39-$3.38 billion in a year for inpatient settings (Johnston et al., 2019).

The fact that bacteria may develop resistance to antibiotics was first noted by Abraham and Chain in 1940 (Abraham & Chan, 1940). In their work authors describe an enzyme made by bacteria *B. coli* capable of destroying penicillin (Abraham & Chan, 1940). Antibiotic resistance development after using antibiotic therapy was also noted by Dr. Fleming, a Scottish scientist, who won a Nobel prize for discovering penicillin in 1945 (Sillankorva et al., 2019). This is what he wrote about development of antibiotic resistance in 1945 when emergence of drug resistance seemed a remote perspective: “The thoughtless person playing with penicillin treatment is morally responsible for the death of the man who succumbs to infection with the penicillin-resistant organism” (Sillankorva et al., 2019). Even though humanity received this warning almost a century ago, misuse, overuse, and abuse of antibiotics that saved millions of lives since their discovery continues and only recently have practitioners started paying attention to resistance development mechanisms and the driving forces behind it.

Although drug resistance occurs naturally, the biggest share of antibiotic resistant strains is created by human behavior and namely, high consumption rates of antibiotics in human and animal medicine, as well as in the livestock industry where antibiotics are used as growth promoters (Skandalis et al., 2021). In multiple studies, antibiotic use has been shown to accelerate the process of resistance development by creating selective pressure on bacteria (Wu et al., 2016; Wind et al., 2017). Although not every genus and species of bacteria are equally capable of developing resistance after experiencing such a pressure. For example, *Treponema pallidum* – a causative agent of syphilis is capable of developing resistance to azithromycin while there are no reports of resistance against penicillin which is still used successfully to treat syphilis even after several decades since its discovery (Lukehart et al., 2004). On the other hand, one of the most prevalent sexually transmitted infections, gonorrhea, will likely become untreatable in the next couple of decades due to increased resistance to currently used antibiotics (Bodie et al., 2019).

Vast majority of clinically significant bacteria respond to such a pressure by producing enzymes capable of destroying antibiotics, modifying target molecules of antibiotics, or using special pumps in their membranes to remove antibiotics (Reygaert, 2018). For example, Wind et al. (2017) reported that minimal inhibitory concentrations (MIC) of azithromycin in *Neisseria gonorrhoeae* isolates was increased within several weeks of exposure to this particular antibiotic (Wind et al., 2017). Similar phenomenon was observed by Yang et al. (2020) when they noticed a strong correlation between antibiotic prescribing and the prevalence of fluoroquinolone-resistant gram-negative bacteria in Chinese tertiary hospitals.

Apart from community- and global-level threats of antibiotic exposure (e.g., resistance development), dangerous side effects on individual level have also been noted (Dik et al., 2016; Czepiel et al., 2019). Antibiotic use has been linked to multiple adverse effects such as allergies, *C. difficile* gastroenteritis, and even colon cancer as a result of dysbiosis of gut microflora (Dik et al., 2016; Czepiel et al., 2019). Therefore, once regarded as “safe medications” decades after their use, antibiotics have become potentially dangerous drugs that have to be prescribed only when needed, at right time, at right doses, and at right duration (Dryden et al., 2011).

To alleviate the problem of resistance, one of the solutions would be development and manufacturing of new antibiotics (Morel et al., 2020). However, this process is also halted by pharmaceutical industry citing lack of financial incentives (Morel et al., 2020). Thus, the only option that current medicine has is to reduce antibiotic prescribing rates in an attempt to preserve currently used antibiotics for the future (CDC, 2019a).

The social problem of emerging threat of antibiotic resistance has been targeted by CDC in their recent publication where they classified five organisms of clinical significance as “urgent threats to humans” (CDC, 2019a). In addition to that, CDC pioneered in introducing the concept of antibiotic stewardship in nursing homes and healthcare facilities in an effort to reduce antibiotic prescribing rates (CDC, 2015).

Combatting both antibiotic misuse and overuse have long been considered a cornerstone of antibiotic stewardship programs nationwide (CDC, 2021a). According to the CDC (2021a), antibiotic overuse (unnecessary use) refers to using antibiotics for medical conditions where antibiotic therapy is not indicated. For example, prescribing antibiotics for viral infections would be classified as antibiotic overuse (CDC, 2021a). Misuse refers to prescribing wrong antibiotics for longer durations, or for inappropriate dosages (CDC, 2021a). Both practices have been lumped together under the umbrella of so called “inappropriate antibiotic use” and have been documented to increase overall antibiotic prescribing rates in clinical settings (Rowe & Linder, 2019). According to the CDC (2021b), the goal of antibiotic stewardship is to prescribe “the right antibiotic, at the right dose, for the right duration, and at the right time.” Thus, targeting inappropriate antibiotic use was an excellent area for reducing antibiotic prescribing rates and has been utilized extensively by the CDC (CDC, 2015).

Although this concept seems quite attractive from public health perspective, it does not take into account patient-specific factors which might also influence antibiotic prescribing rates without inappropriate use of antibiotics (CDC, 2015). For example, clinical guidelines claim that patients diagnosed with Chronic Obstructive Pulmonary Disease (COPD) may benefit from antibiotic therapy for acute bronchitis as opposed to healthy patients (Vollenweider et al., 2018). Therefore, it becomes quite logical that populations with high prevalence of COPD will also have high consumption rates of antibiotics while those prescriptions cannot be classified as inappropriate antibiotic use.

Another example would be a high prevalence of sexually transmitted infections (e.g., gonorrhea, chlamydia, and syphilis) which are also treated using antibiotics by sexually transmitted infection (STI) clinics and health departments across the nation

(Garcia & Wray, 2021). High prevalence of STIs is also expected to increase antibiotic prescribing rates without classifying those prescriptions as inappropriate.

Two other examples that might also fall in this category of diseases that may benefit from more antibiotic use are obesity and diabetes – chronic conditions highly prevalent among poor and disadvantaged populations–that alter body metabolism to the extent that make hosts susceptible to bacterial and viral infections (Meydan et al., 2018). There are numerous studies that explore relationship between metabolic changes in human body as a result of obesity and diabetes and bacterial infections such as skin and soft tissue infections, sepsis, and pneumonia – just to list a few of them (Meydan et al., 2018). It also sounds logical that populations with high prevalence of obesity and diabetes require frequent visits to healthcare providers which might in fact end up with prescribing antibiotics, while those antibiotics cannot be classified as inappropriate (Meydan et al., 2018). Quite contrary, they will be classified as antibiotics prescribed as indicated (Kim et al., 2019).

The research problem I addressed is the social context of antibiotic prescribing which, if better understood, can lead to well-designed public health policy and practice initiatives. There is limited research and antibiotic stewardship initiatives do not take into consideration patient-specific risk factors such as acute and chronic medical conditions that may also contribute to high antibiotic prescribing rates in addition to inappropriate antibiotic use commonly cited by CDC (2015). The effect of poverty and other social determinants on antibiotic prescribing rates mediated through underlying health conditions remains unexplored and underrated by public health world and policy-makers.

This gap in literature shifts the blame of high antibiotic prescribing rates to prescribers and identifies them as the major (if not the only) source of the problem in humans (CDC, 2015). Rewarding those with low prescribing rates and penalizing those with higher rates without taking into consideration patient mix will inevitably create mixed messages to prescribers and the patients. For example, such an approach in antibiotic stewardship programs will create a threat that prescribers will not prescribe antibiotics to their patient even if indicated. Therefore, my study needs to be conducted for two reasons. First, the public health community has to explore the relationship between chronic health conditions that might drive antibiotic prescribing rates. Estimating the influence of those health conditions on antibiotic prescribing rates will help to explain variability of antibiotic prescribing rates independent of inappropriate antibiotic use. This will help to design adjustment coefficients and adjustment variables for future investigations and allow public health professionals and policymakers to adjust antibiotic prescribing rates by patient-level factors (Ibrahim & Polk, 2012; Momattin et al., 2018). This process can help the public health community compare the risk-adjusted rates in different communities/facilities for benchmarking purposes which is currently not done by antibiotic stewardship programs nationwide (CDC, 2022a).

Second, this study also addressed the role of poverty (measured by income) as a social determinant on development of chronic medical conditions which may subsequently increase antibiotic prescribing rates through mediating effects. This study was conducted to fill the gap in knowledge about impact of social factors on antibiotic prescribing rates which subsequently affects the probability of drug-resistance development in bacteria. The findings from this study place social determinants on agenda to current policymakers and create the need for social change through improving social determinants in an attempt to reduce antibiotic prescribing rates. This can potentially benefit individual patients since it reduces the number of adverse effects associated with antibiotics. It may also benefit national and global communities by reducing prevalence of drug-resistant strains and save costs associated with tackling resistant bacteria and the dangerous outcomes associated with them.

Background

If one conducts a literature review on antibiotic resistance one may discover that there is plenty of literature about resistance as a national and global threat, prevalence of those bacteria, resistance mechanisms and their development, how quickly those bacteria spread in our clinics and hospitals as well as communities through water and hands of healthcare personnel or community members, and how antibiotic therapy promotes selection of resistant strains (see CDC, 2019a). Those strains later travel across the globe and if today they are discovered in India, the next day, they may be found in community hospitals across the United States (Kelly et al., 2017). That is the reason behind the statement made by World Health Organization in 2021 that the burden of multidrug-resistant strains is rising to “dangerously high levels in all parts of the world” (World Health Organization, 2021). By looking at the literature, one may discover that there is a sharp contrast between the severity of a problem that we deal with in the form of multidrug-resistant bacteria and the amount of literature that quantifies impact of antibiotic use on drug-resistant strain development. The data of linear regression models that show the probability of drug-resistant strain development and how it may be increased by every step in antibiotic use are still lacking. The public health community has conducted a good deal of scientific work to characterize problem of inappropriate antibiotic use and concluded that there is a significant portion of antibiotic misuse and overuse by healthcare providers to the extent that nearly 50% of antibiotics in nursing homes are prescribed inappropriately (Pulia et al., 2018). Thus, modern discourse in antibiotic stewardship programs across the nation is shifting blame on prescribers who allegedly prescribe precious drugs inappropriately and thus create a good environment for breeding drug-resistant strains as a result of selective pressure on bacteria (CDC, 2015).

Although inappropriate prescribing by healthcare providers is well documented in the literature and provides significant portion of drug-resistant strain development, it still remains unclear why certain areas of the US have higher antibiotic prescribing rates than the others (King et al., 2020). The question is of paramount importance because high degree of variations in antibiotic prescribing rates among the states cannot be explained by simply inappropriate prescribing practices by healthcare providers (King et al., 2020). Another connected question in this context is clustering of high prescribing rates in certain areas of the United States, namely in the Southern states, although it remains unclear which specific prerequisites or incentives prescribers have in those areas that predispose them to higher rates compared to other parts of the nation (King et al., 2020). This finding is puzzling even further by the fact that the southern region of the United States shows very little decrease in antibiotic prescribing rates over time compared to the other parts of the United States (King et al., 2020). Thus, modern discourse on antibiotic stewardship has been shaped based on the assumption that antibiotic prescribing is an individual choice of a prescriber and big variation in antibiotic prescribing rates is explained by inappropriate antibiotic use alone (King et al., 2020).

In my study I explored several notions of this discourse. First, I focused on outpatient rather than inpatient antibiotic prescribing rates simply because outpatient setting is the largest consumer of antibiotics: 85%-95% of antibiotics are prescribed in outpatient rather than inpatient settings (Duffy et al., 2018). Second, I chose to explore the process from a macro, societal perspective where the unit of analysis was a state rather than individual prescriber prescribing to individual patient (Szklo & Nieto, 2019). My goal in this study was to capitalize on "ecological fallacy" which quite often is referred by public health researchers as a major limitation of ecological studies stating that what matters in epidemiologic research is individual choices that people make and individual exposures which subsequently put them at risk (Szklo & Nieto, 2019). Individual exposures are called risk factors and later, during data analysis researchers may conclude which specific risk (rather than combination of risks) plays a role in inducing disease (Krieger, 1994). This statement reflects reductionist approach of modern medical schools which rarely take into consideration community-wide factors that create health-related problems (Krieger, 2011; Rivas et al., 2017). Reductionism in modern medical research almost exclusively targets individual choices to accomplish common goals in public health (Krieger, 2011). While this approach has dominated the landscape of epidemiologic research for decades, it has failed to address major multifactorial public health issues in the US such as epidemics of opioid use, obesity, diabetes, and even COVID-19 (an infectious disease with only one etiologic agent; Klement, 2020).

Therefore, in my study I diverged from the traditional individualistic approach and present the findings of “group settings” (i.e., states) to explain variability of antibiotic prescribing rates induced by socioeconomic factors using mediation analysis assuming that certain anthropogenic factors and environments (i.e., poverty and the environment created by it) create chronic health conditions which later influence antibiotic prescribing rates.

There is a large body of literature that describes relationship between social determinants (e.g., poverty) and chronic health conditions such as obesity, diabetes, and COPD, just to list a few (Montano, 2017). Although exact causes of chronic medical conditions such as diabetes, obesity, and COPD remain largely unknown to medical community, there is wealth of literature indicating on the link between the social determinants and chronic medical conditions affecting populations (Montano, 2017; Boyce et al., 2020). Moreover, there is literature that supports the evidence that certain social environments designated by zip codes predispose populations to chronic conditions and even to Sexually Transmitted Infections (Andreatos et al., 2017). On the other hand, there is also literature that indicates increased susceptibility to bacterial infections requiring antibiotic therapy among the patients diagnosed with chronic medical conditions (Bongers et al., 2019).

By researching literature about chronic medical conditions and the spatial patterns of their distribution, one may conclude that these conditions look like *syndemics*, meaning that they almost exclusively affect the same types of populations simultaneously (e.g., poor populations with high grades of social deprivation) across the globe (Mendenhall et al., 2017). According to Singer et al. (2017, p 942), *syndemic interaction* is a “co-occurrence of social and health conditions, including social-psychological, social-biological, and psychological-biological interactions, which worsen the condition of the person or population afflicted.” That means that social determinants create medical conditions in several different forms and different clinical presentations although with similar “*mechanisms of action*” (Krieger, 2011). This concept was clearly illustrated by Smith et al. (2020) in a paper where factor analysis was used to measure latent common factors leading to metabolic syndromes such as obesity and diabetes along with five others. The concept of syndemic indicating on the same latent factor behind most prevalent chronic diseases was the idea behind selecting chronic medical conditions for my study.

Literature on relationship between COPD and poverty indicate that (a) COPD is a common disease among smokers and (b) smoking is more prevalent among disadvantaged populations (Wheaton et al., 2017). However, Raju et al. (2019) conducted a cross-sectional study where authors confirmed that rural nonsmoker populations affected by poverty are also at increased risk of COPD. Another study looking at diabetes and social determinants during childhood concluded that the only social factor significantly associated with diabetes after age 60 was having no shoes during childhood, thus indicating epigenetic mechanisms involved in diabetes development (Carrillo-Vega et al., 2019). Studies conducted on obesity showed quite similar pattern in relation to poverty. For example, Ogden et al. (2017), using National Health and Nutrition Examination Survey data, showed that there is dose-response relationship between obesity and household income when it comes to females. Ogden et al. found that participants reporting ≤130% of federal poverty level showed the highest rate of obesity while the ones reporting ≥350% showed the lowest.

On another spectrum of the research, diseases listed above also predispose patients to higher frequency of antibiotic prescriptions compared to healthier patients, and further that these prescriptions are unlikely to be classified as antibiotic over and misuse (Stevermer et al., 2021). For example, the American Academy of Family Physicians recommends using antibiotics during acute exacerbations of COPD (Stevermer et al., 2021). As a result of recommendations like this, in their study, Butler et al. (2019) found that 77.4% of patients with COPD exacerbations received a prescription of antibiotic from primary care providers on a usual treatment arm in England and Wales when researchers tested effectiveness of C-reactive protein in determining the need for antibiotics.

However, because literature about antibiotic prescribing rates among diabetic and obese patients was nonexistent at the time of this study, I employed indirect measures of antibiotic prescribing. For example, by looking at studies that measure the risk of bacterial infections among diabetic and obese patients, one might get an insight on the amount of antibiotics that these two segments of patients may receive since bacterial infections are treated with antibiotics (Kim et al., 2019). It should also be noted that antibiotics prescribed to diabetic and obese patients cannot be classified as inappropriate antibiotic use either and cannot be targeted by antibiotic stewardship programs.

It has been known for decades that obesity and diabetes predispose patients to bacterial and viral infections (Andersen et al., 2016). While treating viral infections with antibiotics may clearly be classified as antibiotic overuse (given the fact that antibiotics are not effective against bacterial infections), treating bacterial infections among those patients can be quite justified from clinicians' and public health perspective (CDC, 2021a). For example, in a prospective cohort study examining the risk of surgical site infections among the patients undergoing total hip arthroplasty, Bongers et al. (2019) found that the risk of surgical site infections among severely obese patients was seven times higher than that of nonobese patients (24% vs. 3%). Based on these data, a reader may speculate that the amount of antibiotics prescribed to obese patients to treat surgical site infections (which are usually bacterial) following total hip arthroplasty would be seven times higher as well (Bongers et al., 2019). By applying Levin's concept and formula about population attributable risk, the practice of prescribing antibiotics for infections after a total hip arthroplasty in obese patients would translate into the higher probability of developing antibiotic resistant bacterial strains when prevalence of obesity is higher in a community (Szklo & Nieto, 2019).

Diabetes, as a major metabolite derangement, was also found to increase chances of developing bacterial infections which require antibiotic therapy. For example, Kim et al. (2019) in a matched case-control study found that diabetes increased odds of developing all kinds of bacterial infections including but not limited to central nervous system infections, infections of bone and joints, and surgical site infections.

The gap in literature is substantial. First, there are very few studies that describe amount of antibiotics used in clinical settings due to various underlying medical conditions among the patients. Second, there are conflicting data describing the size of an effect of underlying health conditions on antibiotic prescribing rates. Third, there are very few studies that explore the link between social determinants of health and antibiotic prescribing rates.

Therefore, my study was needed to estimate direct and indirect effects of poverty on antibiotic prescribing rates through mediators such as chronic health conditions (e.g. obesity, diabetes, and COPD). The study also shed the light on degree of antibiotic prescribing variability caused by social determinants, even though the data used in this study did not separate appropriate and inappropriate prescribing rates.

Problem Statement

The research problem was the fact that current modalities of reporting and quantifying antibiotic use in public health are based on a blunt measure of antibiotic prescribing rates such as antibiotic courses prescribed per 1,000 population provided by CDC (IQVIA data; CDC, n.d.a). The CDC's National Healthcare Safety Network (NHSN) is another program at CDC that also collects and analyzes antibiotic use data from hospitals through antibiotic use module where antibiotic prescribing rates are standardized using Standardized Antimicrobial Administration Ratio (SAAR) and later stratified by facility type, ward, antibiotic class, antibiotic type, and route of administration (van Santen et al., 2018). SAAR, provided by the CDC, calculates observed-to-expected ratio where expected number of regimens is derived from a negative binomial model (van Santen et al., 2018). Although standardization of rates is a useful idea for benchmarking purposes, patient-level factors such as underlying health conditions are not included in those models (van Santen et al., 2018). Thus, antibiotic prescribing rates advocated by CDC through NHSN and Antibiotic Resistance & Patient Safety Portal may be considered as blunt measures due to the fact that they do not take into account patient mix. Antibiotic stewardship programs widely promoted by CDC do not accentuate or discuss factors such as improving social determinants of health or the role of underlying health conditions even though underlying health conditions may theoretically mediate relationship between social determinants and antibiotic prescribing rates (CDC, n.d.a; van Santen et al., 2018). Thus, the research problem is the lack of evidence on mediating effects of underlying health conditions on antibiotic use and the overall effect of social determinants on inflating or deflating antibiotic prescribing rates in communities. Instead, antibiotic stewardship programs widely encourage prescribers to lower prescribing rates through preventing inappropriate antibiotic use (CDC, 2015). This approach undervalues the fact that substantial share of antibiotic prescriptions might not be classified as over- or misuse. This process might have dangerous consequences by rewarding prescribers/facilities with lower prescribing rates and penalizing the ones with high prescribing rates. In addition to that, this practice can also lead to obscuring and neglecting potential link between social determinants of health and antibiotic prescribing rates, thus focusing strictly on medical community rather than looking broadly at the problem through the lenses of social determinants.

The problem of antibiotic resistance is current with growing evidence indicating that high rates of antibiotic prescribing is the driving force of multidrug-resistant strain development (Wind et al., 2017). The problem is also current given the fact that today a pipeline of new antibiotics is drying up with very few drugs emerging on the market (Morel et al., 2020). Pharmaceutical companies often cite the lack of financial incentives to develop new antibiotics (Plackett, 2020). Antibiotic resistance is a growing public health threat that requires multidisciplinary approach which also includes tracking and analyzing data by public health practitioners and policymakers (CDC, 2015). Since the data currently collected by federal and state health departments are not adjusted for patient variation, it remains unclear what percentage of antibiotics can be classified as appropriate (justified from clinical grounds) and what percentage may not (classified as inappropriate antibiotic use; CDC, n.d.a). In addition to that, impact of social determinants on antibiotic use remains unclear to public health community as of today which shifts the blame of high antibiotic prescribing rates to prescribers and ignores the fact that high antibiotic prescribing might be caused by the factors unrelated to clinicians or healthcare facilities. Thus, reducing antibiotic prescribing rates might require broader look and systems thinking rather than largely focusing on antibiotic misuse and overuse as suggested by current mainstream public health science (CDC, 2015).

My research was not meant to counter previous research findings regarding antibiotic misuse and overuse and antibiotic prescribing rates as these issues documented previously that antibiotic misuse and overuse do increase antibiotic prescribing rates (CDC, 2015). My research rather built upon a current knowledge that in addition to antibiotic overuse and misuse commonly cited by CDC, antibiotic prescribing rates might be a function of yet another variable in the equation: social determinants of health and mediating effects of underlying health conditions capable of modifying antibiotic prescribing rates (Mölter et al., 2018). This is a largely underrated and under-investigated area of public health research.

The meaningful gap in current literature was the lack of research on effects of social determinants (and namely poverty) on antibiotic prescribing rates. Mediation effects of underlying health conditions, which might also modify the antibiotic prescribing rates, has also been underexplored. By investigating mediating effects of underlying health conditions on antibiotic prescribing through poverty, I sought to fill this gap in literature and provide insight on the multidimensional nature of antibiotic pharmacoepidemiology.

Purpose of the Study

I conducted a quantitative study. The intent was to explore mediating effect of underlying health conditions on relationship between poverty and antibiotic prescribing rates. The independent variable was prevalence of poverty as a percentage of population with household income <$24,999 across all 50 states. The dependent variable was outpatient antibiotic prescribing rates per 1,000 population in 50 states across the United States. The mediating variables were as follows: (a) prevalence of obesity as a percentage of population with body mass index (BMI) ≥ 30 across all 50 states; (b) prevalence of diabetes as a percentage of population ever being told by healthcare provider they have diabetes, across all 50 states; and (c) prevalence of COPD as a percentage of population ever being told by healthcare provider they have COPD, across all 50 states. The covariates included the prevalence of population aged ≥65 years across all 50 states and physician density per 100,000 population across all 50 states.

Research Questions and Hypotheses

Research Question 1: Is there an association between poverty and outpatient antibiotic prescription rates?

Null hypothesis: $H_0$1: There is no association between poverty and outpatient antibiotic prescription rates.

Alternative Hypothesis: H_a1: There is an association between poverty and outpatient antibiotic prescription rates.

Research Question 2: Is there an association between poverty and outpatient antibiotic prescription rates adjusted for aging population ≥65 years old, and physician density in states?

Null hypothesis: $H_0$2: There is no association between poverty and outpatient antibiotic prescription rates adjusted for aging population ≥65 years old, and physician density in states.

Alternative Hypothesis: H_a2: There is an association between poverty and outpatient antibiotic prescription rates adjusted for aging population ≥65 years old, and physician density in states.

Research Question 3: Do underlying health conditions (obesity, diabetes, COPD) mediate effect between poverty and outpatient antibiotic prescribing rates adjusted for aging population ≥65 and physician density in the states?

Null hypothesis: $H_0$3: Underlying health conditions (obesity, diabetes, COPD) do not mediate effect between poverty and outpatient antibiotic prescribing rates adjusted for aging population ≥65 and physician density in the states.

Alternative Hypothesis: H_a3: Underlying health conditions (obesity, diabetes, COPD) mediate effect between poverty and outpatient antibiotic prescribing rates adjusted for aging population ≥65 and physician density in the states.

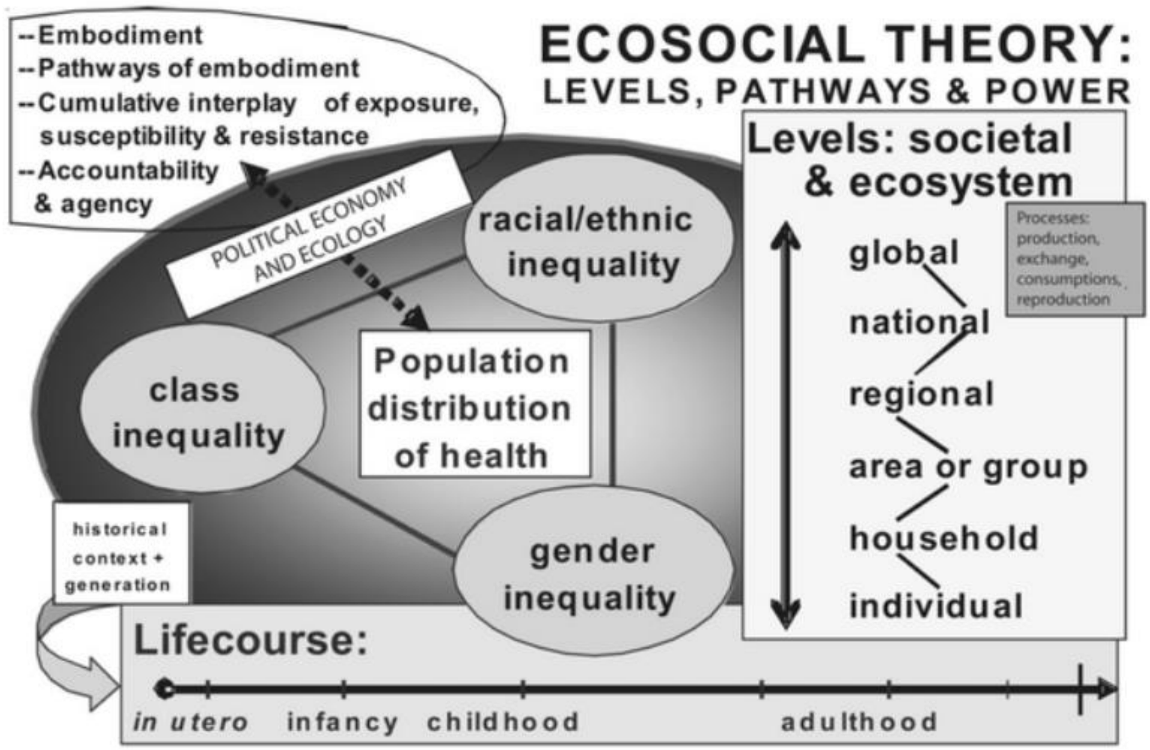
Theoretical Framework for the Study

My research was based on Nancy Krieger's ecosocial theory of disease distribution (Krieger, 2011). Although my research was not necessarily based on disease distribution but rather on using disease distributions as mediators for relationship between social determinants of health and antibiotic prescribing, this theory still fit nicely into overall idea of political ecology of antibiotic use (Krieger, 2011).

The theory of ecosocial disease distribution was developed by Nancy Krieger in 1994 and has four constructs: embodiment, pathways of embodiment, cumulative interplay of exposure, susceptibility, and resistance across the lifecourse, and accountability and agency (see Figure 1; Krieger, 1994). Ecosocial theory posits that the health and healthcare-associated factors do not function independently of the environment where people live and work, but rather are closely intervened by environmental and namely social factors and social determinants that modify the course and health status of individuals living in communities with certain characteristics (e.g., poverty, physician density, etc.; Krieger, 1994).

Figure 1

Ecosocial Theory and Core Constructs



Note. From *Epidemiology and the People's Health: Theory and Context*, by N. Krieger, 2011, Oxford University Press.

The idea of ecosocial theory is opposite to the discourse currently in place in modern medicine which posits that risk-factors of majority of diseases and namely of chronic diseases are associated with personal behavioral and genetic factors (Krieger, 1994). Ecosocial theory was suitable for my research because it explains relationships with the social environment from an epigenetic perspective which promotes a different discourse and namely a discourse of modifying phenotypic characteristics of individuals without alterations of genetic makeup (Waddington, 1968). This process subsequently leads to development of underlying health conditions which may potentially increase the rate of prescribed antimicrobials.

The major hypothesis in reference to ecosocial theory that I proposed was that social determinants modify antibiotic prescribing rates through mediating effects of diseases created and propagated by those social determinants. In other words, my research sought to extend ecosocial theory in a manner that recognizes mediating factors through which social determinants affect health of populations and subsequently antibiotic prescribing rates.

This theory was related to the study approach because my analysis was based on quantitative data and used the ecological study approach, which allowed me to quantify effects on populations rather than individuals on a macro, societal level (Szklo & Nieto, 2019). The ecological study design was well suited to answer the questions about variations in antibiotic prescribing rates depending on community rather than individual characteristics given the fact that the unit of analysis is a community (in my research it was a state; Szklo & Nieto, 2019).

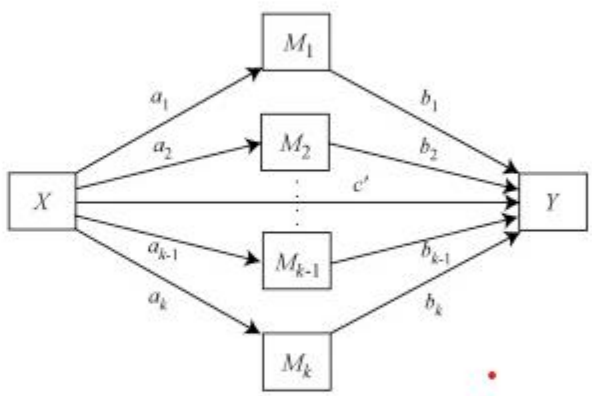
One of the constructs of ecosocial theory, namely pathways of embodiment, points towards the mechanisms by which social factors become embodied in individuals and transform their health (Krieger, 2011). In my research, this particular construct indicated how social determinants embody into antibiotic prescribing rates through mediators such as underlying health conditions (Krieger, 2011). Thus, ecosocial theory was a well-suited theory to fit my research approach and research question: Does social factor (e.g. poverty) have any relationship with antibiotic prescribing rates through mediating effects of underlying health conditions (e.g. COPD, obesity, and diabetes) on a macro, societal level?

Conceptual Framework

My conceptual framework is based on a model provided by Andrew Hayes (2018). The conceptual model below describes parallel mediation (Model 4) where X is an independent variable, Y is dependent variable, and M1 and M2 are mediators (Hayes, 2018).

Figure 2

Parallel Multiple Mediator Model



Note. From *(Hayes & Rockwood, 2017).*

Nature of the Study

My study was a cross-sectional study which prevents researchers from clearly establishing cause and effect relationship among the variables (Szklo & Nieto, 2019). However, in this case it is quite unlikely that effect (antibiotic prescribing) causes poverty or underlying health conditions such as obesity, diabetes, or COPD. Therefore, my study may potentially indicate a logical direction of events from exposure (poverty) to outcome (antibiotic prescribing) through mediating effects of underlying health conditions. For my research, I retrieved the data from Behavioral Risk Factor Surveillance System (BRFSS). BRFSS is a nationally representative survey of noninstitutionalized U.S. population that the CDC conducts on annual basis to measure health indicators of the U.S. population along with various behavioral and demographic factors (CDC, 2014). BRFSS data in my study was used as state prevalence estimates of variables such as poverty (defined as household income <$24,999), COPD, obesity, and diabetes. Outcome variable (outpatient antibiotic prescribing rates per 1,000 population) was retrieved from Antibiotic Resistance & Patient Safety Portal available from CDC where CDC posts data on antibiotics dispensed from community pharmacies (data provided by IQVIA on an annual basis; CDC, n.d.a). Covariates such as prevalence of population aged ≥65 years were obtained from BRFSS data, while physician density per 100,000 population by state was obtained from Association of American Medical Colleges (AAMC; CDC, n.d.b; AAMC, 2021).

The study design of my research was ecological where the unit of analysis was states (Szklo & Nieto, 2019). The ecological design of my study capitalized on so called “ecological fallacy” and makes it a strength rather than a limitation to explore relationship between independent and dependent variables using mediation analysis (see Hayes, 2018). The strength of mediation analysis is to identify direct and indirect effects generated by independent variable on dependent variable through mediators (in my study underlying health conditions; see Hayes, 2018).

Definitions

Poverty: a prevalence of population with annual household income <$24,999.

Outpatient prescribing rate: number of antibiotic courses prescribed per 1,000 individuals in a population in an outpatient setting.

Obesity: a prevalence of population with BMI ≥ 30.

Diabetes: a prevalence of population ever being told by healthcare provider that he/she has diabetes.

COPD: a prevalence of population ever being told by healthcare provider that he/she has COPD.

Elderly population: prevalence of population aged ≥ 65 years.

Physician density: number of physicians of all specialties per 100,000 population.

Assumptions

In my study, I made four core assumptions. First, I assumed that data provided by BRFSS were accurate and describe weighted prevalence of underlying health conditions in US population in each state. Second, I assumed that the responses provided by BRFSS respondents were accurate and described their income, age, and health indicators. Third, I also assumed that data provided by IQVIA and posted on Antibiotic Resistance & Patient Safety Portal of CDC were valid and described amount of antibiotics dispensed from community pharmacies throughout the nation. Last, I assumed that Association of

American Medical Colleges provides accurate data about physician density per 100,000 population in each state.

Scope and Delimitations

My study was based on secondary data. Therefore, I was limited to the variables provided by data sources and was unable to modify or redefine questions asked by CDC on BRFSS or antibiotic prescribing data. Further, my study did not differentiate inappropriately prescribed medications from appropriately prescribed ones given the fact that the secondary data source that I used provides only the aggregate rate of antibiotics dispensed. As such, the data about antibiotics dispensed per 1,000 individuals in the population may have some generalizability issues given the fact that it excludes antibiotics dispensed in inpatient settings and antibiotics dispensed from federal facilities.

Limitations

One major limitation of the study was the fact that it was based on ecological data analysis. Ecological studies are quite often classified as inferior to other observational studies because the unit of analysis is community level rather than individual level (Szklo & Nieto, 2019). This approach creates a so called ecological fallacy–when scientists have a hard time delineating effects on individual participants and instead have to draw conclusions based on community-wide exposures and outcomes (Szklo & Nieto, 2019). Therefore, the relationship between variables that my study explored cannot be attributed to individual participants of the study but rather the characteristics of individual states where they reside. Thus, ecological design is a blunt measure of exposure-outcome relationships and results of these studies should be interpreted with caution because they describe relationships on a community rather than individual levels (Szklo & Nieto, 2019).

This study may suffer from internal validity issues given the fact that response rate of BRFSS in 2019 was only 47.9% (CDC, 2021c). In addition to that, obesity rates produced by BRFSS have been reported to underestimate true prevalence rates reported by other national surveys where participants' measured height and weight were used rather than self-reported data (Hsia et al., 2020). For example, according to Hsia et al. (2020), self-reported height and weight of participants was potentially responsible for lower estimates of obesity prevalence while rates of diabetes were quite similar to National Health and Nutrition Examination Survey (NHANES) estimates. Therefore, the study may potentially have suffered from self-report bias given the fact that BRFSS is a telephone survey rather than medical records-based data source (CDC, 2014). However, as Hsia et al. (2020) reported, the differences between BRFSS and NHANES are unlikely to over or underestimate results obtained through BRFSS substantially. Another potential limitation was the fact that my study did not differentiate between diabetes Types 1 and 2, instead relying on a BRFSS question inquiring about diagnosis of any diabetes made by healthcare provider (see CDC, 2019b).

Construct validity likely did not affect the outcome measures given the fact that measuring antibiotic prescribing rate requires only the number of antibiotics dispensed from the pharmacies which is easily classifiable pharmacy data (CDC, n.d.a). In addition to that, BRFSS prevalence estimates have quite acceptable construct validities because they measure actual diagnosis (e.g., diabetes, COPD) reported by participants using yes/no format (CDC, 2019b). Additional variables in analysis (e.g. age and income of populations) were also unlikely to suffer from poor construct validity due to the fact that they measure quite specific participant characteristics in BRFSS without applying advanced measurement techniques (CDC, 2019b).

In ecological studies, there are numerous confounders that may complicate or obscure relationships between exposure and outcome variables (Szklo & Nieto, 2019). For example, in this particular study, there was a chance that those relationships are confounded by training of prescribers who prescribe antibiotics depending on their level of training, specialization, age, gender, diagnostic patterns, and prioritization of antibiotic stewardship issues given the fact that the outcome variable is an overall antibiotic prescribing rate in outpatient settings (combined rate for appropriate and inappropriate antibiotic prescriptions; Borek et al., 2020).

The study may also have suffered from small selection bias given the fact that IQVIA data provided by CDC only provides the number on antibiotics courses dispensed from community pharmacies for outpatient prescriptions and excludes antibiotic prescriptions dispensed from federal facilities (CDC, n.d.a).

Although there is always a chance that antibiotics picked up from pharmacies were not taken by the patients as directed, this was unlikely to affect the study results because this study measured antibiotics dispensed by pharmacies (reflecting prescribing rates) rather than antibiotics consumed (see CDC, n.d.a).

Finally, another limitation of the study is a small sample size because this study enrolled the 50 states of the United States and DC as units of analysis. Thus, sample size was 51.

To address confounders in a study, I included additional variables in my analysis as covariates such as prevalence of aging population (defined as population aged ≥65 years) and physician density in each state per 100,000 population. The rationale of including those two variables in analysis stemmed from the fact that (a) physician density may improve access to care and subsequently might also increase/decrease antibiotic prescribing rates, (b) elderly populations usually have higher healthcare visits compared to young populations and may also receive higher volume of antibiotic prescriptions (Streeter et al., 2020; Kabbani et al., 2018).

Significance of the Study

Current discourse of antibiotic stewardship is based on reducing sheer number of prescriptions and is based on assumption that prescribers are the only responsible party for high rate of antibiotics prescribed (CDC, 2015). Stewardship programs are focused on reducing inappropriate prescribing which makes lots of sense although this approach is missing a very significant piece of a puzzle: the patient mix (Ibrahim & Polk, 2012; Momattin et al., 2018). *Patient mix* is a term that describes the variety of patients being treated by healthcare providers (Ibrahim & Polk, 2012; Momattin et al., 2018). Patient mix is a very significant predictor of prescribing patterns which indicates that factors other than prescribers' behavior might inflate the number of antibiotics prescribed while this inflated amount cannot be labeled as inappropriate. On the other hand, social factors that underly chronic health conditions are behind patient mix. In other words, social factors that promote development of chronic health conditions may potentially inflate the number of antibiotics prescribed through indirect path. Therefore, modern antibiotic stewardship discourse does not involve systems thinking when addressing antibiotic prescribing because it is strictly focused on prescribers while ignoring social and medical patient-specific factors leading to high prescribing rates.

The significance of this study was dual. First, this study uncovered the relationship between underlying health conditions as potential drivers of high prescribers. This can further refine stewardship programs by designing patient-specific adjustment factors for benchmarking purposes. Second, this study assessed the effects of social environment, as measured by states, which is also amenable to social change through various policies and government actions. For example, if study had shown that relationship between physician density and antibiotic prescribing truly exists, this may lead to modifications of government policies in providing better physician-to-population ratios across the states and communities in an effort to reduce antibiotic prescribing.

Summary

In this chapter, I outlined the basic structure of my work including theoretical and conceptual framework along with a literature review to justify the use of variables in my analysis. I also provided research questions along with null and alternative hypotheses. In Chapter 2, I will provide a detailed literature review and data analysis plan.

Chapter 2: Literature Review

My problem statement was informed by the fact that high rate of antibiotic use creates selective pressure on bacteria which subsequently develop resistance (Wu et al., 2016; Wind et al., 2017). Therefore, reducing antibiotic prescribing rates is one of the paramount goals of modern public health discourse in an effort to save those medications for critically ill patients and future generations (López Romo & Quirós, 2019). Reducing antibiotic prescribing rates is also desirable due to adverse effects that antibiotics exert on patients in the form of allergy, *C. difficile* infection, and other medical conditions requiring inpatient and outpatient care (Czepiel et al., 2019; Dik et al., 2016).

This chapter is divided into three parts where every part represents the vertices of the triangle in mediation analysis. Though explained more in Chapter 3, Vertex 1 is that an independent variable exerts effects on a dependent variable (in the case of this research, the relationship between poverty and antibiotic prescribing). Vertex 2 is how an independent variable exerts effects on mediators (e.g., the relationship between poverty and mediators such as obesity, diabetes, and COPD). Vertex 3, then, is how mediators exert effects on a dependent variable (for this study, the relationship between the mediators and bacterial infections as proxy indicators of antibiotic prescribing).

Literature Search Strategy

For my study I accessed following library databases and search engines: PubMed, EBSCO, ProQuest, and ProQuest Central, Dissertations and Theses at Walden University, and Google scholar. I used key search terms in various combinations to identify research. These terms in combination included:

- *COPD* and *poverty* or *low-income* or *low socioeconomic* or *disadvantaged* or *poor* or *impoverished*;
- *Diabetes* and *poverty* or *low-income* or *low socioeconomic* or *disadvantaged* or *poor* or *impoverished*;
- *Obesity* and *poverty* or *low-income* or *low socioeconomic* or *disadvantaged* or *poor* or *impoverished*;
- *COPD* and *antibiotic use*, *COPD* and *antibiotic treatment*;
- *Obesity* and *antibiotic use*;
- *Diabetes* and *antibiotic use*;
- *Antibiotic use* and *poverty* or *poverty* or *low-income* or *low socioeconomic* or *disadvantaged* or *poor* or *impoverished*.

Literature search covered papers published during 2017-2021. Since there was no research and no data on the quantity of antibiotic use for obese and diabetic patients, I had to use proxy measure of antibiotic exposure for diabetic and obese patients. I choose to use bacterial infections among diabetic and obese patients assuming that they would almost always require antibiotic therapy (since bacterial infections are treated with antibiotics; Mushtaq & Kazi, 2020). Therefore, I also searched for following key terms: *Diabetes* and *infections*; *Diabetes* and *sepsis*; *Diabetes and community-acquired pneumonia*, *Diabetes* and *skin and soft tissue infections*; *Obesity* and *infections*; *Obesity* and *sepsis*; *Obesity* and *community-acquired pneumonia*; *Obesity* and *skin and soft tissue infections*.

Theoretical Foundation

My study was based on the ecosocial theory developed by Nancy Krieger in 1994. The theory is based on assumption that humans, much like any other biological creatures, are influenced by ecological and social environment which along with other factors have an ability to modify the health status of individuals living in certain environment and create diseases (Krieger, 1994). This is evidenced by the fact that certain social groups with quite similar genetic makeup show different rates of different diseases correlated to environmental factors (Jerram et al., 2017). Another evidence is that those diseases are clustered at certain locations and at certain environments indicating that epigenetic factors play much bigger role in disease development and progression than previously thought (Zang et al., 2021).

Krieger's theory has four constructs: embodiment, pathways to embodiment, cumulative interplay of exposure, susceptibility, and resistance across the life course and accountability and agency (see Figure 1; Krieger, 2011). The reason why I selected this theory was dual. First, it capitalized on the notion of ecological fallacy and posits that ecological and social factors are behind human health status (Krieger, 2011). This statement is supported by researchers who promote the epigenetic theory of disease causation and distribution (Lacal & Ventura, 2018). However, this entire approach is undervalued and underexplored by modern public health community which consistently promotes genetics and an individual risk-based approach to explain disease causation (Krieger, 1994). This idea of individual risk-based approach is embedded into the Rothman's disease causation pies, where necessary and sufficient causes of disease are considered as driving forces of disease development while ignoring environment as an essential element in the process (Krieger, 1994). In contrast to disease causation models, the idea of ecosocial theory fit nicely into my study's design because I chose to look at the problem of antibiotic prescribing from a macro societal perspective, given the fact that individual patient-level data may not completely explain high variability in prescribing rates (CDC, n.d.a). Although individual factors play significant role in antibiotic prescribing (e.g., physician's preference, specialty, age, training, patient-specific factors, etc.), it does not explain dynamic interplay of social and political economy of the community which might also drive antibiotic prescribing at record levels despite tireless efforts of CDC to prevent inappropriate antibiotic use through antibiotic stewardship programs (CDC, 2015). For example, physician density per 100,000 population in a state/community is a variable that can potentially influence access to care and subsequently the rate of antibiotic prescribing (Basu et al., 2019). This idea seems quite intuitive although hard to measure using study designs such as case-control or cohort study, because those study designs usually look at individual patient/prescriber characteristics and relationships between exposure and outcome variables at individual level (Szklo & Nieto, 2019). Thus, my choice to use ecological study fit with the ecosocial theory because I explored antibiotic prescribing from a macro perspective, considering environmental and social factors (Krieger, 2011).

Another fascinating feature of ecosoial theory, which directly applied to my study, was the construct called embodiment and most specifically the theory's attention to pathways of embodiment (see Krieger, 2011). The idea behind this construct is that social/ecological environment affects our body and there are different ways through which our body responds to stimulus from the environment (Krieger, 2011). For example, by creating unfavorable environment through deleterious social determinants, there are some individuals who develop diabetes, some who develop obesity, and the others develop COPD (Krieger, 1994). In my study, I hypothesized that mediators such as obesity, diabetes, and COPD are the pathways of embodiment with a end result of higher rates of antibiotic prescribing.

Conceptual Framework

Conceptual framework of this study is based on the parallel multiple mediator model effects where independent variable (poverty) exerts direct effect on dependent variable (antibiotic prescribing rates) and also indirect effect through mediators such as obesity, diabetes, and COPD (see Figure 2; Hayes, 2018).

Literature Review Related to Key Variables and/or Concepts

Association Between Poverty and Antibiotic Use

In my literature review, I reviewed research linking poverty as the independent variables and antibiotic prescribing rate as the dependent variable. There is limited literature on this topic. Van der Zande et al. (2019) conducted a qualitative study using purposive sampling of 41 general practitioners working in North-west England. Although this study was classified as qualitative research, it can be viewed as a mixed methods study where the goal of researchers was to investigate contextual factors (if any) behind antibiotic prescribing for three different categories of general practitioners: The ones with high, medium, and low rates of prescribing (Van der Zande et al., 2019). As it appears, physicians at all three different levels have different contextual factors leading them to high, low or medium prescribing rates. Although link between poverty and antibiotic prescribing was never discussed in this paper, it was obvious that contextual patient-specific factors made a difference in prescribing rates among physicians (Van der Zande et al., 2019).

In another study authored by Mölter et al., (2018) relationship between patient deprivation (measured using Index of Multiple Deprivation) and antibiotic prescribing was explored using the data from 7,216 general practitioners of England. This was a cross-sectional, ecological study that used the National Health Service (NHS) prescription services data of 2016 (Mölter et al., 2018). Using hot-spot analysis Mölter et al. (2018) concluded that the areas with high social deprivation in terms of income, education, and employment had 22% higher antibiotic prescribing rates ($p<0.001$) (Mölter et al., 2018). The study suffered from ecological fallacy and prevented researchers to investigate individual risks of patients associated with high antibiotic prescribing rates (Mölter et al., 2018). Besides, Index of Multiple Deprivation is a composite measure which also prevented Mölter et al. (2018) to explore effect of each social determinant on high prescribing rates.

In another cross-sectional, ecological study authored by Volpi et al. (2019) study authors looked at Medicare part D beneficiary data along with US census bureau to see whether patients' income at county level (prevalence of population with certain income levels) had any impact on antibiotic prescription rates. As Volpi et al. (2019) concluded, there was a dose-response relationship between income and antibiotic prescribing in unadjusted linear regression model (higher income was associated with reduced antibiotic prescribing), while model adjusted for age, gender, and race explained roughly 48% of variability of antibiotic prescribing ($p < 0.01$) and showed 15% reduction in antibiotic prescribing with every percent increase in prevalence of populations with annual income ≥$65,000 (Volpi et al., 2019). Study had serious limitations: ecological fallacy which prevented authors from exploring individual patient-level data; Self-reported data on income, poor representation of the entire US population, and inability to adjust on additional variables except for age, gender, and race due to the fact that authors used secondary data (Volpi et al., 2019).

Although studies listed above showed clear relationship between income and antibiotic prescribing rates, Petersen et al. (2021) showed no statistically significant relationship between poverty and antibiotic prescribing rates (adjusted prevalence ratio: 1.1; 95% Confidence intervals: 0.8, 1.4) (Petersen et al., 2021). Moreover, trends in antibiotic use did not vary significantly between populations above or below poverty level (Petersen et al., 2021). Study authors used National Health and Nutrition Examination Survey (NHNES) data to examine prevalence of non-topical antibiotics used within the past 30 days, trends in the prevalence of antibiotic use compared to previous rounds of NHNES, and the factors associated with antibiotic use (Petersen et al., 2021). Major strength of a study was a large sample size (with 96,766 participants aged >16 years) and nationally representative sample (Petersen et al., 2021). Limitation of a study was a self-reported information on antibiotic use within the past 30 days (Petersen et al., 2021).

Linking Poverty with Mediators

Poverty and Obesity

Kim et al. (2020) conducted a cross-sectional study using Healthy Communities Study data to examine relationship between neighborhood community characteristics and obesity among children. As Kim et al. (2020) concluded, living in a wealthy neighborhood protected children from obesity if the socio-economic status of a family was high ($\beta=-0.22$, $p<0.01$). Protective effect was not observed among children from poor families living in a wealthy neighborhood indicating that family's income was a major determinant of obesity rather than neighborhood characteristics in preventing obesity (Kim et al., 2020). The study's major limitation was the fact that Healthy Communities Study is not a nationally representative sample, while the major strength was the sample size (4,114 children enrolled) (Kim et al., 2020).

In another cross-sectional study authored by Fan et al. (2019) authors explored relationship between neighborhood characteristics and obesity using the National Health and Nutrition Examination Survey (NHANES) and US census data. In this analysis authors demonstrated that neighborhood socio-economic status had a strong relationship with obesity for women (41.7% prevalence of obesity in poor communities vs. 26.4 in a wealthy communities) but not for men (30.8 vs. 26.8; Fan et al., 2019). The major strength of the study was the fact that NHANES actually measures participants' height and weight and does not rely on self-reported data (Fan et al., 2019).

Quite similar finding was observed by Zare et al. (2021) where authors found that income inequality (measured by Gini index of a community) had strong relationship with obesity among women but not among men in Modified Poisson regression analysis. Zare et al. (2021) also used NHANES data (cross-sectional) for their study. The strength of their study was a large sample size (data from 36,665 adults) and the nationally representative data (Zare et al., 2021). The limitation was the fact that income in NHANES is reported as a categorical rather than continuous variable which limits researchers' ability to explore full extent of its effects on obesity (Zare et al., 2021).

Testa et al. (2019) explored relationship between waist-to-height ratio as a better substitute for BMI to measure obesity and food insecurity using National Longitudinal Study of Adolescent to Adult Health and Modified Retail Food Environment Index (CDC). According to Testa et al. (2019), living in a food desert (as a substitute for poor socio-economic neighborhood) was associated with higher odds of developing higher waist-to-height ratio among males and females in a logistic regression analysis adjusted for various confounders (adjusted odds ratio: 1.2, 95%CI: 1.1, 1.4). The major strengths of the study were the fact that this survey explored risk-factors among the same participants in four different waves (prospective cohort study design) and a large sample size (N=20,000; Testa et al., 2019). Limitation is the fact that obesity is manifested in a later stages of life rather than during adolescence (Testa et al., 2019).

Poverty and Diabetes

In a longitudinal study conducted by Carrillo-Vega et al. (2019) using third and fourth Mexican Health and Aging Study (MHAS) data. Study enrolled 8,848 adults aged >50 years. In logistic regression analysis adjusted for various factors not having shoes (as an indicator of poverty during childhood) was associated with 1.47 odds of developing diabetes with 95% CI:1.16, 1.86 (Carrillo-Vega et al., 2019). The study indicates that childhood poverty plays major role in developing diabetes at advanced age (Carrillo-Vega et al., 2019). The major limitation of the study was a potential for recall bias among study participants (Carrillo-Vega et al., 2019).

In another study authored by Consolazio et al. (2020) with an ecological design (cross-sectional study) neighborhood property value was associated with the risk of type 2 diabetes development. Consolazio et al. (2020) used Maastricht (Netherlands) Study data along with statistics Netherlands to calculate risk of diabetes. As authors reported, the residents of neighborhoods with lowest property value were 2.38 times more likely to develop diabetes (95% CI: 1.58, 3.58) compared to the residents of the neighborhoods with highest property value (Consolazio et al., 2020). The biggest limitation of the study was a cross-sectional design which prevented researchers from exploring cause-effect relationship between diabetes and residence (Consolazio et al., 2020). There is also a possibility of reverse causation which could affect the study results given the fact that it was a cross-sectional design (Consolazio et al., 2020).

In another ecological study Jacobs et al. (2019) linked area deprivation index of communities in Germany (a composite score made of 7 indicators) to type 2 diabetes incidence. In logistic regression model Jacobs et al. (2019) found that the odds of developing diabetes was pretty similar for males (adjusted odds ratio: 2.41) and females (adjusted odds ratio: 2.40) and was higher for the ones living in the most deprived areas (Jacobs et al., 2019). The limitation of the current study was cross-sectional design along with ecological data and the use of a composite measure which prevented researchers from evaluating effects of separate indicators of deprivation score (Jacobs et al., 2019).

As it appears, according to Berkowitz et al. (2018), food insecurity (as an indicator of poverty) does not only induce diabetes (by rather unknown mechanism) as suggested by previous studies, but it also makes glycemic control more challenging. Based on a longitudinal, prospective cohort study conducted by Berkowitz et al., (2018), patients experiencing food insecurity had higher HbA1c (glycated hemoglobin ─ an indicator of glucose levels for the last 3 months) levels compared to those who did not experience food insecurity (7.6% vs. 7.0%) and this level showed no improvement over time ($p = 0.5$) (Berkowitz et al., 2018). Study authors enrolled 391 diabetic adults aged >21 years from four clinics of Massachusetts and followed the cohort for 37 months (Berkowitz et al., 2018). Limitation of the study included potential for self-report bias and subjective interpretation of being food insecure (Berkowitz et al., 2018). Additionally, food insecurity was estimated only once during the entire study (Berkowitz et al., 2018). Thus, there is a possibility that it was changing over time (Berkowitz et al., 2018).

Poverty and COPD

In a prospective cohort study authored by Borne et al. (2019) researchers followed 117,479 residents of Malmoe (Sweden) aged 40-89 for 14 years to estimate relationship between patient-specific characteristics and discharge diagnosis of COPD. As Borne et al. (2019) noted, there was a dose-response relationship with income and COPD diagnosis at hospital discharge for smoker patients, but not for non-smokers: Lower income residents and the residents who rented apartment had a higher risk of COPD (hazard ratios 2.23 and 1.41 respectively; Borne et al., 2019). The strength of the study was a large sample size and a medical record-based diagnosis and exposure factors (Borne et al., 2019). Major limitation was inability to measure intensity of smoking, medications used, and lifestyle changes for 14 years of observation (Borne et al., 2019).

Axelsson Fisk and Merlo (2017) put these studies a step further by exploring relationship between COPD hospitalizations and absolute vs. relative income using National Inpatient Register and National Board of Health and Welfare of Sweden datasets. For populations of Sweden aged 55-60 years absolute rather than relative income was highly predictive of hospitalization risk due to COPD as illustrated by receiver operator curve (0.65 vs 0.55) while both measures showed statistically significant relationship in logistic regression model with COPD risk, meaning that poor populations, as measured by absolute income had higher risk of being hospitalized with COPD (Axelsson Fisk & Merlo, 2017).

Although Borne et al. (2019) showed statistically significant relationship between income and COPD diagnosis at discharge for smokers, Raju et al. (2019) in their study noted that the positive relationship between COPD and poverty exists even for non-smokers. In a cross-sectional study conducted using National Health Interview Survey data Raju et al. (2019) concluded that residing in a poor, rural area was associated with 1.34 odds ($p < .01$) of developing COPD even for non-smokers. Overall, rural and poor areas had the prevalence of COPD almost twice as high as urban and wealthy areas (15.4% vs. 8.4%; Raju et al., 2019). The major strength of the study was nationally-representative sample, while limitation was self-reported data and cross-sectional design (Raju et al., 2019).

Boyce et al. (2020) on the other hand found, inverse relationship between the county-level prevalence of poverty and age-adjusted mortality due to COPD in ecological study using death certificate data from the state of Texas. In Pearson correlation age-adjusted deaths due to COPD showed negative, but statistically significant correlation with poverty (R = -0.211, p < 0.01) potentially due to Hispanic paradox, but positive correlation with the county-level prevalence of smoking (R = 0.501, p < 0.01) (Boyce et al., 2020). The major limitation of the study was ecological fallacy (Boyce et al., 2020).

Linking Mediators to Antibiotic Therapy Using Bacterial Infections as a Proxy Measure

Obesity and Infections

Hussain et al. (2019) conducted a case-control study to compare prevalence of surgical-site infections (SSI) among obese and non-obese patients where obesity was defined as a BMI ≥30. Hussain et al., (2019) enrolled 152 cases and 152 controls from Royal Hobart Hospital (RHH) who went through elective surgical procedures during 2012-2016. Although the difference between obese and non-obese did not reach statistical significance, SSI prevalence among obese patients was twice as high as the prevalence among the non-obese: 8.6% vs 4.6%; p = 0.25. (Hussain et al., 2019). Hussain et al. (2019) also noted that doses of pre-operative antibiotic prophylaxis required for obese patients were higher than for non-obese patients indicating that obese patients use more antibiotics and those additional doses cannot be classified as “inappropriate antibiotic therapy". The biggest limitation of the study was a small sample size which potentially would have prevented the difference between obese and non-obese patients to reach statistical significance (Hussain et al.,2019).

Hsu et al. (2018) conduced a case-control study to evaluate relationship between obesity and urinary tract infection among 472 children aged <2 years who presented to emergency department with fever (defined as ≥ 38°C). Urinary tract infection is a condition that is usually caused by bacterial organisms and requires antibiotic therapy (Hsu et al., 2018). As Hsu et al. (2018) concluded, obese children where 2.46 (95% CI: 1.54, 3.93) times more likely to develop urinary tract infections than non-obese children. Strength of the study was the fact that authors relied on medical records rather than self-reported data of patients/parents, while the major limitation was a small sample size (Hsu et al., 2018).

In another study also conducted on young population aged 2-20 years Okubo et al. (2018) enrolled 133,602 children from KID's Inpatient database (national pediatric inpatient database KID) to investigate impact of obesity on lower respiratory tract infections and their severity. As Okubo et al. (2018) concluded, obesity increased the risks of mechanical ventilation and comorbid bacteremia and septicemia (adjusted OR 1.58, 95% CI: 1.03, 2.44). That being said, it is quite intuitive that obese children would require antibiotic therapy at higher frequency and with higher doses than non-obese children (Okubo et al., 2018). The biggest strength of this study was a large sample size and reliance on medical documentation while limitation was potential miscoding/undercoding of bacteriemia and septicemia, or alternatively: underreporting of obesity in discharge diagnosis codes (Okubo et al., 2018).

Periodontal disease – another medical condition requiring antibiotic therapy was observed to be highly correlated with obesity as Deshpande and Amrutiya (2017) suggested in their cross-sectional study. In their study Deshpande and Amrutiya (2017) enrolled 100 patients aged >18 years during 2015-2016 where half of their participants were obese and another half were non-obese (obesity measured by BMI and waist circumference). Obese patients had significantly higher scores on all metrics used in dentistry to measure periodontal disease on two-sample independent *t* test (Deshpande & Amrutiya, 2017). Although study suffered from major limitations such as maladjustment for various confounders, small sample size, and non-blinded design for investigators and evaluators, it demonstrated that obese patients are more likely to suffer from oral health issues that require appropriate antibiotic therapy (Deshpande & Amrutiya, 2017).

Diabetes and Infections

Kim et al. (2019) conducted a matched case-control study to compare risks of infections and its complications among diabetic and non-diabetic patients. Researchers used National Health Insurance Service-National Sample Cohort with 199,278 patients' data and concluded that adjusted for demographic and comorbid conditions diabetic patients had the 10.17 incidence rate ratios (IRR) of developing hepatic abscess, 8.72 IRR of infections of central nervous system, and 3.52 IRR of skin and soft tissue infections (Kim et al., 2019). The major strength of the study was a big sample size and the fact that it used population-based data (Kim et al., 2019). Limitations included: not being able to distinguish between type 1 and 2 diabetes, and not being able to adjust for various confounders such as obesity and smoking, and severity of diabetes (Kim et al., 2019).

Guo and Shen (2021) investigated 397 trauma patients in a retrospective cohort study to find out effect of HbA1c levels on sepsis and mortality. As Guo and Shen (2021) concluded, HbA1c levels higher than 6.5% increased odds of developing sepsis (76.1% vs 35.9%, $p < 0.001$). Authors also found that one of the biggest risk-factors of developing sepsis was diabetes (odds ratio: 3.1; Guo & Shen, 2021). Major limitation of the current study was a small sample size and a potential for misclassification bias because HbA1c test results were not available for all patients in a study (Guo & Shen, 2021).

Abu-Ashour et al. (2018) conducted a matched cohort study where authors investigated a risk of infection development among 12,845 cohort of patients based on Canadian Primary Care Sentinel Surveillance Network (CPCSSN) database. As Abu-Ashour et al. (2018) reported, in logistic regression analysis after adjustment for several demographic factors diabetic patients had increased risk of all types of infections compared to non-diabetic patients (adjusted odds ratio = 1.21, 95% CI: 1.07, 1.37). The major limitation of the study was a potential misclassification bias given the fact that diabetic patients may utilize medical services at a higher rate and may in fact get diagnosed with infections more often than non-diabetic patients (Abu-Ashour et al., 2018). Another misclassification bias could be underdiagnosis of diabetes and underdiagnosis of infections while major strength was a large sample size (Abu-Ashour et al., 2018).

Although all previous studies looking at the link between infections (and especially bacterial infections) and diabetes claim that diabetes significantly increases the odds of infection development, study conducted by Wang et al. (2021) claims that there is no causal link between diabetes type 2 alone and bacterial infections such as sepsis, pneumonia, skin and soft tissue infections. Wang et al. (2021) conducted a two-sample Mendelian randomization on 659,316 patients where Mendelian randomization showed no relationship between type 2 diabetes and bacterial infections: for sepsis: $p = 0.9$; for pneumonia $p = 0.2$; for urinary tract infections: $p = 0.2$. (Wang et al., 2021). The major strength of the study was a large sample size while limitations included issues with generalizability because the study covered only the population with European origin (Wang et al., 2021).

COPD and Antibiotic Therapy

Thu et al. (2021) conducted an open-label randomized controlled trial where exposure variable was using fluoroquinolone and beta-lactam antibiotics and the outcome variable was clinical and bacteriological efficacy at day 20 against exacerbations of COPD. The trial enrolled 139 patients aged >45 years diagnosed with COPD (stages I-IV) and randomized them to fluoroquinolone and fluoroquinolone plus beta lactam groups (Thu et al., 2021). Study showed that monotherapy was as effective as combination therapy in clinical improvement of signs and symptoms and in vast majority of cases COPD exacerbations were caused by bacteria (*S. pneumoniae*, *H. influenzae*, *P. aeruginosa*, and *A. baumannii*) that could be targeted and treated with antibiotics (Thu et al., 2021). The major limitation of a study was the absence of control groups and inability to adjust for severity factors (Thu et al., 2021).

Apart from a study conducted by Thu et al. (2021), other studies showed high prevalence of antibiotic use for COPD patients. For example, Tichter and Ostrovskiy (2018) in their cross-sectional study covering 4.5 patients admitted to ER measured the prevalence, trends, and predictors of antibiotic therapy among COPD patients using National Hospital Ambulatory Medical Care Survey (NHAMCS) data. As Tichter and Ostrovskiy (2018) concluded, antibiotics were prescribed to roughly 39% of patients diagnosed with acute exacerbations of COPD and trends did not fluctuate significantly over time. Major limitations of the study were reliance on secondary data where misclassification of codes is quite common and besides, there is a chance that antibiotics prescribed to the patients were prescribed for a different reason and prior to admitting to ER (Tichter & Ostrovskiy, 2018).

In another study Stevermer et al. (2021) conducted a systematic review of randomized controlled trials to find out the evidence on success of therapeutic measures commonly used to treat acute exacerbations of COPD using database Inception. Stevermer et al. (2021) concluded that pulled effect of antibiotic therapy was substantial in clinical improvement of signs and symptoms (odds ratio: 2.03; 95% CI: 1.47, 2.80).

Thus, current evidence suggests that antibiotics prescribed to patients diagnosed with COPD are quite justified and appropriate from clinical perspective.

Covariates: Age and Physician Density

Kabbani et al., (2018) conducted a cross sectional study using IQVIA data to explore characteristics of populations for whom antibiotics were dispensed in outpatient settings during 2011-2014. As Kabbani et al. (2018) reported, amount of antibiotics dispensed to populations aged ≥75 was the highest than among populations aged 65-74 years and was enough to medicate every single person in that particular age group (1,157 prescriptions per 1,000 population). The major limitation of the study was the fact that data used for analysis did not differentiate appropriate from inappropriate antibiotics use, and besides these data do not reflect the actual antibiotics consumed, it only described the antibiotics dispensed from community pharmacies (Kabbani et al., 2018). This study indicates that aging population is the largest consumer of antibiotics and age as a covariate must be included in analysis of this project (Kabbani et al., 2018).

Another reason why including age as a covariate is needed in my analysis is the fact that the rate of chronic conditions included in my study also continuous to increase with advanced age. For example, according to the National Diabetes Statistics Report (CDC, 2022b) crude prevalence of diabetes shows dose-response relationship with variable age and is the highest for persons aged ≥65 years (26.8%). Thus, age as a confounder must be considered in this type of analysis.

Physician density is a measure associated with improved access to care and improved health outcomes (Basu et al., 2019). In a cross-sectional, ecological study authored by Basu et al. (2019) study authors used the data from American Medical Association Physician and US Census Bureau to investigate whether physician supply had any effect on mortality of populations. As Basu et al., (2019) concluded in Mixed-Effects Models, addition of 10 primary care providers resulted in increased life expectancy by 51.5 days. The major limitation of a study was ecological fallacy where unit of analysis was a county-level information (Basu et al., 2019). This study indicates that physician supply may increase access to care and improve health outcomes (Basu et al., 2019). Thus, including physician density in my analysis was justified on the grounds that physician density and the prevalence of aging population (aged ≥65 years) may serve as confounders and must be included in analysis as covariates.

Summary and Conclusions

In this chapter I provided evidence that independent variable such as poverty may be related to antibiotic prescribing (Mölter et al., 2018). Mediators such as obesity, diabetes, and COPD are also associated with antibiotic prescribing due to the fact that they increase the odds of bacterial infection development such as sepsis, surgical site infections, pneumonia, etc. (Kim et al., 2019; Stevermer et al., 2021). Chronic conditions listed above are also related to poverty and in fact, are the “outcomes” of poor socio-economic conditions (Fan et al., 2019; Raju et al., 2019). In other words, conceptual framework that I am proposing is based on mediating effects of underlying health conditions through which social and economic factors such as obesity may exert their effects on antibiotic prescribing rates. Literature review that I provided has one major limitation: There are no studies that measure antibiotic prescribing rates among patients diagnosed with obesity and diabetes. Thus, I had to use bacterial infections as a proxy measure of antibiotic use given the fact that bacterial infections such as surgical-site infections, pneumonia, skin, and soft tissue infections are usually treated with antibiotics (Wilson et al., 2019). Using antibiotics for those types of infections (i.e. caused by bacterial organisms) cannot be classified as inappropriate antibiotic use (Wilson et al., 2019). If studies indicate that underlying health conditions such as diabetes and obesity predispose patients to frequent bacterial infections, the logical consequence of this fact would be higher than expected frequency of antibiotic use by healthcare providers. Another logical conclusion is that healthcare providers treating high volume of patients diagnosed with diabetes and obesity would naturally have higher prescribing rates of antibiotics. Therefore, targeting providers like this by antibiotic stewardship programs would be unlikely to produce reduction in antibiotic prescribing rates. This study was planning to test hypothesis that high prevalence of chronic medical conditions such as obesity and diabetes would increase antibiotic prescribing rates.

COPD, another chronic condition in this study also requires antibiotic therapy during exacerbations (Stevermer et al., 2021). Thus, there was no need to use proxy measure such as frequency of bacterial infections to demonstrate the need of antibiotic therapy in this particular group of patients. Although there is still an evidence that COPD patients are often treated inappropriately with antibiotics, overall using antibiotics for COPD exacerbations cannot be labeled as “inappropriate antibiotic use” (Stevermer et al., 2021).

As far as using age and physician density as covariates, there is literature that indicates on importance of variable age as a factor associated with mediators and outcome measure of this study (Kabbani et al., 2018; CDC, 2022b). Although there is significant gap in literature on impact of physician density on antibiotic prescribing rates, this variable is expected to play significant role in model adjustment process because low density would lead to poor access to healthcare resources, lower/higher prescribing rates, and confound relationship between exposure and outcome variables (Basu et al., 2019).

Chapter 3: Research Method

In this chapter, I evaluate the association between poverty (independent variable) and the rate of antibiotic prescribing (dependent variable). Mediators such as obesity, diabetes, and COPD have been found to be associated with antibiotic prescription due to the fact that they increase the odds of bacterial infection development (e.g., sepsis, surgical site infections, pneumonia, etc.; Kim et al., 2019; Stevermer et al., 2021). The chronic conditions listed above are also related to poverty and, in fact, are outcomes of poor socioeconomic conditions (Fan et al., 2019; Raju et al., 2019). In other words, the conceptual framework that I used is based on mediating effects of underlying health conditions through which social and economic factors such as obesity may exert their effects on antibiotic prescribing rates.

My literature review had one major limitation: There are no studies that measure antibiotic prescribing rates among patients diagnosed with obesity and diabetes. Thus, I had to use bacterial infections as proxy measure of antibiotic use given the fact that bacterial infections such as surgical-site infections, pneumonia, skin, and soft tissue infections are usually treated with antibiotics (Wilson et al., 2019). Using antibiotics for those types of infections (i.e., caused by bacterial organisms) cannot be classified as inappropriate antibiotic use (Wilson et al., 2019). If studies indicate that underlying health conditions such as diabetes and obesity predispose patients to frequent bacterial infections, the logical consequence of this fact would be higher than expected frequency of antibiotic use by healthcare providers. Another logical conclusion is that healthcare providers treating high volume of patients diagnosed with diabetes and obesity would naturally have higher prescribing rates of antibiotics. Therefore, targeting providers like this by antibiotic stewardship programs would be unlikely to produce reduction in antibiotic prescribing rates. This study tested the hypothesis that high prevalence of chronic medical conditions such as obesity and diabetes will increase antibiotic prescribing rates.

COPD, another chronic condition in this study, also requires antibiotic therapy during exacerbations (Stevermer et al., 2021). Thus, there was no need to use proxy measure such as frequency of bacterial infections to demonstrate the need of antibiotic therapy in this particular group of patients. Although there is still evidence that COPD patients are often treated inappropriately with antibiotics, overall using antibiotics for COPD exacerbations cannot be labeled as inappropriate antibiotic use (Stevermer et al., 2021).

As far as using age and physician density as covariates, there is literature that indicates the importance of the variable age as a factor associated with mediators and outcome measure of this study (see Kabbani et al., 2018; CDC, 2022b). Although there is significant gap in literature on impact of physician density on antibiotic prescribing rates, this variable was expected to play significant role in model adjustment process because low density would lead to poor access to healthcare resources, lower/higher prescribing rates, and confound relationship between exposure and outcome variables (Basu et al., 2019).

Research Design and Rationale

In this study, the independent variable was prevalence of poverty (defined as the prevalence of population with household income < $24,999) and the dependent variable was outpatient antibiotic prescribing rates per 1,000 population in 50 states across the US. There were three mediators in the study: prevalence of obesity, COPD, and diabetes across all 50 states. There were two covariates: prevalence of aging population defined as the prevalence of population aged ≥65 years, and physician density by state per 100,000 population.

This was a quantitative, cross-sectional study with ecological design, meaning that the study unit was a state's population rather than individual patient-level data. The research questions sought the relationship between the prevalence of poverty and antibiotic prescribing rates mediated by certain chronic health conditions and adjusted for two covariates (elderly population and physician density), which were also measured using the state prevalence data across all 50 states.

The design choice was consistent to advance knowledge in this discipline due to several reasons: First, there are no individual patient-level data available to draw relationship between poverty and antibiotic prescribing rates through mediatory effects of chronic health conditions. Second, ecological design helps explain complex relationships between variables within the environmental context where they operate (Szklo & Nieto, 2019). For example, effect of physician density on antibiotic prescribing in each state is impossible to measure in other study designs while in ecological design, it can help to explain variability of antibiotic prescribing rates across different states because it defines availability of physicians and the access to care across all 50 states (Basu et al., 2019). Thus, an ecological, cross-sectional study provided a snapshot of current prescribing rates in different states influenced by independent variable, covariates, and mediating variables.

Methodology

The target population of this study is the entire United states. Study unit ─ individual state, rather than individual patient. Population size determination was not necessary given the fact that this study enrolled all 50 states. Sampling of population/states was not conducted and all 50 states and DC were enrolled in the study.

For this study data provided by several sources were used. More specifically: BRFSS (CDC), Antibiotic Resistance & Patient Safety Portal (CDC), and physician density by state (Association of American Medical Colleges). The data on point estimates for each variable describing prevalence in each state are available publicly from those highly reputable agencies and there was no cost associated with their acquisition and use.

Operationalization

- Operational definition of poverty: household income <$24,999.
- Operational definition of obesity: Body Mass Index (BMI) ≥ 30.
- Operational definition of diabetes: ever being told by healthcare provider to have diabetes.
- Operational definition of COPD: ever being told by healthcare provider to have COPD.

- Operational definition of antibiotic prescribing rate: antibiotic courses dispensed in community pharmacies.
- Operational definition of elderly population: population aged ≥ 65 years.
- Operational definition of physician density: number of physicians per 100,000 population.

Data Analysis Plan

For data analysis, I used SPSS and a macro created by F. Hayes called Process specifically designed for mediation analysis. Data cleaning and screening procedures were not applicable to the current study because the study used all point estimates provided in the datasets.

Research Question 1: Is there an association between poverty and outpatient antibiotic prescription rates?

Null hypothesis: $H_0 1$: There is no association between poverty and outpatient antibiotic prescription rates.

Alternative Hypothesis: $H_a 1$: There is an association between poverty and outpatient antibiotic prescription rates.

Statistical tests that are used to test the hypothesis: Linear regression using ordinary least squares method. The essential procedure that is used prior to running linear regression analysis is checking for assumptions of linear regression as a required procedure. Interpretation of linear regression analysis results was conducted in the light of widely accepted principles such defining statistically significant relationship between variables as low as p value less than 0.05. Effect size was defined using the size of a R^2.

Research Question 2: Is there an association between poverty and outpatient antibiotic prescription rates adjusted for aging population ≥65 years old, and physician density in states?

Null hypothesis: $H_0 2$: There is no association between poverty and outpatient antibiotic prescription rates adjusted for aging population ≥65 years old, and physician density in states.

Alternative Hypothesis: $H_a 2$: There is an association between poverty and outpatient antibiotic prescription rates adjusted for aging population ≥65 years old, and physician density in states.

Statistical tests that were used to test the hypothesis: Multiple Linear regression using ordinary least squares method. The essential procedure that was used prior to running linear regression analysis is checking for assumptions of linear regression as a required procedure. Interpretation of linear regression analysis results was conducted in the light of widely accepted principles such defining statistically significant relationship between variables as low as p value less than 0.05. Effect size was defined using the size of a R^2.

Rationale for inclusion of potential covariates and/or confounding variables: Inclusion of physician density and aging population is necessary because they may serve as significant cofounders. There was a possibility that states with higher prevalence of aging population or physician density may in fact, had higher antibiotic prescribing rates (Basu et al., 2019; Kabbani et al., 2018). Adjusted analysis took care for confounding effects of aging population and physician density.

Research Question 3: Do underlying health conditions (obesity, diabetes, COPD) mediate effect between poverty and outpatient antibiotic prescribing rates adjusted for aging population ≥65 years old and physician density in the states?

Null hypothesis: $H_0$3: Underlying health conditions (obesity, diabetes, COPD) do not mediate effect between poverty and outpatient antibiotic prescribing rates adjusted for aging population ≥65 years old and physician density in the states.

Alternative Hypothesis: H_a3: Underlying health conditions (obesity, diabetes, COPD) mediate effect between poverty and outpatient antibiotic prescribing rates adjusted for aging population ≥65 years old and physician density in the states.

Statistical tests that were used to test the hypothesis: Parallel mediation analysis adjusted for covariates (physician density and aging population) using SPSS. In mediation analysis direct and indirect effects along with total effects were measured.

Rationale for inclusion of potential covariates and/or confounding variables: Inclusion of physician density and aging population was necessary because they may have served as significant cofounders (Basu et al., 2019; Kabbani et al., 2018). There is a possibility that states with higher prevalence of aging population or physician density may in fact have higher antibiotic prescribing rates (Basu et al., 2019; Kabbani et al., 2018). Adjusted analysis took care for confounding effects of aging population and physician density.

Including chronic health conditions in mediation analysis helped to identify mediatory effects of chronic health conditions on relationship between poverty and antibiotic prescribing rates.

Table 1

Variables and Their Measurements Used in the Study

List of variables	Type of variable	Measurement
Poverty	Independent	Percentage of population with household income <$24,999 in each state
Antibiotic prescriptions per 1,000 population	Dependent	Antibiotics prescribed per 1,000 population in each state
Prevalence of obesity	Mediator	Percentage of population with BMI ≥30 in each state
Prevalence of diabetes	Mediator	Percentage of population ever being diagnosed with diabetes in each state
Prevalence of COPD	Mediator	Percentage of population ever being diagnosed with COPD in each state
Physicians per 100,000 population	Covariate	Number of physicians with all specialties per 100,000 population in each state
Prevalence of population aged ≥65 years	Covariate	Percentage of population aged ≥65 years in each state

Threats to Validity

The major threat of validity for the current study is the fact that it relies on point estimates that have been generated by federal government to estimate prevalence of population with certain characteristics (e.g., poverty, population aged ≥65 years, chronic health conditions such as diabetes, obesity, COPD). The reason for this threat is the fact that BRFSS uses complex sampling design which allows to calculate prevalence of those conditions with certain degree of certainty (CDC, n.d.b.). Although CDC also provides 95% confidence intervals for each point estimate, it still leaves some room for overlapping prevalence estimates between the states (CDC, n.d.b). For example, there is a chance that the point estimate for diabetes for one state is included within 95% confidence interval limits for another. Thus, there is a chance that the true prevalence of diabetes for that particular state is the same as another state's even though their point estimates are different (CDC, n.d.b.).

Another threat to validity would be undercounting of antibiotic courses dispensed from community pharmacies because Antibiotic Resistance & Patient Safety Portal does not include antibiotic courses dispensed from federal facilities (CDC, n.d.a.). This might create some sort of external validity threat because these data cannot be generalized to entire US population since it describes only outpatient antibiotics except for federal pharmacies (CDC, n.d.a.).

Self-reported data on chronic health conditions might also introduce internal bias given the fact that BRFSS collects self-reported data from participants, although fears about self-report bias are largely exaggerated when it comes to reporting diagnosis of medical conditions, age, or income (Hsia et al., 2020; CDC, 2019b). Selection bias should also be noted here due to the fact that in 2020 (the year when data were collected) BRFSS response rate was only 47.9% (CDC, 2021c). Construct validity will not be an issue for the current study given the fact that none of the variables listed in the research questions requires complex measurement techniques and are based on simple yes/no response format from study participants (CDC, 2019b).

Ethical Procedures

The study used ecological research design that looks at prevalence of certain medical and social conditions of the entire population living in all 50 states and DC. The datasets proposed for the study are aggregate data and de-identified, hence, no individual patients were identified through the use of these data. However, I applied and received

Institutional Review Board (IRB) approval from Walden University to make sure the study adheres to all requirements of scientific research outlined by scientific community of Walden (IRB approval number: 05-05-22-0992865). Although data cannot be traced to individual participant, it is still imperative to clearly identify sources of data that I have used to conduct this research. All data used in this study are publicly available from CDC and Association of American Medical Colleges free of charge and can be used for future publications by me while accurately referencing sources of the data.

Summary

In summary, I used an ecological design and quantitative study methods to answer research questions concerning relationship between poverty expressed as income <$24,999 and antibiotic prescribing rates. To answer the first research question, I examined relationship between only two variables (poverty and prescribing rates) using linear regressions analysis while in second research question the same statistical technique was used to examine relationship between poverty and prescribing rates adjusted for the prevalence of elderly population and the physician density by state per 100,000 population. To answer the third research question mediation analysis was used utilizing special software to examine direct, indirect, and total effects of poverty on prescribing mediated by underlying health conditions such as COPD, obesity, and diabetes. In this chapter I have also discussed ethical procedures for the study. In the next chapter I will present study findings.

Chapter 4: Results

The purpose of the current study was to explore the relationship between poverty and antibiotic use mediated by prevalence of diabetes, obesity, and COPD across all 50 states of the United States. To explore these relationships, I used three research questions:

Research Question 1: Is there an association between poverty and outpatient antibiotic prescription rates?

Null hypothesis: $H_0$1: There is no association between poverty and outpatient antibiotic prescription rates.

Alternative Hypothesis: H_a1: There is an association between poverty and outpatient antibiotic prescription rates.

Research Question 2: Is there an association between poverty and outpatient antibiotic prescription rates adjusted for aging population ≥65 years old, and physician density in states?

Null hypothesis: $H_0$2: There is no association between poverty and outpatient antibiotic prescription rates adjusted for aging population ≥65 years old, and physician density in states.

Alternative Hypothesis: H_a2: There is an association between poverty and outpatient antibiotic prescription rates adjusted for aging population ≥65 years old, and physician density in states.

Research Question 3: Do underlying health conditions (obesity, diabetes, COPD) mediate effect between poverty and outpatient antibiotic prescribing rates adjusted for aging population ≥65 and physician density in the states?

Null hypothesis: $H_0 3$: Underlying health conditions (obesity, diabetes, COPD) do not mediate effect between poverty and outpatient antibiotic prescribing rates adjusted for aging population ≥65 and physician density in the states.

Alternative Hypothesis: $H_a 3$: Underlying health conditions (obesity, diabetes, COPD) mediate effect between poverty and outpatient antibiotic prescribing rates adjusted for aging population ≥65 and physician density in the states.

In Chapter 4, I present data collection and results to describe the variables of interest using descriptive statistics and describe statistical tests used to address three research questions. Finally, I explore whether statistical tests meet assumptions and present the results of data analysis for each of the three research.

Data Collection

The timeframe of the data used in this study is 2020 calendar year. The data from CDC's Antibiotic Resistance & Patient Safety Portal and BRFSS website were downloaded from the CDC's website on prevalence indicators in 2020, while data on physician density for the 2020 calendar year was available from the 2021 report from the Association of American Medical Colleges (AAMC, 2021; CDC, n.d.a; CDC, n.d.b).

As noted previously, I downloaded 2020 data from BRFSS website (publicly available data on prevalence estimates for each state on chronic medical conditions and demographics of state's populations), IQVIA data from Antibiotic Resistance & Patient Safety Portal (publicly available data on antibiotics dispensed from community pharmacies in each state), and a report on active MDs by state per 100,000 population from the Association of American Medical Colleges (also publicly available; AAMC, 2021; CDC, n.d.a; CDC, n.d.b).

There were no discrepancies in data collection and analysis plans, as outlined in Chapter 3. Response rates for BRFSS (percentage of respondents who actually responded to phone calls placed by BRFSS interviewers) is the only indicator that is worth noting here and was 47.9% (CDC, 2021c). Response rate was not applicable to other data sources. The data presented by study sources are highly representative across the United States given the fact that BRFSS collects data using complex sampling methodology by combining randomly selected landline and cell phone numbers and analyzes using technique called raking, which makes data highly representative for all U.S. states and populations (CDC, 2015).

Baseline Descriptive Statistics of the Data

Variables included in the study are presented in Table 2. Justification of variables in the models to answer Research Questions 1, 2, and 3 are outlined in Chapter 2.

Table 2

Descriptive Statistics of Variables Used in the Study

		Prescriptions per 1,000 population	Prevalence of poverty	Physician density per 100,000	Prevalence of population aged ≥65 years	Prevalence of COPD	Prevalence of obesity	Prevalence of diabetes
N	Valid	51	52	52	52	52	52	52
	Missing	1	0	0	0	0	0	0
Mean		619.86	24.14	266.82	22.39	6.61	32.04	10.89
Std. Error of Mean		20.69	1.18	13.94	.31	.27	.56	.30
Median		618.00	22.15	248.20	22.45	6.20	31.70	10.70
Mode		547[a]	17.2[a]	203.2	22.0[a]	6.2	28.0[a]	8.8[a]
Std. Dev		147.74	8.53	100.54	2.24	1.98	4.07	2.17
Variance		21825.89	72.71	10108.09	5.02	3.93	16.53	4.69
Skewness		.62	3.82	4.06	-.72	1.37	-.13	.42
Std. Error of Skewness		.33	.33	.33	.33	.33	.33	.33
Kurtosis		.26	20.56	22.08	1.44	2.54	-.68	-.52
Std. Error of Kurtosis		.66	.65	.65	.65	.65	.65	.65
Range		626	58.1	685.4	10.9	9.9	15.5	8.3
Minimum		348	14.7	163.6	15.9	3.7	24.2	7.5
Maximum		974	72.8	849.0	26.8	13.6	39.7	15.8

Note. [a.] Multiple modes exist. The smallest value is shown.

The full dataset included 52 observations (all 50 states, Puerto Rico, and DC). However, data on antibiotic prescribing rates per 1,000 population was missing for Puerto Rico. Therefore, descriptive statistics and analysis tables included only 51 observations and excluded data on Puerto Rico in listwise fashion.

Using Table 2 on descriptive statistics of all variables used in the study, one may conclude that all variables show normal distribution (as judged by visual inspection) except for the prevalence of poverty and physician density (right skewed with coefficients 3.86 and 4.06 respectively). Highly skewed distribution of the data on physician density was caused by one outlier (physician density of 843 per 100,000 in

DC). However, I decided to keep this value in the dataset given the fact that it represents the actual value rather than a typing error. In addition to that, variables such as prevalence of aging population (aged ≥65 years) and the prevalence of obesity were skewed to the left (coefficients -.72 and -.13 respectively) indicating that few states had extreme prevalence values in obesity and elderly population rates.

Kurtosis of distribution also provided some clues on score distributions. For example, distribution of scores for variables such as physician density and prevalence of poor populations were highly leptokurtic indicating that states suffer from extremes in terms of physician distribution and the prevalence of elderly populations (i.e., there are states with very high and very low prevalence of physicians and elderly populations).

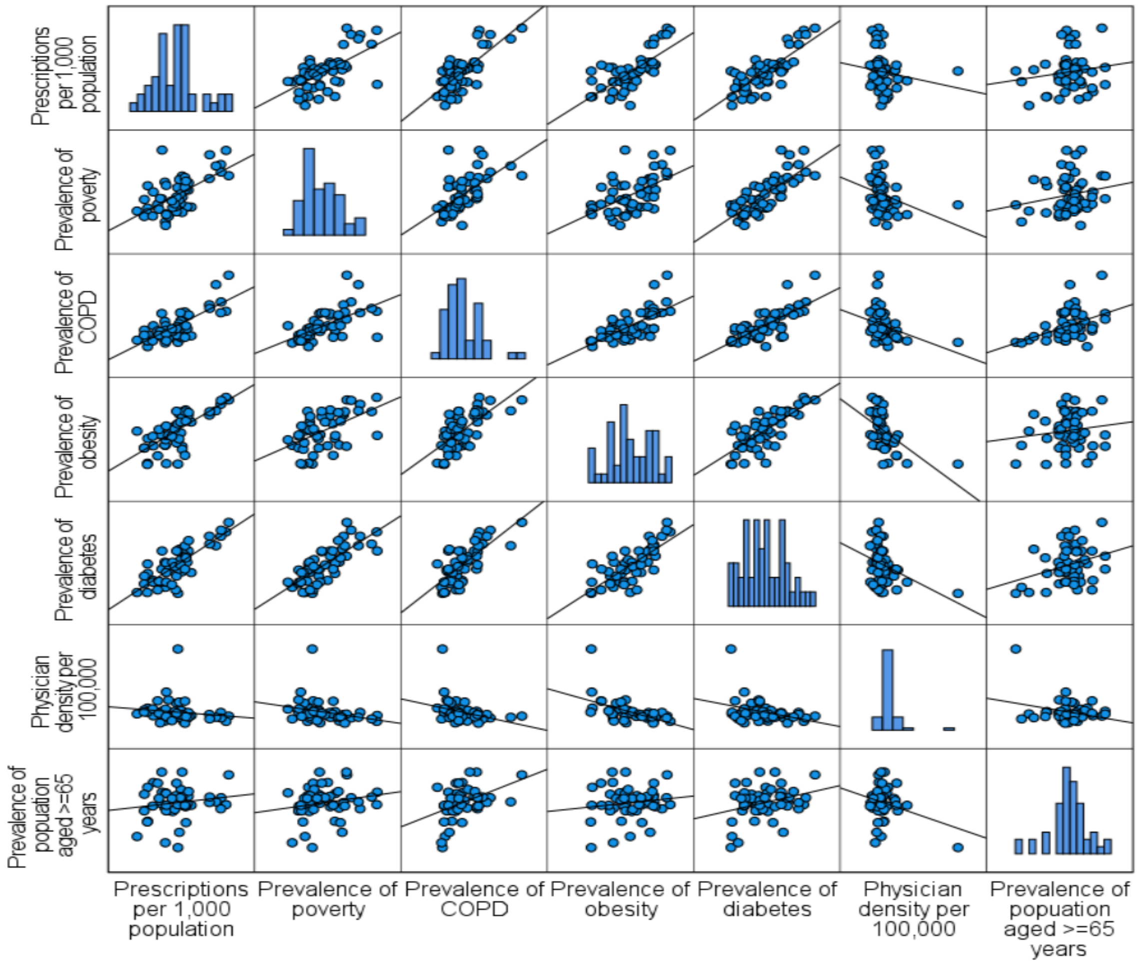
The outcome variable (antibiotics prescribed per 1,000 population) showed on average 619.86 prescriptions per 1,000 individuals in a population as a mean value across all 50 states and DC. There was a high variability of prescribing rates across the states. For example, West Virginia showed 974 prescriptions per 1,000 while Alaska showed only 348 per 1,000 population (range 626).

Distribution of mediators (COPD, diabetes, and obesity) did not vary significantly across the states. However, it should be noted that skewness of diabetes and obesity were of different directions (diabetes prevalence was right skewed while obesity was left skewed). Distribution of prevalence of poverty was affected by the outlier of Puerto Rico which had a prevalence of 72.8%. However, as noted above, data on Puerto Rico was excluded from regression analysis because the outcome variable (antibiotic prescriptions per 1,000) was not available for this particular state. The mean and median of poverty prevalence were close to each other and were 24.1 and 22.1 respectively. After excluding Puerto Rico from analysis, the mean prevalence for poverty was reduced to 23% indicating that on average 23% of US population across all 50 states and DC had household income of <$24,999.

The scatterplot matrix presented in Figure 3 indicates on relationships of variables to each other and most importantly, against outcome variable such as prescriptions per 1,000 population. By visual inspection it can be established that all variables included in the study show linear relationship to outcome variable, although this relationship was somewhat weak for variables physician density per 1,000 population and prevalence of population aged ≥65 years.

Figure 3

Scatterplot Matrix of all Variables in the Study



Research Question 1

Statistical Assumptions for Linear Regression Analysis for Research Question 1

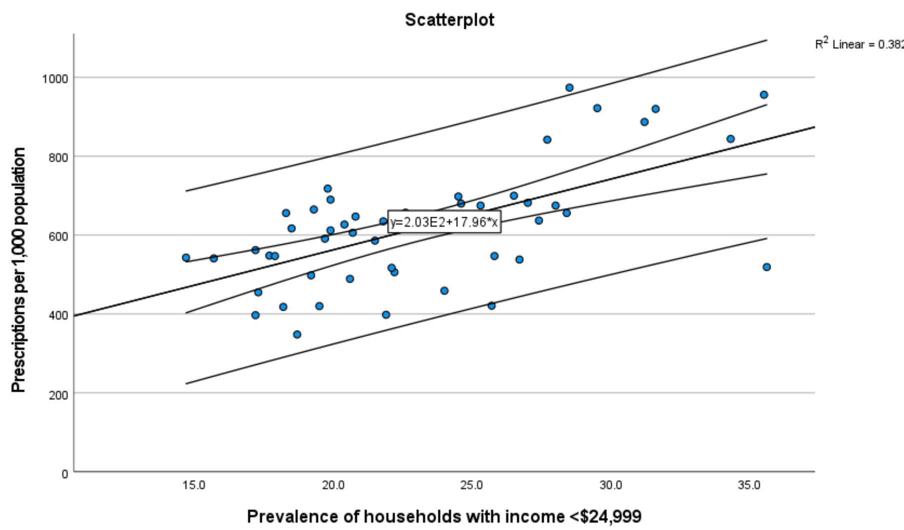
A linear regression was run to explore the relationship between the prevalence of poverty (defined as the prevalence of population with household income <$24,999) and antibiotic prescribing rate per 1,000 population.

Assumption 1 was satisfied because variables (prevalence of poverty and antibiotic prescribing rates) are measured on continuous scale even though they are rates and thus can be treated as a continuous variables.

Assumption 2. To assess linearity a scatterplot was plotted with the prevalence of poor population in each state against antibiotic prescribing rate in each state (figure 4). Visual inspection of the plot indicated a linear relationship between the variables.

Figure 4

Scatterplot: Prevalence of Households With Income <$24,999 Against Prescriptions per 1,000 Population in Each State

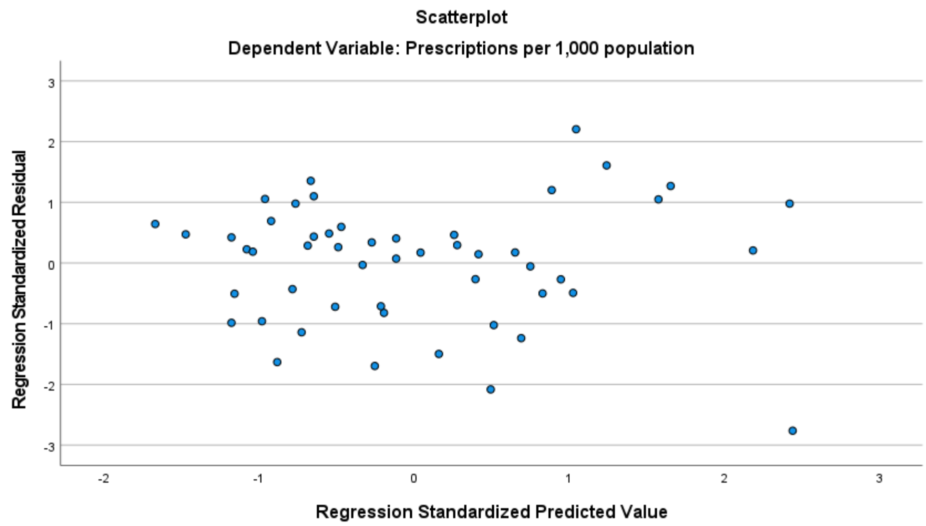


Assumption 3. Outliers. No outliers with ≥3 standard deviations for residuals have been detected after plotting regression standardized residuals against regression standardized predicted values (figure 5).

Assumption 4. Independence of observation. There was independence of observations as checked using Durbin-Watson statistic (2.32).

Figure 5

Scatterplot: Regression Standardize Predicted Values Plotted Against Regression Standardized Residuals

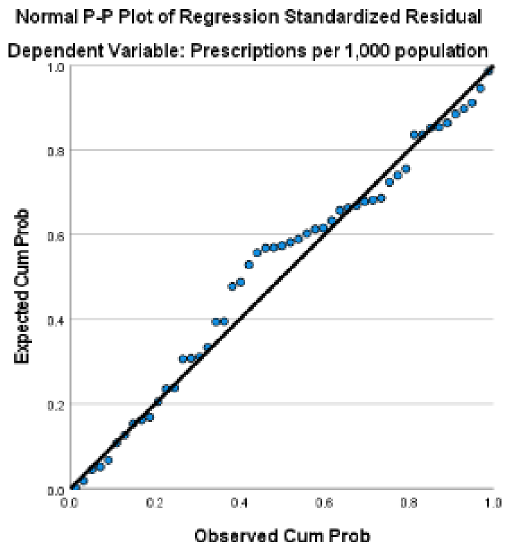


Assumption 5. Homoscedasticity. There was homoscedasticity, as assessed by visual inspection of a plot of standardized residuals versus standardized predicted values (figure 5).

Assumption 6. Residuals were normally distributed as assessed by visual inspection of a histogram and P-P Plot (figure 6).

Figure 6

Probability Plot: Observed Cumulative Probability Against Expected (Normal) Cumulative Probability of Standardized Residuals



Linear equation was: Antibiotic prescribing rate per 1,000 population = 203.417 + 17.964 X prevalence of poverty (table 3). Prevalence of poverty significantly predicted antibiotic prescribing rate, F (1, 49) = 30.35, p < .001, accounting for 38.2% of the variation in antibiotic prescribing with adjusted R^2 = 38.2%, a substantial size effect according to Cohen (1988). One percent increase in poverty prevalence leads to increase by 18 prescriptions written per 1,000 population with 95% CI [11.4, 24.5]. I have also made predictions for populations with poverty prevalence of 10%, 20%, and 30%. For 10% prevalence, I predicted 383 antibiotic courses prescribed per 1,000 population, 95% CI [290.6, 475.5]; for 20% it was predicted as 563 courses prescribed per 1,000, 95% CI [523.7, 601.7]; and for 30% it was predicted as 742 courses per 1,000, 95% CI [686.8, 797.9].

Table 3

Linear Regression: Prevalence of Poverty Regressed Against the Rate of Prescriptions per 1,000 Population

Prescriptions per 1,000 population	*B*	95%CI for *B*		*SE B*	*β*	R^2	ΔR^2
		LL	UL				
Model						.38	.37
Constant	203.42*	47.97	358.87	77.36			
Prevalence of poverty	17.96***	11.41	24.52	3.26	.62		

Note. Model =" Enter" method in SPSS Statistics; *B*=unstandardized regression coefficient; CI=Confidence interval; LL=Lower limit; UL=Upper limit; *SE B* = Standard error of the coefficient; *β* = Standardized coefficient; R^2= Coefficient of determination; Δ R^2= adjusted R^2.

*$p < .05$. **$p < .01$. ***$p < .001$

Research Question 2

A multiple regression was run to predict antibiotic prescribing rate per 1,000 population from prevalence of poverty, prevalence of populations aged ≥65 years, and physician density per 100,000 population. There was linearity as assessed by partial regression plots and a plot of studentized residuals against the predicted values. There was independence of residuals, as assessed by a Durbin-Watson statistic of 2.3. There was homoscedasticity, as assessed by visual inspection of a plot of studentized residuals versus unstandardized predicted values. There was no evidence of multicollinearity, as assessed by tolerance values greater than 0.1. There was one studentized deleted residual greater than ±3 standard deviations, one observation with leverage value with 0.7, however, none of the values for Cook's distance were above 1. Thus, it was assumed that assumption of normality was met, as assessed by a Q-Q Plot. The multiple regression model statistically significantly predicted antibiotic prescribing rate per 1,000 population, F (3, 47) = 9.811, $p < .001$, adj. $R^2 = .35$. Only one variable (prevalence of poverty) out of three statistically significantly predicted the outcome ($p < .001$). Regression coefficients and standard errors can be found in Table 4 below.

Table 4

Multiple Regression: Prevalence of Poverty (Adjusted for Prevalence of Population Aged ≥65 Years and Physician Density per 100,000 Population) Regressed Against the Rate of Prescriptions per 1,000 Population

Prescriptions per 1,000 population	*B*	95% CI for *B*		*SE B*	*B*	R^2	ΔR^2*
		LL	UL				
Model						.39	.35
Constant	120.542	-294.14	535.23	206.13			
Prevalence of poverty	18.06***	11.01	25.10	3.50	.62		
Physician density per 100,000	.06	-.30	.42	.18	.04		
Prevalence of Population aged >=65 years	2.89	-12.92	18.71	7.86	.04		

Note. Model=” Enter” method in SPSS Statistics; *B*=unstandardized regression coefficient; CI=Confidence interval; *LL*=Lower limit; *UL*=Upper limit; *SE B* = Standard error of the coefficient; β = Standardized coefficient; R^2= Coefficient of determination; ΔR^2= adjusted R^2.

*$p < .05$. **$p< .01$. ***$p < .001$

Each covariate included into multiple regression model was also regressed against antibiotic prescribing rate individually. Although none of them showed statistically significant relationship with antibiotic prescribing rate, those covariates were kept in model due to their potential significance, as suggested by literature review outlined in Chapter 2.

Linear regression equation to measure relationship between the prevalence of elderly population and antibiotic prescribing rates was the following: Antibiotic prescribing rate per 1,000 population = 390.61 + 10.24 X prevalence of elderly population aged ≥65 years. Prevalence of elderly population did not predict antibiotic prescribing rate at statistically significant level, F (1, 49) = 1.23, p = .27. Additional details are given in table 5 below.

Table 5

Linear Regression: Prevalence of Population Aged ≥65 Years Regressed Against the Rate of Prescriptions per 1,000 Population

Prescriptions per 1,000 population	*B*	95% CI for *B*		*SE B*	*β*	R^2	ΔR^2
		LL	UL				
Model						.03	.01
Constant	390.61	-26.02	807.24	207.32			
Prevalence of Population aged ≥65years	10.24	-8.28	28.77	9.22	.16		

Note. Model=” Enter” method in SPSS Statistics; *B*=unstandardized regression coefficient; CI=Confidence interval; *LL*=Lower limit; *UL*=Upper limit; *SE B* = Standard error of the coefficient; *β* = Standardized coefficient; R^2= Coefficient of determination; Δ R^2= adjusted R^2.

The linear equation to measure relationship between physician density and antibiotic prescribing rates was the following: Physician density per 100,000 population = 679.30 + .22 X physician density. Physician density did not predict antibiotic prescribing rate at statistically significant level either, F (1, 49) = 1.18, p = .28. Additional details are given in table 6 below.

Table 6

Linear Regression: Physician Density per 100,000 Population Regressed Against the Rate of Prescriptions per 1,000 Population

Prescriptions per 1,000 population	*B*	95% CI for *B*		*SE B*	*β*	R^2	ΔR^2
		LL	UL				
Model						.02	.004
Constant	679.30	561.75	796.85	58.50			
Physician density	-.22	-.64	.19	.21	-.15		

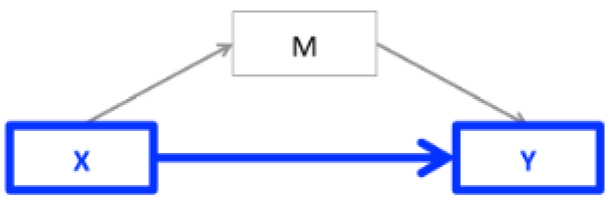
Note: Model=” Enter” method in SPSS Statistics; *B*=unstandardized regression coefficient; CI=Confidence interval; *LL*=Lower limit; *UL*=Upper limit; *SE B* = Standard error of the coefficient; *β* = Standardized coefficient; R^2= Coefficient of determination; Δ R^2= adjusted R^2.

Research Question 3

Analysis to address Research Question 3 was conducted in three steps. First, I explored the relationship between independent and dependent variable (X→Y; Figure 7), expressed using equation for simple linear regression: $Y = i_y + cX + e_y$ (see Hayes, 2018)

Figure 7

Step 1 in Mediation Analysis. Exploring Relationship Between Independent and Dependent Variables

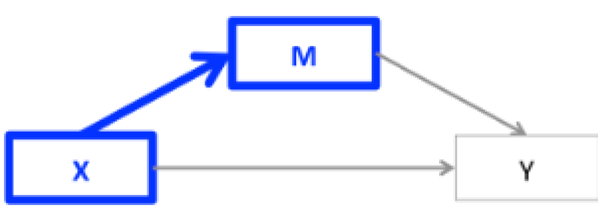


Note. From Kim (2016).

Second, I explored the relationship between the independent variable and each mediator (X→M; Figure 8). This was expressed using the equation for simple linear regression: $M = i_M + aX + e_M$ (see Hayes, 2018).

Figure 8

Step 2 in Mediation Analysis. Exploring Relationship Between Independent Variable and Each Mediator

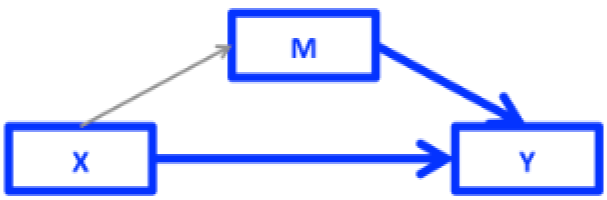


Note. From Kim (2016).

Last, I explored the relationship between mediators and the dependent variable and adding relationship between independent variable and dependent variable (X+M→Y; Figure 9). This was expressed using the equation for multiple linear regression: $Y = i_y + c'X + bM + e_y$ (see Hayes, 2018).

Figure 9

Step 3 in Mediation Analysis. Exploring Relationship Between Mediators And Dependent Variable Adjusted For Independent Variable



Note. From Kim (2016).

Since the very first step was already explored in Research Questions 1 and 2, I started analysis for Research Question 3 with Step 2: exploring relationship between independent variable and each mediator in the project.

Macro called PROCESS calculates model estimates using bootstrapping method (Hayes, 2018). That means that normality assumption typically required for linear regressions does not apply here, nor Sobel's test, because this method does not require specific distribution of scores for variables (Jung, 2021). For this analysis I used 5,000 bootstrap samples for parallel mediation model number 4 specified in SPSS macro called PROCESS.

Relationship Between Independent Variable (Prevalence of Poverty) and Mediator COPD Adjusted for Physician Density and Prevalence of Population Aged ≥65years

The multiple regression model statistically significantly predicted prevalence of COPD, $F(3, 47) = 14.25$, $p < .001$, $R^2 = .48$. Based on analysis the model with three variables (prevalence of poverty adjusted for physician density and prevalence of population aged ≥65years) explained 48% variability in COPD prevalence which is considered a substantial effect size (Cohen, 1988). In this model only one variable (prevalence of poverty) was statistically significantly associated with COPD prevalence (p<.001) and increased COPD prevalence by 0.2 units with every unit increase in prevalence of poverty. Regression coefficients and 95% Confidence intervals can be found in the table 7 below.

Table 7

Multiple Regression Using Macro PROCESS. Outcome Variable: Prevalence Of COPD

Prevalence of COPD	*B*	*95.0% CI for B*		*SE B*	*β*	R^2
		LL	*UL*			
Model						.48
Constant	-3.43	-8.60	1.73	2.57		
Prevalence of poverty	.2***	.12	.29	.04	.52	
Physician density per 100,000	-.002	-.01	.00	.00	.09	
Prevalence of population aged ≥65years	.26	.06	.46	.09	.30	

Note. B=unstandardized regression coefficient; CI=Confidence interval; *LL*=Lower limit; *UL*=Upper limit; *SE B* = Standard error of the coefficient; *β* = Standardized coefficient; R^2= Coefficient of determination.

*$p < .05$. **$p < .01$. ***$p < .001$

Relationship Between Independent Variable (Prevalence of Poverty) and Mediator (Prevalence of Obesity) Adjusted for Physician Density and Prevalence of Population Aged ≥65years

The multiple regression model statistically significantly predicted prevalence of obesity, F (3, 47) =12.76, $p < .001$, $R^2 = .45$. Based on analysis the model with three variables (prevalence of poverty adjusted for physician density and prevalence of population aged ≥65years) explained 45% variability in obesity prevalence which is considered a substantial effect size (Cohen, 1988). In this model two variables: prevalence of poverty and physician density were statistically significantly associated with obesity prevalence (p<.001) and increased obesity prevalence by 0.3 unit for every unit increase in poverty and reduced obesity prevalence by .01 unit per every unit increase in physician density (standardized coefficients were pretty similar for both variables: 0.42 and 0.43 respectively). Regression coefficients and 95% confidence intervals can be found in the table 8 below

Table 8

Multiple Regression Using Macro PROCESS. Outcome Variable: Prevalence of Obesity

Prevalence of obesity	*B*	95.0% CI for *B*		*SE B*	*β*	R^2
		LL	UL			
Model						.45
Constant	31.5***	20.55	42.37	5.42		
Prevalence of poverty	.3***	.16	.53	.09	.42	
Physician density per 100,000	-.01***	-.03	- .01	.01	.43	
Prevalence of population aged ≥65years	-.11	.54	.30	.21	.07	

Note. *B*=unstandardized regression coefficient; CI=Confidence interval; *LL*=Lower limit; *UL*=Upper limit; *SE B* = Standard error of the coefficient; *β* = Standardized coefficient; R^2= Coefficient of determination.

*p < .05. **p < .01. ***p < .001

Relationship Between Independent Variable (Prevalence of Poverty) and Mediator (Prevalence of Diabetes) Adjusted for Physician Density and Prevalence of Population Aged ≥65years

The multiple regression model statistically significantly predicted prevalence of diabetes, $F(3, 47) = 27.49$, $p < .001$, $R^2 = .64$. Based on analysis the model with three variables (prevalence of poverty adjusted for physician density and prevalence of population aged ≥65years) explained 64% variability in diabetes prevalence which is considered a substantial effect size (Cohen, 1988). Similar to other models discussed above, prevalence of poverty was significantly associated with diabetes prevalence (p<.001) and increased diabetes prevalence by 0.29 units for every unit increase in poverty. Regression coefficients and 95% confidence intervals can be found in the table 9 below.

Table 9

Multiple Regression Using Macro PROCESS. Outcome Variable: Prevalence of Diabetes

Prevalence of diabetes	*B*	95.0% CI for *B*		*SE B*	*β*	R^2
		LL	UL			
Model						.64
Constant	2.1	-2.37	6.56	2.22		
Prevalence of poverty	.29***	.21	.37	.04	.71	
Physician density per 100,000	-.003	-.007	.001	.002	-.13	
Prevalence of population aged ≥65years	.12	-.05	.29	.08	.13	

Note: *B*=unstandardized regression coefficient; CI=Confidence interval; *LL*=Lower limit; *UL*=Upper limit; *SE B* = Standard error of the coefficient; *β* = Standardized coefficient; R^2= Coefficient of determination.

*p < .05. **p < .01. ***p < .001

Relationship Between Independent Variable (Prevalence of Poverty) and Dependent Variable (Antibiotic Prescribed per 1,000 Population) Adjusted for Physician Density, Prevalence of Population Aged ≥65years, Prevalence of COPD, Obesity, and Diabetes

The multiple regression model statistically significantly predicted antibiotic prescribing rate per 1,000 population, $F(3, 47) = 9.8$, $p < .001$, $R^2 = .77$. Based on analysis the model with six independent variables explained 77% variability in antibiotic prescribing rate which is considered a high effect size (Cohen, 1988). In this model all three mediators (COPD, obesity, and diabetes) were significantly associated with antibiotic prescribing rate with diabetes showing the highest increase in prescribing per every unit increase of its prevalence (unstandardized B=28.04) followed by COPD (unstandardized B=25.48) and obesity (unstandardized B=11.98). In addition to that, physician density was also significantly associated with prescribing rate and increased prescribing by 0.39 units per every unit increase in physician density. It should be noted that in this model prevalence of poverty was no longer significant and its point estimate (unstandardized B) was way below the estimates of poverty prevalence in all previous models (steps 1 and 2 of mediation analysis). Regression coefficients and 95% confidence intervals can be found in the table 10 below.

Table 10

Multiple Regression Using Macro PROCESS. Outcome Variable: Prescriptions per 1,000 Population

Prescriptions per 1,000 population	*B*	95.0% CI for *B*		*SE B*	*β*	R^2
		LL	*UL*			
Model						.77
Constant	-227.5	-651.76	196.77	210.52		
Prevalence of poverty	.64	-6.27	7.56	3.43	.02	
Physician density per 100,000	.39***	.12	.66	.13	.27	
Prevalence of population aged ≥65years	-5.68	-17.39	6.04	5.8	-.09	
Prevalence of COPD	25.48***	6.74	44.23	9.3	.34***	
Prevalence of obesity	11.98*	1.84	22.12	5.03	.33	
Prevalence of diabetes	28.04*	5.13	50.95	11.37	.39	

Note. B=unstandardized regression coefficient; CI=Confidence interval; LL=Lower limit; UL=Upper limit; *SE B* = Standard error of the coefficient; *β* = Standardized coefficient; R^2= Coefficient of determination.

*p < .05. **p< .01. ***p < .001.

Direct, Indirect, and Total Effects of Poverty on Antibiotic Prescribing Rate per 1,000 Population

Mediation analysis is based on the notion that total effect of X on Y is a summary of direct and indirect effects and indicates on increase/decrease of variable Y in response to increase/decrease of variable X by one unit (Hayes, 2018). In this project, total effect of X variable on Y is calculated in a linear regression model specified in a research question 2 where prevalence of poverty adjusted for physician density and prevalence of population aged ≥65 years were regressed against antibiotic prescribing rate per 1,000 population. The unstandardized B coefficient of regressions analysis (B=18.06) is labeled as “total effect” (Hayes, 2018). Indirect effect, on the other hand, is a multiplication of *a* on *b* unstandardized coefficients as summarized in figure 2 and indicates that for every unit increase in X variable the Y variable is changed by *ab* units due to the influence of X variable on mediators specified in the model (see Figure 2; Hayes, 2018).

For example, for COPD prevalence unadjusted coefficient *a* would derive from a table 7 where COPD prevalence served as dependent variable for prevalence of poverty as independent variable, while coefficient *b* was derived from table 10 where prevalence of COPD served as one of the six independent variables regressed against prescribing rate per 1,000 population (dependent variable). In this particular case indirect effect of COPD is *ab* =0.2 X 25.48=5.2. Indirect effects of all three mediators were summarized in SPSS output and labeled as “total indirect effects” (Table 13).

In parallel mediation analysis “direct effect” of X on Y is a difference between total and indirect effects and indicates what would be the effect of X on Y in the absence of mediators specified in the model (Hayes, 2018).

As table 11 below indicates, total effect of poverty prevalence on antibiotic prescribing rate was statistically significant ($p < .001$) and was quite substantial with 18.06 units increased per every percent increase of poverty prevalence.

Table 11

Total Effects of X (Prevalence of Poverty) on Y (Antibiotics Prescribed per 1,000 Population)

				95% CI		
Effect	*SE*	*t*	*p*	LL	UL	*c-cs*
18.06	3.5	5.15	< .001	11.00	25.10	.62

However, as summarized in Table 12 below, direct effect of poverty on antibiotic prescribing rate was poor (.64) and not statistically significant (*p* = .85).

Table 12

Direct Effects of X (Prevalence of Poverty) on Y (Antibiotics Prescribed per 1,000 Population)

				95% CI		
Effect	*SE*	*t*	*p*	LL	UL	*c'-cs*
.64	3.43	.19	.85	-6.27	7.56	.02

Overall, total effect of poverty on antibiotic prescribing rate was largely explained by indirect effects of mediators with the highest effect produced by diabetes (unstandardized effect = 8.12), COPD (unstandardized effect = 5.21), obesity (unstandardized effect = 4.09). In summary, total indirect effects for all three variables was 17.41 and all three mediators were statistically significant as judged by 95% bootstrap CIs summarized in table 13 below (95% CI: 9.20, 24.92).

Table 13

Indirect Effects of X (Prevalence of Poverty) on Y (Antibiotics Prescribed per 1,000 Population)

			Bootstrap 95% CI		
	Effect	Bootstrap *SE*	*LL*	*UL*	Completely standardized effects
Total indirect effects	17.41	3.96	9.20	24.92	.60
Prevalence of COPD	5.21	2.22	.62	9.58	.18
Prevalence of Obesity	4.09	2.23	.19	8.88	.14
Prevalence of Diabetes	8.12	3.75	1.50	16.44	.28

According to Hair et al., (2014), the strength of mediation is measured using variance accounted for (VAF) it and is arbitrarily set to >80% to classify mediation process as “fully mediated”. Current analysis indicates that it is a fully-mediated process because indirect effects (17.41) comprised of 96% of total effects (18.06) of prevalence of poverty on antibiotic prescribing rate per 1,000 (Kenny, 2021). This fact is also supported by statistically insignificant effect of direct effect of X on Y indicating on the absence of partial mediation (MacKinnon et al., 2007). In conclusion, effect of poverty on antibiotic prescribing rate was fully mediated by mediators specified in the model (prevalence of COPD, diabetes, and obesity). For every standard deviation increase in poverty prevalence, antibiotic prescribing rate was increased by 0.6 standard deviations (completely standardized effect of all mediators combined).

Summary

In summary, the linear regression analysis that I used to answer Research Question 1 allowed me to reject null hypothesis and accept alternative hypothesis indicating that there is a linear relationship between the prevalence of poverty and the rate of antibiotic prescribing per 1,000 population. The relationship (R^2=.38) is considered substantial according to Cohen (1988). Thirty eight (38%) percent of variability in antibiotic prescribing rate can be explained by poverty alone. In unadjusted simple linear regression analysis, every unit increase in the prevalence of poverty, antibiotic prescribing rate is increased by 18 units which corresponds to 18 prescriptions per 1,000 population for every percent increase in poverty in the state.

The multiple regression analysis that I conducted to answer Research Question 2 also indicated that there is a strong relationship (R^2=.39) between prevalence of poverty and antibiotic prescribing rate even after adjusting for physician density and aging population. In fact, adding covariates (physician density and the prevalence of population aged ≥ 65 years) did not improve model significantly. Similar to Research Question 1, in Research Question 2, the alternative hypothesis was accepted and the null hypothesis rejected: Every unit increase with the prevalence of poverty, antibiotic prescribing was increased by 18.1 units.

In Research Question 3, the null hypothesis was also rejected and alternative accepted because the model satisfied all criteria for mediation: poverty influenced the rate of antibiotic prescribing in a simple linear regression model. Poverty also influenced development of chronic health conditions such as COPD, obesity, and diabetes ($a1 = 0.2$, $a2 = 0.34$, and $a3 = 0.29$; $p < .001$ respectively). Chronic health conditions on their end also influenced antibiotic prescribing after adjusting for prevalence of poverty and covariates ($b1 = 25.48$, $p < .001$; $b2$=11.98, $p < .05$; $b3 = 28.04$; p <.05; respectively). After using 5,000 bootstrap samples total indirect effect of all three mediators combined ($a1b1+ a2b2+a3b3$) was 17.41 (95% bootstrap CI: 9.2, 24.91) indicating that effect of poverty on antibiotic prescribing was fully mediated through chronic health conditions (96% of total effects was due to indirect effects; see MacKinnon et al., 2007). Essentially, no direct effects of poverty were observed: Antibiotic prescribing rate was increased by .02 standard deviations for every standard deviation increase in poverty due to direct effects of poverty (Table 12).

After conducting a parallel mediation model analysis using ordinary least squares method, I concluded that prevalence of poverty influenced antibiotic prescribing rate per 1,000 population in a positive, liner manner: Every unit increase in prevalence of poverty antibiotic prescribing rate increased in 18 courses per 1,000 population due to effects of underlying health conditions. Populations with higher prevalence of poverty also experienced higher prevalence of COPD increase by .2 units, diabetes with .29 units, and obesity with .34 units. On the other hand, chronic medical conditions such as diabetes, COPD, and obesity influenced prescribing rate: For every unit increase in prevalence of poverty, prescribing rate increased by 8.12, 5.2, and 4.1 courses of antibiotics per 1,000 population respectively due to effects of poverty on prevalence of chronic medical conditions specified in the model. Overall, poverty by itself had no statistically significant effect on antibiotic prescribing rates without mediating effect of chronic health conditions (p =.85). A total of 96% of effects of poverty on prescribing rates were through mediators such as prevalence of COPD, obesity, and diabetes. In the next chapter I will discuss the implications of findings in the context of the theoretical and conceptual frameworks specified in previous chapters.

Chapter 5: Discussion, Conclusions, and Recommendations

The purpose of the current study was to explore effects of poverty on antibiotic prescribing rate through mediators COPD, diabetes, and obesity. These chronic conditions have been chosen to be included in the model based on the previous literature indicating the link between poverty and chronic health conditions and also the link between chronic health conditions and antibiotic prescribing either directly (in case of COPD) or indirectly (in case of obesity and diabetes). The study is ecological given the fact that unit of analysis was state populations rather than an individual patient and used estimated prevalence of chronic health conditions (COPD, diabetes, obesity) per 100 population (percentage of population with certain health conditions) along with other characteristics such as prevalence of population aged ≥65 years and physician density per 100,000 population (CDC, n.d.b). The outcome variable was also an estimated number of prescriptions for antibiotics dispensed from community pharmacies per 1,000 population in a state (CDC, n.d.a).

The study was conducted for a reason: since antibiotic use is the biggest driving force of drug-resistance development in bacteria, federal and state public health agencies actively promote antibiotic stewardship to reduce prescribing assuming that reduced rate of inappropriate prescribing would slow down the process substantially (CDC, 2021b). For this particular reason, all metrics and indicators proposed by federal, and state public health agencies measure prescribing rate without considering patient-specific factors such as underlying health conditions which may in fact require antibiotics (CDC, 2022a). On the other hand, sequential effects of social determinants on antibiotic prescribing through mediators remains poorly explored and is not considered while designing and implementing antibiotic stewardship initiatives. This current study was undertaken to (a) investigate effects of underlying health conditions on antibiotic prescribing rates and (b) explore a wider picture of prescribing through the lenses of social factors such as low income.

To summarize findings of the current study, I should highly emphasize the fact that relationships between the prevalence of poverty in each state and the rate of antibiotic prescribing was highly significant with a substantial effect size in Research Questions 1 and 2 indicating that social factors are the drivers of prescribing in the communities, in addition to physician's behavior, and inappropriate prescribing.

In Research Question 3, findings indicate that the effect of poverty on prescribing rates was largely due to mediators such as COPD, diabetes, and obesity rather than poverty by itself, indicating that in fact, underlying health conditions fully mediate prescribing rates. Since mediation in the current study was full, with 96% of total effects caused by indirect effects, the whole conceptual model can be simplified as X (prevalence of poverty) → M (prevalence of COPD, obesity, and diabetes) → Y (Antibiotic prescribing rates per 1,000 population). My findings indicate that the conceptual model no longer includes direct effect of X on Y.

Interpretation of the Findings

The findings of the current study align with the findings summarized in literature and extend knowledge on the complex relationship of social determinants on antibiotic prescribing. In previous chapters, I summarized literature that indicates that social deprivation increases the rate of prescribing although exact causes of higher prescribing rates among poor and deprived populations remain unclear (Mölter et al., 2018; Volpi et al., 2019). Literature on antibiotic prescribing in the United States also emphasizes the fact that there is a marked regional variation when it comes to prescribing antibiotics, although exact causes have not been fully investigated (King et al., 2020). There is abundance of literature where social determinants are linked to development of chronic health conditions used in this study (COPD, obesity, diabetes; Wheaton et al., 2017). There is also some literature on benefits on antibiotic therapy for COPD patients and almost no literature directly measuring antibiotic prescribing rates in diabetic and obese patients (Stevermer et al., 2021). In addition, there is literature indicating that diabetic and obese patients are at increased risk of bacterial infections which subsequently require antibiotic therapy (Andersen et al., 2016).

The current study confirmed, in Research Question 3, the relationship between the independent variable and mediators to be statistically significant for all three mediators. The relationship of all three mediators showed a significant relationship of the dependent variable on the antibiotic prescribing rate. The current study confirms existence of links between those factors outlined in literature.

Up to present, it has been believed that reduction in prescribing was only possible after implementation of antibiotic stewardship programs targeting inappropriate prescribing (CDC, 2021b). Based on this study, there are reasonable considerations that antibiotic prescribing may be viewed as a complex social problem, where social factors and namely, poverty influences prescribing rates through mediators such as chronic health conditions. Findings of the study provided an alternative explanation for increased antibiotic prescription rates rather than the focus only on the prescribers because substantial amount of all prescriptions of antibiotics might be associated with patient-specific factors such as chronic health conditions predisposing patients to bacterial illnesses (which on the other hand, require antibiotic prescriptions). Although the possibility of inappropriate prescribing cannot be excluded from this analysis given the fact that current study looked at all prescriptions (appropriate and inappropriate combined), it leaves a little room for “blaming” prescribers for inappropriate prescribing. The evidence for this claim can be found in table 10 where all three mediators along with covariates where regressed against antibiotic prescribing rate and mediators were found to be highly significant in this relationship. It should also be noted that physician density was significant ($p < .01$) but with very small effect size (unstandardized B = .39) while prevalence of population aged ≥ 65 years was not ($p = .33$). Relationship with aging population was not significant because states with higher prevalence of poverty (and hence higher antibiotic prescribing rates) have lower life expectancy (Egen et al., 2017). Thus, adjusting for those covariates did not change models significantly.

Contrary to the previous studies indicating that aging population was the biggest consumer of antibiotics, prevalence of population aged ≥65 years was not statistically significant when regressed against antibiotic prescribing rates in a simple linear regression model ($p = .27$). Physician density also showed non-significant negative relationship with antibiotic prescribing rate in a simple linear regression model ($p = .28$).

In the context of theoretical framework my study fits nicely into the ecosocial model proposed by Nancy Krieger (1994). Study shows that construct "embodiment" truly works when it comes to antibiotic prescribing rates: Poverty "creates" chronic health conditions such as COPD, obesity, and diabetes and later the process of "embodiment" transforms them into increased antibiotic prescribing rates. Although antibiotic stewardship initiatives usually target prescriber behaviors, it will be practically impossible to substantially reduce prescribing rates without considering social determinants of populations. One additional detail that would also highlight substantial effect of poverty can be found in table 3 that answered research question 1. In this table prevalence of poverty is regressed against prescribing rate with a constant (B for intercept) of 203.4 (95% CI: 47.97, 358.87). Based on equation for simple linear regression $Y=b_0+bX$ constant (b_0) indicates on the meaning of Y when variable X=0. Although constant has no practical utilization in regression analysis and has been cited rarely, in this study 203.4 would be antibiotic prescribing rate nationwide if prevalence of poverty could be reduced to 0. It should also be noted that from the table 2 (descriptive statistics) average prescribing rate per 1,000 population was 619.86 (min = 348; max = 974). Such a dramatic reduction in prescribing would be unlikely to be achieved by antibiotic stewardship programs alone, without targeting social determinants too.

As far as conceptual framework, this study also fits nicely into the multiple mediation model by temporal spacing of events: First, appears poverty on stage, which later "creates" chronic health conditions, which later "embodies" into antibiotic prescribing rate. This temporal sequence is the main reason why the study fits in both: theoretical and conceptual frameworks (MacKinnon et al., 2007).

Limitations of the Study

The biggest limitation of the study is that the current study looked at all antibiotics prescribed in outpatient settings per 1,000 population and didn't separate appropriate from inappropriate prescriptions. Another limitation is the fact that the outcome variable described prescriptions written in outpatient settings which excludes a small subset (5%-15%) of prescriptions written in inpatient settings (Duffy et al., 2018).

There is also a chance that mediators specified in this study are also mediated by some other factors not explored in the current parallel mediation model. For example, exacerbations of COPD which usually require antibiotic therapy can also be mediated by air pollution (Hoffmann et al., 2022).

All those limitations can be attributed to ecological design of the study which usually suffers from so called ecological fallacy – when characteristics of a community cannot be attributed to individual patient-level data (Szklo & Nieto, 2019). Although this study may be generalized to other places in the world, limitations listed above must be noted and the findings of the study interpreted with caution.

The study is unlikely to suffer from threats of validity and reliability due to simple constructs and measurements, although it should be noted that response rate for BRFSS in 2020 was 47.9% of respondents (CDC, 2021c).

Recommendations

Recommendations for further research summarized in this chapter are based on the use of an ecological design in this study which prevented me to explore patient-level data (Szklo & Nieto, 2019). Based on the current study, I would recommend conducting additional research using patient-level data such as prospective cohort and case-control studies. Ideally the studies should look at appropriate prescribing rates among socially deprived and wealthy populations to find out whether social determinants truly exert strong effect on physician's desire to treat patients with antibiotics. Additional studies should also be looking at the effect of underlying health conditions and their impact on antibiotic prescribing rates. Research can also be done to evaluate effect of changes (either improvement or worsening) of socio-economic status of populations and its impact on antibiotic prescribing rates as an outcome measure. This type of study would serve as additional evidence that social factors (poverty) can modify the effect of antibiotic prescribing rates in communities.

Implications

Social change that can be accomplished through the current research can be implemented at all levels of society. For example, at societal level it would be prudent to advise public health professionals and policymakers to use system's approach and system's thinking when designing antibiotic stewardship programs. This would also encourage public health professionals to create a multidisciplinary team with other stakeholders from the fields such as economic development, education, social services, etc. This would ensure implementation and strengthening of social programs aiming to improve social determinants of population through various non-medicalized approaches.

At organizational level and societal levels these findings would also help antibiotic stewardship programs at federal and state levels to implement adjusted risk coefficients when calculating antibiotic prescribing rates for individual physicians and facilities to eliminate bias in evaluating performance of those players. The bias may arise because unadjusted rates do not take into account patient mix and underlying health conditions of populations treated. Thus, adjustment would standardize rates while accounting for those patient-specific factors and produce comparable indicators across facilities and healthcare providers.

Methodological, theoretical and empirical implications include viewing antibiotic prescribing in a broader context. For example, while constructing conceptual frameworks and specifics of the model considering additional potential mediators that might influence mediators specified in my study. Additionally, it would be desirable to investigate antibiotic prescribing as a moderated mediation model with various interactions in place, or alternatively with different chronic or acute health conditions as mediators.

Thus, recommendations for practice include but are not limited to policy changes when it comes to antibiotic stewardship programs on societal and organizational levels. Current work would also help prescribers to shift the blame away from the ones with higher prescribing rates compared to the peers, because current discourse often considers peer-to-peer comparison as an acceptable approach without considering patients' underlying health conditions and severity of those conditions (Clegg et al., 2019).

Conclusions

Finally, at the end of this work, I would review the approach currently used in antibiotic stewardship programs: Antibiotic prescribing rates cannot be reduced by targeting prescribers only through federal and state antibiotic stewardship programs. The reason is quite simple: Medical practice is highly influenced by patient-specific factors and those factors are highly influenced by socio-economic (poverty) conditions of patients being treated. Without looking broadly at the antibiotic prescribing process, without reducing levels of poverty we will continue breeding drug-resistant strains in our communities and pay enormous price later, when those strains infect different segments of our society, and we will run out of effective antibiotics to treat them.

References

Abraham, E. P., & Chain, E. (1988). An enzyme from bacteria able to destroy penicillin. 1940. *Reviews of Infectious Diseases*, *10*(4), 677–678.

Abu-Ashour, W., Twells, L. K., Valcour, J. E., & Gamble, J.-M. (2018). Diabetes and the occurrence of infection in primary care: a matched cohort study. *BMC Infectious Diseases*, *18*(1), 67. https://doi.org/10.1186/s12879-018-2975-2

Andersen, C. J., Murphy, K. E., & Fernandez, M. L. (2016). Impact of obesity and metabolic syndrome on immunity. *Advances in Nutrition, 7*(1), 66–75. https://doi.org/10.3945/an.115.010207

Andreatos, N., Grigoras, C., Shehadeh, F., Pliakos, E. E., Stoukides, G., Port, J., Flokas, M. E., & Mylonakis, E. (2017). The impact of HIV infection and socioeconomic factors on the incidence of gonorrhea: A county-level, US-wide analysis. *PloS one*, *12*(9), e0183938. https://doi.org/10.1371/journal.pone.0183938

Association of American Medical Colleges. (2021). *2020 State Physician Workforce Data Report*. Retrieved on May 23, 2022 from https://store.aamc.org/downloadable/download/sample/sample_id/506/

Axelsson Fisk, S., & Merlo, J. (2017). Absolute rather than relative income is a better socioeconomic predictor of chronic obstructive pulmonary disease in Swedish adults. *International Journal for Equity in Health, 16*(1), 70. https://doi.org/10.1186/s12939-017-0566-2

Basu, S., Berkowitz, S. A., Phillips, R. L., Bitton, A., Landon, B. E., & Phillips, R. S. (2019). Association of primary care physician supply with population mortality in the United States, 2005-2015. *JAMA internal medicine*, *179*(4), 506–514. https://doi.org/10.1001/jamainternmed.2018.7624

Berkowitz, S. A., Karter, A. J., Corbie-Smith, G., Seligman, H. K., Ackroyd, S. A., Barnard, L. S., Atlas, S. J., & Wexler, D. J. (2018). Food insecurity, food "deserts," and glycemic control in patients with diabetes: A longitudinal analysis. *Diabetes care, 41*(6), 1188–1195. https://doi.org/10.2337/dc17-1981

Bodie, M., Gale-Rowe, M., Alexandre, S., Auguste, U., Tomas, K., & Martin, I. (2019). Addressing the rising rates of gonorrhea and drug-resistant gonorrhea: There is no time like the present. *Canada communicable disease report = Releve des maladies transmissibles au Canada*, *45*(2-3), 54–62. https://doi.org/10.14745/ccdr.v45i23a02

Bongers, J., Smulders, K., & Nijhof, M. W. (2019). Severe obesity increases risk of infection after revision total hip arthroplasty. *The Journal of Arthroplasty*, *34*(12), 3023–3029. https://doi.org/10.1016/j.arth.2019.07.028

Borek, A. J., Anthierens, S., Allison, R., Mcnulty, C., Anyanwu, P. E., Costelloe, C., Walker, A. S., Butler, C. C., Tonkin-Crine, S., & On Behalf Of The Step-Up Study Team (2020). Social and contextual influences on antibiotic prescribing and antimicrobial stewardship: A qualitative study with clinical commissioning group and general practice professionals. *Antibiotics*, *9*(12), 859. https://doi.org/10.3390/antibiotics9120859

Borné, Y., Ashraf, W., Zaigham, S., & Frantz, S. (2019). Socioeconomic circumstances and incidence of chronic obstructive pulmonary disease (COPD) in an urban population in Sweden. COPD: *Journal of Chronic Obstructive Pulmonary Disease*, *16*(1), 51–57. https://doi.org/10.1080/15412555.2019.1582618

Boyce, L., Prybutok, G., & Oppong, J. (2020). Spatial variation in chronic obstructive pulmonary disease mortality rates in Texas counties (1999 - 2016). *Texas Public Health Journal*, *72*(3), 25–30.

Butler, C. C., Gillespie, D., White, P., Bates, J., Lowe, R., Thomas-Jones, E., Wootton, M., Hood, K., Phillips, R., Melbye, H., Llor, C., Cals, J., Naik, G., Kirby, N., Gal, M., Riga, E., & Francis, N. A. (2019). C-reactive protein testing to guide antibiotic prescribing for COPD exacerbations. *The New England Journal of Medicine*, *381*(2), 111–120. https://doi.org/10.1056/NEJMoa1803185

Carrillo-Vega, M. F., Albavera-Hernández, C., Ramírez-Aldana, R., & García-Peña, C. (2019). Impact of social disadvantages in the presence of diabetes at old age. *BMC Public Health*, *19*(1), 1013. https://doi.org/10.1186/s12889-019-7348-2

CDC. (2014). *About BRFSS*. https://www.cdc.gov/brfss/about/index.htm

CDC. (2015). *The core elements of antibiotic stewardship for nursing homes*. https://www.cdc.gov/longtermcare/index.html

CDC. (2019a). *Antibiotic resistance threats in the United States, 2019*. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

CDC. (2019b*). 2019 BRFSS questionnaire.* https://www.cdc.gov/brfss/questionnaires/pdf-ques/2019-BRFSS-Questionnaire-508.pdf

CDC. (2021a). *Antibiotic use questions and answers*. https://www.cdc.gov/antibiotic-use/q-a.html#anchor_1572453021219

CDC. (2021b). *Improving antibiotic use*. https://www.cdc.gov/antibiotic-use/stewardship-report/index.html

CDC. (2021c). *Behavioral Risk Factor Surveillance System. 2020 Summary Data Quality Report*. https://www.cdc.gov/brfss/annual_data/2020/pdf/2020-sdqr-508.pdf

CDC. (2022a). *Antibiotic use and resistance module*. Retrieved on December 29, 2021 https://www.cdc.gov/nhsn/pdfs/pscmanual/11pscaurcurrent.pdf

CDC. (2022b). *National diabetes statistics report.* Retrieved on February 23, 2022 from https://www.cdc.gov/diabetes/data/statistics-report/index.html

CDC. (n.d.a). *Antibiotic resistance & patient safety portal*. Retrieved on December 29, 2021 from https://arpsp.cdc.gov/profile/antibiotic-use/all-classes

CDC. (n.d.b). *Behavioral risk factor surveillance system*. Retrieved on December 30, 2021 from https://www.cdc.gov/brfss/index.html

Clegg, H. W., Bean, R. A., Ezzo, S. J., Hoth, A. N., Sheedy, D. J., & Anderson, W. E. (2019). Impact of education and peer comparison on antibiotic prescribing for pediatric respiratory tract infections. *Pediatric quality & safety*, *4*(4), e195. https://doi.org/10.1097/pq9.0000000000000195

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences*. (2nd ed). New York: Routledge.

Consolazio, D., Koster, A., Sarti, S., Schram, M. T., Stehouwer, C., Timmermans, E. J., Wesselius, A., & Bosma, H. (2020). Neighbourhood property value and type 2 diabetes mellitus in the Maastricht study: A multilevel study. *PloS one*, *15*(6), e0234324. https://doi.org/10.1371/journal.pone.0234324

Czepiel, J., Dróżdż, M., Pituch, H., Kuijper, E. J., Perucki, W., Mielimonka, A., Goldman, S., Wultańska, D., Garlicki, A., & Biesiada, G. (2019). *Clostridium difficile* infection: review. *European journal of clinical microbiology & infectious diseases: official publication of the European Society of Clinical Microbiology*, *38*(7), 1211–1221. https://doi.org/10.1007/s10096-019-03539-6

Deshpande, N. C., & Amrutiya, M. R. (2017). Obesity and oral health - Is there a link? An observational study. *Journal of Indian Society of Periodontology, 21*(3), 229–233. https://doi.org/10.4103/jisp.jisp_305_16

Dik, V. K., van Oijen, M. G., Smeets, H. M., & Siersema, P. D. (2016). Frequent use of antibiotics is associated with colorectal cancer risk: Results of a nested case-control study. *Digestive diseases and sciences*, *61*(1), 255–264. https://doi.org/10.1007/s10620-015-3828-0

Dryden, M., Johnson, A. P., Ashiru-Oredope, D., & Sharland, M. (2011). Using antibiotics responsibly: right drug, right time, right dose, right duration. *The Journal of antimicrobial chemotherapy*, *66*(11), 2441–2443. https://doi.org/10.1093/jac/dkr370

Duffy, E., Ritchie, S., Metcalfe, S., Van Bakel, B., & Thomas, M. G. (2018). Antibacterials dispensed in the community comprise 85%-95% of total human antibacterial consumption. *Journal of Clinical Pharmacy & Therapeutics*, *43*(1), 59–64. https://doi.org/10.1111/jcpt.12610

Egen, O., Beatty, K., Blackley, D. J., Brown, K., & Wykoff, R. (2017). Health and social conditions of the poorest versus wealthiest counties in the United States. *American journal of public health, 107*(1), 130–135. https://doi.org/10.2105/AJPH.2016.303515

Fan, J. X., Wen, M., & Li, K. (2019). Associations between obesity and neighborhood socioeconomic status: Variations by gender and family income status. *SSM - population health, 10,* 100529. https://doi.org/10.1016/j.ssmph.2019.100529

Garcia, MR. & Wray, AA. (2021). Sexually transmitted infections. In: StatPearls [Internet]. *Treasure Island (FL): StatPearls Publishing; 2021* Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560808/

Guo F, & Shen H. (2021). Glycosylated hemoglobin as a predictor of sepsis and all-cause mortality in trauma patients. *Infection and Drug Resistance, ume 14*, 2517–2526.

Hair, J. F., Hult, G. T. M., Ringle, C. M., & Sarstedt, M. (2014). *A Primer on Partial Least Squares Structural Equation Modeling.* Thousand Oaks: Sage

Hayes, A. (2018). *Introduction to mediation, moderation, and conditional process analysis, second edition: A regression-based approach (methodology in the social sciences).* (2nd ed.). New York, NY: Guilford Press.

Hayes, A. F., & Rockwood, N. J. (2017). Regression-based statistical mediation and moderation analysis in clinical research: Observations, recommendations, and implementation. Behavior research and therapy, 98, 39–57. https://doi.org/10.1016/j.brat.2016.11.001

Hoffmann, C., Maglakelidze, M., von Schneidemesser, E., Witt, C., Hoffmann, P., &

Butler, T. (2022). Asthma and COPD exacerbation in relation to outdoor air pollution in the metropolitan area of Berlin, Germany. *Respiratory research, 23*(1), 64. https://doi.org/10.1186/s12931-022-01983-1

Hsia, J., Zhao, G., Town, M., Ren, J., Okoro, C. A., Pierannunzi, C., & Garvin, W. (2020). Comparisons of estimates from the behavioral risk factor surveillance system and other national health surveys, 2011-2016. *American journal of preventive medicine, 58*(6), e181–e190. https://doi.org/10.1016/j.amepre.2020.01.025

Hsu, P. C., & Chen, S. J. (2018). Obesity and risk of urinary tract infection in young children presenting with fever. *Medicine, 97*(49), e13006. https://doi.org/10.1097/MD.0000000000013006

Hussain, Z., Curtain, C., Mirkazemi, C., Gadd, K., Peterson, G. M., & Zaidi, S. (2019). Prophylactic cefazolin dosing and surgical site infections: Does the dose matter in obese patients? *Obesity surgery, 29*(1), 159–165. https://doi.org/10.1007/s11695-018-3497-0

Ibrahim, O. M., & Polk, R. E. (2012). Benchmarking antimicrobial drug use in hospitals. *Expert Review of Anti-Infective Therapy, 10*(4), 445–457. https://doi.org/10.1586/eri.12.18

Jacobs, E., Tönnies, T., Rathmann, W., Brinks, R., & Hoyer, A. (2019). Association between regional deprivation and type 2 diabetes incidence in Germany. *BMJ open diabetes research & care, 7*(1), e000857. https://doi.org/10.1136/bmjdrc-2019-000857

Jerram, S. T., Dang, M. N., & Leslie, R. D. (2017). The role of epigenetics in type 1 diabetes. *Current diabetes reports, 17*(10), 89. https://doi.org/10.1007/s11892-017-0916-x

Johnston, K. J., Thorpe, K. E., Jacob, J. T., & Murphy, D. J. (2019). The incremental cost of infections associated with multidrug-resistant organisms in the inpatient hospital setting-A national estimate. *Health services research, 54*(4), 782–792. https://doi.org/10.1111/1475-6773.13135

Jung S. J. (2021). Introduction to mediation analysis and examples of its application to real-world data. *Journal of preventive medicine and public health = Yebang Uihakhoe chi*, *54*(3), 166–172. https://doi.org/10.3961/jpmph.21.069

Kabbani, S., Palms, D., Bartoces, M., Stone, N., & Hicks, L. A. (2018). Outpatient antibiotic prescribing for older adults in the United States: 2011 to 2014. *Journal of the American Geriatrics Society, 66*(10), 1998–2002. https://doi.org/10.1111/jgs.15518

Kelly, A. M., Mathema, B., & Larson, E. L. (2017). Carbapenem-resistant Enterobacteriaceae in the community: a scoping review. *International journal of antimicrobial agents, 50*(2), 127–134. https://doi.org/10.1016/j.ijantimicag.2017.03.012

Kenny, D. (2021). *Mediation*. Retrieved on May 28, 2022 from https://davidakenny.net/cm/mediate.htm#RR

Kim, B. (2016). *Introduction to Mediation Analysis*. University of Virginia Library. Retrieved on May 28, 2022 from https://data.library.virginia.edu/introduction-to-mediation-analysis/

Kim, E. J., Ha, K. H., Kim, D. J., & Choi, Y. H. (2019). Diabetes and the risk of infection: A national cohort study. *Diabetes & Metabolism Journal*, *43*(6), 804–814. https://doi.org/10.4093/dmj.2019.0071

Kim, Y., Landgraf, A., & Colabianchi, N. (2020). Living in high-SES neighborhoods is protective against obesity among higher-income children but not low-income children: Results from the Healthy Communities Study. *Journal of Urban Health: Bulletin of the New York Academy of Medicine*, *97*(2), 175–190. https://doi.org/10.1007/s11524-020-00427-9

King, L. M., Bartoces, M., Fleming-Dutra, K. E., Roberts, R. M., & Hicks, L. A. (2020). Changes in US outpatient antibiotic prescriptions from 2011-2016. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*, *70*(3), 370–377. https://doi.org/10.1093/cid/ciz225

Klement R. J. (2020). The SARS-CoV-2 crisis: A crisis of reductionism? *Public health*, *185*, 70–71. https://doi.org/10.1016/j.puhe.2020.06.019

Krieger N. (1994). Epidemiology and the web of causation: has anyone seen the spider? *Social science & medicine (1982)*, *39*(7), 887–903. https://doi.org/10.1016/0277-9536(94)90202-x

Krieger, N. (2011). *Epidemiology and the people's health: Theory and context*. New York, NY: Oxford University Press.

Lacal, I., & Ventura, R. (2018). Epigenetic inheritance: Concepts, mechanisms and perspectives. *Frontiers in molecular neuroscience*, *11*, 292.

https://doi.org/10.3389/fnmol.2018.00292

López Romo, A., & Quirós, R. (2019). Appropriate use of antibiotics: an unmet need. *Therapeutic advances in urology, 11*, 1756287219832174. https://doi.org/10.1177/1756287219832174

Lukehart, S. A., Godornes, C., Molini, B. J., Sonnett, P., Hopkins, S., Mulcahy, F., Engelman, J., Mitchell, S. J., Rompalo, A. M., Marra, C. M., & Klausner, J. D. (2004). Macrolide resistance in *Treponema pallidum* in the United States and Ireland. *The New England Journal of Medicine*, *351*(2), 154–158. https://doi.org/10.1056/NEJMoa040216

MacKinnon, D. P., Fairchild, A. J., & Fritz, M. S. (2007). Mediation analysis. *Annual review of psychology*, *58*, 593–614. https://doi.org/10.1146/annurev.psych.58.110405.085542

Mendenhall, E., Kohrt, B. A., Norris, S. A., Ndetei, D., & Prabhakaran, D. (2017). Non-communicable disease syndemics: poverty, depression, and diabetes among low-income populations. *The Lancet*, *389*(10072), 951–963. https://doi.org/10.1016/S0140-6736(17)30402-6

Meydan, C., Bekenstein, U., & Soreq, H. (2018). Molecular regulatory pathways link sepsis with metabolic syndrome: Non-coding RNA elements underlying the sepsis/metabolic cross-talk. *Frontiers in molecular neuroscience, 11*, 189. https://doi.org/10.3389/fnmol.2018.00189

Mölter, A., Belmonte, M., Palin, V., Mistry, C., Sperrin, M., White, A., Welfare, W., & Van Staa, T. (2018). Antibiotic prescribing patterns in general medical practices in England: Does area matter? *Health & place*, *53*, 10–16. https://doi.org/10.1016/j.healthplace.2018.07.004

Momattin, H., Al-Ali, A. Y., Mohammed, K., & Al-Tawfiq, J. A. (2018). Benchmarking of antibiotic usage: An adjustment to reflect antibiotic stewardship program outcome in a hospital in Saudi Arabia. *Journal of infection and public health, 11*(3), 310–313. https://doi.org/10.1016/j.jiph.2017.08.008

Montano D. (2017). Association between socioeconomic determinants and the metabolic syndrome in the German health interview and examination survey for adults (DEGS1) - a mediation analysis. *The review of diabetic studies: RDS*, *14*(2-3), 279–294. https://doi.org/10.1900/RDS.2017.14.279

Morel, C. M., Lindahl, O., Harbarth, S., de Kraker, M., Edwards, S., & Hollis, A. (2020). Industry incentives and antibiotic resistance: an introduction to the antibiotic susceptibility bonus. *The Journal of antibiotics*, *73*(7), 421–428. https://doi.org/10.1038/s41429-020-0300-y

Mushtaq, A., & Kazi, F. (2020). New guidelines to treat bacterial infections. *The Lancet. Infectious diseases, 20*(11), 1239. https://doi.org/10.1016/S1473-3099(20)30799-4

Ogden, C. L., Fakhouri, T. H., Carroll, M. D., Hales, C. M., Fryar, C. D., Li, X., & Freedman, D. S. (2017). Prevalence of obesity among adults, by household income and education - United States, 2011-2014. *MMWR. Morbidity and mortality weekly report, 66*(50), 1369–1373. https://doi.org/10.15585/mmwr.mm6650a1

Okubo, Y., Nochioka, K., & Testa, M. A. (2018). The impact of pediatric obesity on hospitalized children with lower respiratory tract infections in the United States. *The clinical respiratory journal*, *12*(4), 1479–1484. https://doi.org/10.1111/crj.12694

Petersen, M. R., Cosgrove, S. E., Quinn, T. C., Patel, E. U., Kate Grabowski, M., & Tobian, A. (2021). Prescription antibiotic use among the US population 1999-2018: National Health and Nutrition Examination Surveys. *Open forum infectious diseases*, *8*(7), ofab224. https://doi.org/10.1093/ofid/ofab224

Plackett, B. (2020). Why big pharma has abandoned antibiotics. *Nature*, *586*(7830), S50. https://doi.org/10.1038/d41586-020-02884-3

Pulia, M., Kern, M., Schwei, R. J., Shah, M. N., Sampene, E., & Crnich, C. J. (2018). Comparing appropriateness of antibiotics for nursing home residents by setting of prescription initiation: a cross-sectional analysis. *Antimicrobial resistance and infection control*, *7*, 74. https://doi.org/10.1186/s13756-018-0364-7

Raju, S., Keet, C. A., Paulin, L. M., Matsui, E. C., Peng, R. D., Hansel, N. N., & McCormack, M. C. (2019). Rural residence and poverty are independent risk factors for chronic obstructive pulmonary disease in the United States. *American Journal of Respiratory and Critical Care Medicine*, *199*(8), 961–969. https://doi.org/10.1164/rccm.201807-1374OC

Reygaert W. C. (2018). An overview of the antimicrobial resistance mechanisms of bacteria. *AIMS microbiology*, *4*(3), 482–501. https://doi.org/10.3934/microbiol.2018.3.482

Rivas, A. L., Leitner, G., Jankowski, M. D., Hoogesteijn, A. L., Iandiorio, M. J., Chatzipanagiotou, S., Ioannidis, A., Blum, S. E., Piccinini, R., Antoniades, A., Fazio, J. C., Apidianakis, Y., Fair, J. M., & Van Regenmortel, M. (2017). Nature and consequences of biological reductionism for the immunological study of infectious diseases. *Frontiers in immunology, 8*, 612. https://doi.org/10.3389/fimmu.2017.00612

Rowe, T. A., & Linder, J. A. (2019). Novel approaches to decrease inappropriate ambulatory antibiotic use. *Expert review of anti-infective therapy, 17*(7), 511–521. https://doi.org/10.1080/14787210.2019.1635455

Sillankorva, S., Pereira, M. O., & Henriques, M. (2019). Editorial: Antibiotic alternatives and combinational therapies for bacterial infections. *Frontiers in microbiology, 9,* 3359. https://doi.org/10.3389/fmicb.2018.03359

Singer, M., Bulled, N., Ostrach, B., & Mendenhall, E. (2017). Syndemics and the biosocial conception of health. *The Lancet, 389*(10072), 941–950. https://doi.org/10.1016/S0140-6736(17)30003-X

Skandalis, N., Maeusli, M., Papafotis, D., Miller, S., Lee, B., Theologidis, I., & Luna, B. (2021). Environmental spread of antibiotic resistance. *Antibiotics (Basel, Switzerland), 10*(6). https://doi.org/10.3390/antibiotics10060640

Smith, K. W., Krieger, N., Kosheleva, A., Urato, M., Waterman, P. D., Williams, D. R., Carney, D. R., Chen, J. T., Bennett, G. G., & Freeman, E. (2020). A structural model of social determinants of the metabolic syndrome. *Ethnicity & disease, 30*(2), 331–338. https://doi.org/10.18865/ed.30.2.331

Stevermer, J. J., Fisher, L., Lin, K. W., Liu, R., Goodenberger, D., Schellhase, K., Vaughan, B., & Bird, M. D. (2021). Pharmacologic management of COPD exacerbations: A clinical practice guideline from the AAFP. *American Family Physician*, *104*(1), 1–online.

Streeter, R. A., Snyder, J. E., Kepley, H., Stahl, A. L., Li, T., & Washko, M. M. (2020). The geographic alignment of primary care Health Professional Shortage Areas with markers for social determinants of health. PloS one, 15(4), e0231443. https://doi.org/10.1371/journal.pone.0231443

Suay-García, B., & Pérez-Gracia, M. T. (2019). Present and future of Carbapenem-resistant Enterobacteriaceae (CRE) Infections. *Antibiotics (Basel, Switzerland)*, *8*(3), 122. https://doi.org/10.3390/antibiotics8030122

Szklo, M., & Nieto, F. J. (2019). *Epidemiology: Beyond the basics (4th ed.).* Sudbury, MA: Jones and Bartlett.

Tängdén, T., Cars, O., Melhus, A., & Löwdin, E. (2010). Foreign travel is a major risk factor for colonization with *Escherichia coli* producing CTX-M-type extended-spectrum beta-lactamases: a prospective study with Swedish volunteers. *Antimicrobial agents and chemotherapy*, *54*(9), 3564–3568. https://doi.org/10.1128/AAC.00220-10

Testa, A., & Jackson, D. B. (2019). Food insecurity, food deserts, and waist-to-height ratio: Variation by sex and race/ethnicity. *Journal of Community Health*, *44*(3), 444–450. https://doi.org/10.1007/s10900-018-00601-w

Thu, P., Huong, M., Thi, N. T., Thanh, H. N., & Minh, K. P. (2021). Combination antibiotic therapy versus monotherapy in the treatment of acute exacerbations of chronic obstructive pulmonary disease: an open-label randomized trial. *BMC infectious diseases, 21*(1), 1019. https://doi.org/10.1186/s12879-021-06687-3

Tichter, A. M., & Ostrovskiy, G. (2018). Emergency department antibiotic use for exacerbations of COPD. *Open access emergency medicine: OAEM, 10*, 193–200. https://doi.org/10.2147/OAEM.S178134

van der Zande, M. M., Dembinsky, M., Aresi, G., & van Staa, T. P. (2019). General practitioners' accounts of negotiating antibiotic prescribing decisions with patients: a qualitative study on what influences antibiotic prescribing in low, medium and high prescribing practices. *BMC family practice*, *20*(1), 172. https://doi.org/10.1186/s12875-019-1065-x

van Duin, D., & Doi, Y. (2017). The global epidemiology of carbapenemase-producing Enterobacteriaceae. *Virulence*, *8*(4), 460–469. https://doi.org/10.1080/21505594.2016.1222343

van Santen, K. L., Edwards, J. R., Webb, A. K., Pollack, L. A., O'Leary, E., Neuhauser, M. M., Srinivasan, A., Pollock, D. A. (2018). The standardized antimicrobial administration ratio: A new metric for measuring and comparing antibiotic use. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*, *67*(2), 179–185. https://doi.org/10.1093/cid/ciy075

Vollenweider, D. J., Frei, A., Steurer-Stey, C. A., Garcia-Aymerich, J., & Puhan, M. A. (2018). Antibiotics for exacerbations of chronic obstructive pulmonary disease. *The Cochrane database of systematic reviews*, *10*(10), CD010257.

Volpi, C., Shehadeh, F., & Mylonakis, E. (2019). Correlation of antimicrobial prescription rate and county income in Medicare part D. *Medicine*, *98*(22), e15914. https://doi.org/10.1097/MD.0000000000015914

Waddington C. H. (1968). Towards a theoretical biology. *Nature*, *218*(5141), 525–527. https://doi.org/10.1038/218525a0

Wang, H., Guo, Z., Zheng, Y., Yu, C., Hou, H., & Chen, B. (2021). No casual relationship between T2DM and the risk of infectious diseases: A two-sample mendelian randomization study. *Frontiers in Genetics, 12,* 1–11.

Wheaton, A. G., Liu, Y., Croft, J. B., VanFrank, B., Croxton, T. L., Punturieri, A., Postow, L., & Greenlund, K. J. (2019). Chronic obstructive pulmonary disease and smoking status - United States, 2017. *MMWR. Morbidity and mortality weekly report*, *68*(24), 533–538. https://doi.org/10.15585/mmwr.mm6824a1

Wilson, H. L., Daveson, K., & Del Mar, C. B. (2019). Optimal antimicrobial duration for common bacterial infections. *Australian prescriber*, *42*(1), 5–9. https://doi.org/10.18773/austprescr.2019.001

Wind, C. M., de Vries, E., Schim van der Loeff, M. F., van Rooijen, M. S., van Dam, A. P., Demczuk, W., Martin, I., & de Vries, H. (2017). Decreased azithromycin susceptibility of Neisseria gonorrhoeae isolates in patients recently treated with azithromycin. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*, *65*(1), 37–45. https://doi.org/10.1093/cid/cix249

World Health Organization. (2021). *Antibiotic resistance*. Retrieved on December 26, 2021 from https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance

Wu, H. H., Liu, H. Y., Lin, Y. C., Hsueh, P. R., & Lee, Y. J. (2016). Correlation between levofloxacin consumption and the incidence of nosocomial infections due to fluoroquinolone-resistant Escherichia coli. *Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi, 49*(3), 424–429. https://doi.org/10.1016/j.jmii.2011.12.019

Yang, P., Chen, Y., Jiang, S., Shen, P., Lu, X., & Xiao, Y. (2020). Association between the rate of fluoroquinolones-resistant gram-negative bacteria and antibiotic consumption from China based on 145 tertiary hospitals data in 2014. *BMC infectious diseases, 20*(1), 269. https://doi.org/10.1186/s12879-020-04981-0

Yi, J., & Kim, K. H. (2021). Identification and infection control of carbapenem-resistant Enterobacterales in intensive care units. *Acute and critical care, 36*(3), 175–184. https://doi.org/10.4266/acc.2021.00409

Zang, E., Lynch, S. M., & West, J. (2021). Regional differences in the impact of diabetes on population health in the USA. *Journal of epidemiology and community health, 75*(1), 56–61. https://doi.org/10.1136/jech-2020-214267

Zare, H., Gaskin, D. D., & Thorpe, R. J., Jr (2021). Income inequality and obesity among US Adults 1999-2016: Does sex matter? *International journal of environmental research and public health, 18*(13), 7079. https://doi.org/10.3390/ijerph18137079