HEALTHCARE SYSTEM DISTRUST AND NON-PRESCRIPTION ANTIBIOTIC USE IN THE UNITED STATES AND MEXICO: A CROSS-SECTIONAL SURVEY OF ADULT ANTIBIOTIC USERS

by

Brooke Hawkes

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As members of the Master's Committee, we certify that we have read the thesis prepared by: Brooke Hawkes

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and recommend that it be accepted as fulfilling the thesis requirement for the Master's Degree.

Katherine Ellingson
Kate Ellingson — Date: Apr 25, 2022

Melanie Bell — Date: Apr 25, 2022

Kacey Ernst — Date: May 4, 2022

Jill Guernsey de Zapien
Jill Guernsey De Zapien — Date: Apr 25, 2022

Final approval and acceptance of this thesis is contingent upon the candidate's submission of the final copies of the thesis to the Graduate College.

I hereby certify that I have read this thesis prepared under my direction and recommend that it be accepted as fulfilling the Master's requirement.

Katherine Ellingson
Kate Ellingson — Date: Apr 25, 2022
Epidemiology and Biostatistics

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We respectfully acknowledge that the University of Arizona is on the land and territories of Indigenous peoples. Today, Arizona is home to 22 federally recognized tribes, with Tucson being home to the O'odham and the Yaqui. Committed to diversity and inclusion, the University strives to build sustainable relationships with sovereign Native Nations and Indigenous communities through education offerings, partnerships, and community service.

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ABSTRACT

Background: Antimicrobial resistance is a growing public health threat and one that requires urgent attention. Antimicrobial stewardship programs are being utilized to encourage the appropriate use of antibiotics in a clinical setting, however, less has been done to address non-prescription use. There is limited research on predictors of non-prescription antibiotic use, but healthcare system distrust could be a potential motivator. The objectives of this study are to determine if there is a relationship between non-prescription antibiotic use and healthcare system distrust in the United States and Mexico, as well as how race, ethnicity, and proximity to the United States-Mexico border affect this association.

Methods: This cross-sectional survey collected responses from August 2020 to August 2021 in the United States and Mexico. Data analysis included chi-square and t-tests to determine differences in characteristics by non-prescription or prescription antibiotic use. Logistic regression models were specified to calculate odds ratios (ORs) with 95% confidence intervals (CIs) to model use of non-prescription antibiotics by the level of healthcare system distrust. Models adjusted for significant confounders were fit with interaction terms for race. ethnicity, and proximity to the border for United States participants.

Results: The mean healthcare system distrust score for this sample was 28.3 on a 10-50 scale (50=highest distrust) and 48.6% had used non-prescription antibiotics. After adjusting for significant covariates, the odds of using non-prescription antibiotics was 3.51 (95% CI: 1.9, 6.5) times higher for those in the highest distrust quartile versus the lowest. A significant interaction was not detected when models were fit for race, ethnicity, or proximity to the border interaction terms.

Conclusions: Our results suggest that individuals with higher levels of healthcare system distrust have higher odds of using non-prescription antibiotics compared to those with lower levels of healthcare system distrust. The relationship between healthcare system distrust and non-prescription antibiotic use does not appear to be modified by race, ethnicity, or proximity to the border for United States participants, but further research is needed to understand the complexities of this relationship.

INTRODUCTION

Antibiotic resistance is a growing public health threat and one that requires urgent attention.[1–6] Bacteria have been shown to have the ability to develop resistance to antibiotics since antibiotics were first discovered.[7,8] This was originally addressed through the development of novel antibiotics. In recent decades, however, production of new antibiotics has slowed immensely, and the prevalence of antibiotic-resistant bacterial pathogens has grown at an alarming rate.[2] As a result, infections of the urinary tract, respiratory tract, skin and soft tissue, and gastrointestinal tract, including healthcare-associated infections and sexually transmitted infections, are becoming increasingly difficult to treat with first- second- and third-generation antibiotics.[9] Infection with an antibiotic-resistant bacterial pathogen can result in longer hospital stays, higher medical costs, and increased mortality.[9]

The discovery and widespread distribution of antibiotics was one of the greatest achievements in modern medicine and has saved countless lives. For most of human history, infectious diseases have been the leading cause of morbidity and mortality.[10] In the United States, deaths due to infectious disease in 1900 were 45.5% of all deaths, but by 1997 made up only 4.5% of deaths.[11] In 1928, Alexander Fleming revolutionized the world of medicine when he accidentally discovered penicillin due to an uncovered Petri dish contaminated with mold spores.[12] He noticed bacteria in proximity to the mold colonies were dying and upon further investigation discovered the isolated mold was effective against all Gram-positive pathogens.[12] Fleming found isolating mold colonies in large quantities to be quite difficult and it wasn't until 1940 when two scientists, Howard Florey and Ernst Chain, developed an interest in penicillin that they were able to mass-produce the drug and use it during World War II.[12] The mass production of penicillin kickstarted a "Golden Age" of antibiotic discovery for the next twenty years. The discovery and production of novel antibiotics slowed down immensely in the 1960s and have not picked back up since.[13] No new antibiotics have been found through traditional approaches and there are few financial incentives for pharmaceutical companies to invest in finding more.[13] Instead, "quality-of-life" drugs are much more marketable and profitable.[13]

At Fleming's Nobel Prize address in 1945, he warned that "the time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant."[11] The relevance of these cautionary words today is alarming, as resistance to antimicrobial drugs is posing an extreme threat to humanity. A review commissioned by the United Kingdom in 2016 estimated that antimicrobial resistance (AMR) could cause 10 million deaths a year by 2050.[14] In comparison, an estimated 8.2 million currently die from cancer each year.[14] Many factors contribute to this number, but overuse and inappropriate use are two main contributors. As Fleming stated in his address when microbes are exposed to non-lethal quantities of antibiotics, instead of being eliminated they instead build up a resistance that can be passed on to others. The widespread success of antibiotics was revolutionary for infectious disease morbidity and mortality, but poor access to adequate health care has resulted in a lack of global regulatory standards and poor antibiotic use education.[11] Pathogens such as Carbapenem-resistant Acinetobacter, *Candida Auris* (*C. Auris*), Carbapenem-resistant Enterobacteriaceae (CRE), and drug-resistant *Neisseria gonorrhoeae* (*N.* gonorrhoeae) are all pathogens that have been named urgent threats by the Center for Disease Control.[15] A survey conducted throughout 204 countries and territories in 2019 estimated that 1.27 million deaths were directly caused by bacterial AMR.[16]

One solution to the overuse and inappropriate use of antibiotics has been antimicrobial stewardship programs. Antimicrobial stewardship programs - which promote and measure the appropriate use of antibiotics through the selection of optimal drug regimens, dose, duration of therapy, and route of admission[17] - have been implemented to address inappropriate use on a provider level. In the United States, programs such as the CDC's "Be Antibiotics Aware" or John Hopkins' "Prevent Antibiotic OverUSE (PAUSE)" are clinician-focused programs that provide education about appropriate antibiotic use for providers and include educational materials that can be used with patients.[18,19] Since the entirety of antibiotic education is routed through clinicians, it is operating under the assumption that the public trusts and utilizes their healthcare system. It also assumes that individuals that do utilize the healthcare system trust their healthcare providers enough to follow recommendations. As a result, while antimicrobial stewardship programs in clinical settings include an element of patient education, their overwhelming focus on providers does not thoroughly address the issue of self-medicating through non-prescription antibiotic use. Specifically, the concern lies with oral and injectable antibiotics as they are not considered over the counter in the way topical antibiotics can be. Finding ways to incorporate self-medication outside of a clinical setting into antimicrobial stewardship programs would help to limit unnecessary antibiotic use to control the growing rate of antibiotic resistance. Developing our understanding of what motivates someone to self-medicate with antibiotics can help inform the development of a broader base of stewardship programs, including community-based programming. However, studies on the motivations behind non-prescription antibiotic use are limited.

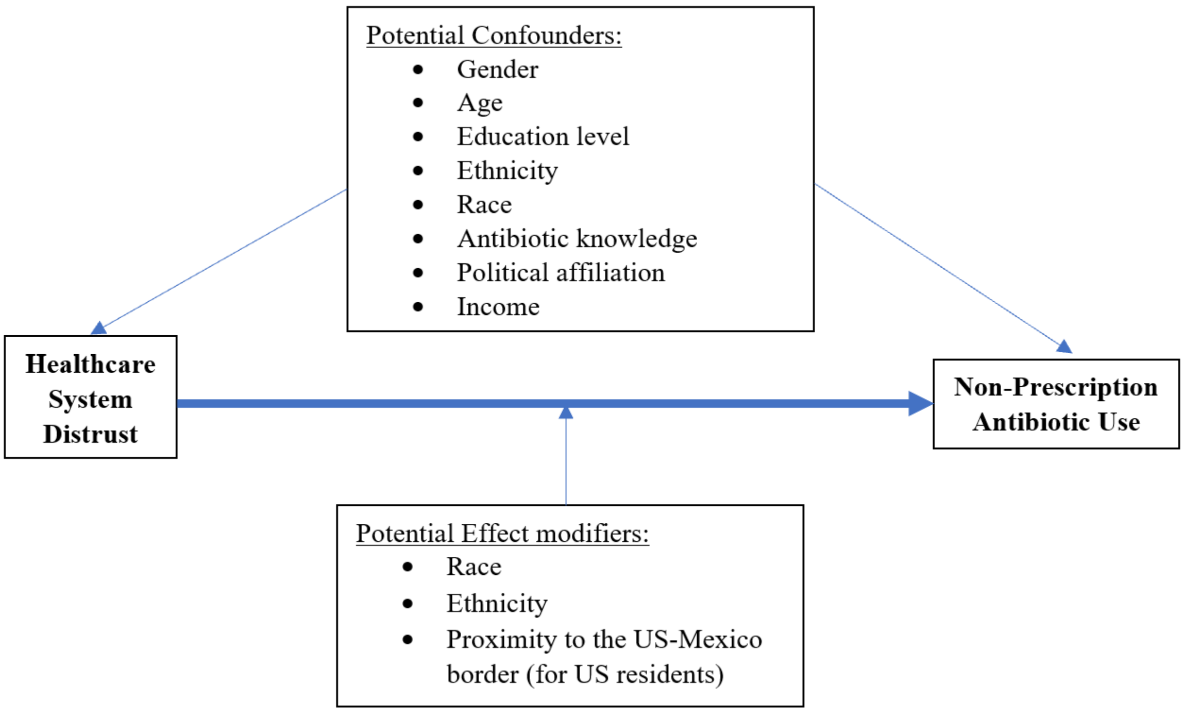
AMR is a global health threat and should be addressed as such. How different countries and regions approach the problem of AMR varies extensively, however its effects will be felt on a global scale. Many low- and middle-income countries have limited enforcement concerning antibiotic self-medication, however, this is a central strategy for promoting appropriate use. In 2010, the Mexican National Health Council announced a new policy that limited antibiotic sales to prescription-only.[20] In theory this new legislation had the potential to significantly lower AMR within Mexico, however many pharmacy associations - particularly small, independent pharmacies - were strongly opposed to this new policy. They argued that it created logistical difficulties, corruption, and had negative economic impacts on both pharmacies and their clients.[20] As a result, pharmacies began installing physicians' consultation offices within or close to their establishments, which introduced a conflict of interest between the two entities.[20,21] Since there is a financial gain for pharmacies to sell more antibiotics, it is unsurprising that the coupling of consultation offices and pharmacies has not resulted in effective antibiotic use regulation. These consultation offices tend to have much faster wait times than a traditional doctor's office.[21] Mexico's healthcare system is overburdened and long wait times are not uncommon, so the popularity and growth of consultation offices are to be expected.[21] Mexico has not seen a notable decrease in AMR and self-medication in the last ten years. Many pathogens are increasing resistance.[22] The ineffectiveness of this legislation suggests that although efforts have been made to decrease AMR in Mexico, there are still gaps that need to be addressed.

The United States has a similar law that also prohibits antibiotic use without a prescription.[23] No studies have been identified on non-prescription antibiotic use in the general United States population, however, surveys conducted on Latin American immigrants and patients attending a sexually transmitted disease clinic reveal that self-medicating is not an uncommon practice, as 14-26% of participants in these groups reported non-prescription antibiotic use within a year of each study.[24–27] Using leftover supplies from a previous prescription or borrowing from a family member or friend are common methods of using antibiotics without a formal prescription.[6,28] There is also evidence that some individuals bring antibiotics into the country from locations where they are more accessible, such as Latin America.[28] Although there is evidence that non-prescription antibiotic use is present in the United States, research is still very limited.

In both the United States and Mexico, healthcare system distrust is a potential motivator and predictor for non-prescription antibiotic use. Healthcare system distrust includes both distrust in one's provider as well as an overarching skepticism of the medical system as a whole, including a sense of whether or not they will be able to access services when necessary. Public skepticism of the healthcare system, including hospitals, health insurance companies, and medical research, is persistent and continues to grow, from anti-vaccination movements to denying the effectiveness of pre-exposure prophylaxis (PrEP) at preventing HIV infections.[29,30] Healthcare system distrust has been highly prevalent during the current COVID-19 pandemic and is thought to play a role in exacerbating COVID-19 disparities.[31] In Mexico, the overburdened healthcare system provided many barriers to vaccine distribution and medical services.[32] This unreliability of care undoubtedly has driven down citizens' trust in their healthcare system. In general, socially and economically marginalized groups have shown higher levels of mistrust, a reflection of historic and ongoing injustices.[33] Healthcare system distrust can have a wide variety of negative consequences, including lower utilization of healthcare services,[34,35] worse management of health conditions,[36,37] and lower involvement in medical research.[38,39] Since healthcare system distrust can result in lower utilization of healthcare services, there is reason to believe this could influence an individual's decision to self-medicate with antibiotics. **The primary objective of this study is to determine if there is a relationship between healthcare system distrust and non-prescription antibiotic use utilizing a survey of adult antibiotic users in the United States and Mexico.**

There are potential confounders when examining this relationship. Previous studies have shown that young adults are the most likely to self-medicate as they become more independent and are encouraged to be independent about self-care.[40,41] Older age is associated with healthcare system distrust.[42] Women have been prescribed antibiotics at higher rates than men,[43] so men may be more likely to self-medicate and previous studies have suggested that women are more likely to feel like they are not being cared for appropriately during their encounters with healthcare professionals.[44] While there are no previous studies examining the relationship between antibiotic knowledge and healthcare system distrust or non-prescription antibiotic use, there is reason to believe that poor knowledge could result in higher distrust and higher non-prescription use. Not knowing how to appropriately use antibiotics or not understanding the consequences of inappropriate use could result in using non-prescription antibiotics inappropriately and at a higher rate. Similarly, someone with low antibiotic knowledge may not trust their healthcare provider's guidance if they do not fully comprehend the science behind the recommendations being given. While there are similarities between the United States and Mexico's healthcare systems, there are many distinct differences that could alter both an individual's trust in their healthcare system and their non-prescription antibiotic use. Since the healthcare systems operate differently, healthcare system distrust differs between the countries as well. Reasons for distrust and levels of distrust may vary. Non-prescription antibiotics are much more readily available in Mexico than in the United States, so this could also alter the relationship between healthcare system distrust and non-prescription antibiotic use.[45] After adjusting for these confounding factors, we hypothesize that higher healthcare system distrust will result in higher levels of non-prescription antibiotic use.

Figure 1. Directed acyclic graph demonstrating the relationship between healthcare system distrust and non-prescription antibiotic use



Our secondary aim is to investigate whether race and/or ethnicity modifies the relationship between healthcare system distrust and non-prescription antibiotic use in the United States and Mexico. Racial and ethnic minorities have been shown to have higher levels of healthcare system distrust, a reflection of historic and ongoing injustices within the medical system.[46] For 40 years and ending in 1972, black individuals apart of a syphilis study were not treated or made aware that a treatment had been discovered for researchers to observe the disease take its course.[47] Today, black women are 3-4 times more likely to die of childbirth compared to white women in the United States.[48] These injustices understandably result in more distrust among racial and ethnic minorities. Black and Hispanic children have also been shown to be prescribed antibiotics at a lower rate than white children.[49] If someone who is black and Hispanic knows they are less likely to be prescribed antibiotics by their provider, their distrust might drive them to access non-prescription antibiotics at a different rate than someone who is not black or Hispanic.[49–52] Past literature also suggests that Latinx communities in the United States are more likely to use non-prescription antibiotics, in part because of larger access within their communities and due to cultural attitudes around antibiotics.[26] There is no literature on how being black or Hispanic impacts the effect of healthcare system distrust on non-prescription antibiotic use. Since previous studies suggest that race and ethnicity impact healthcare system distrust and non-prescription antibiotic use independently, we want to further explore this relationship and observe whether or not these factors result in a multiplicative effect.

Our final aim is to analyze a subsample of United States participants to determine if living within 100km of the United States-Mexico border modifies the relationship between healthcare system distrust and self-medicating with non-prescription antibiotics. Even though Mexico passed a law in 2010 limiting antibiotic sales to prescription-only, antibiotics are still easy to access. Many pharmacies are located along the border and are utilized by both Mexican residents and United States residents.[53] The high circulation of antibiotics along the border could result in people living along the border having higher access to non-prescription antibiotics. The border region has a higher uninsured rate, lower access to healthcare, and higher rates of poverty than the greater United States.[54] These are all factors that affect an individual's trust in their healthcare system. While there is no literature on how living along the border affects the relationship between healthcare system distrust and non-prescription antibiotic use, we are interested in whether it has any multiplicative effect on this relationship. Understanding whether the effect of healthcare system distrust is amplified for those in the US-Mexico border region can help inform the development of community-based antimicrobial stewardship programs in this region.

METHODS

Study Design

A cross-sectional survey was conducted to understand antibiotic seeking in the United States and Mexico during the COVID-19 pandemic. The survey was administered to participants over 18 years old in the United States and Mexico. Recruitment throughout the United States and Mexico was done through Amazon Mechanical Turk (MTurk), a crowdsourcing marketplace that individuals or businesses can use to outsource virtual tasks.[55] Responses were collected from August 8, 2020 to June 28, 2021 and participants received $5 directly through MTurk. We also oversampled at the United States-Mexico border by directly recruiting participants with flyers distributed through academic-community partnerships in the border regions. Community partners posted flyers at health clinics and COVID-19 test sites. Flyers were available in both English and Spanish and had a QR code linking participants to an online survey. Direct recruitment responses were collected from December 18, 2020 to August 4, 2021 and participants were emailed a $5 Amazon gift card. All responses were housed in Qualtrics, an online survey software.[56] Protocol and all recruitment methods went through a full review and received IRB approval (Protocol number: 2007883915).

This analysis was restricted to adult oral or injectable antibiotic users to exclude over-the-counter topical antibiotic use. Topical antibiotics can be bought legally without a prescription in some cases, so our analysis needed to be restricted to non-prescription antibiotic use specifically outside the sanction of the medical system. To account for any insincere responses, anyone who had a completion time of fewer than seven minutes, decided a priori, was excluded. For our primary analysis, we eliminated any participants who did not answer questions concerning non-prescription antibiotic use or demographics. Since our demographics questions were located at the end of our survey, we were not able to assess patterns of missingness for incomplete surveys so opted for a complete case analysis. During the study period, some surveys started receiving responses that were completed by internet bots. To ensure we only included legitimate responses, we added the question: “Please select C to make sure you are human.” We removed anyone with an incorrect response to this question.

Measures

We defined non-prescription antibiotic use by using two true or false questions from the survey: “I have bought non-prescription oral or injectable antibiotics within the past 3 years” and “I have asked my friends or family for leftover oral or injectable antibiotics within the past 3 years.” If a participant responds true to either of the questions, they will be considered to have sought out non-prescription antibiotics. If they answer false for both questions, they will not fall under this classification.

Our primary exposure was healthcare system distrust, measured using a 10-question validated scale: the Healthcare System Distrust Scale.[57] Each question could be answered via a scale of strongly disagree, disagree, not sure, agree, and strongly agree. Individual questions could be scored 1 to 5, with 5 being equivalent to the highest level of distrust. If a question in this scale was left blank, it was given the same number of points as answering, “not sure.” Total scores can range from 10 to 50, with higher scores indicating more distrust. See **Appendix 1** for details on the questions in this scale and possible responses. Our exposure variable was defined by dividing the scores into quartiles, a cutoff that has been previously used with this scale in past literature.[42]

We selected potential covariates for our adjusted model a prior based on past knowledge and a review of the literature.[43,58–60] Categorical variables included gender, age, education level, ethnicity, race, political affiliation, income, and proximity to the United States-Mexico border. These variables were all treated as categorical due to the survey being multiple choice. Variables were collapsed if strata were thin (less than 10) including age, education level, income, and race. The continuous variable, antibiotic knowledge (scale 0-10), was a scale created by compiling questions related specifically to antibiotic knowledge on the survey. This scale was composed of 10 questions with higher scores indicating a higher level of antibiotic knowledge. See **Appendix 2** for the list of questions, possible responses, and how each response was scored. We also tested potential effect modifiers in our secondary analyses. These included race, ethnicity, and proximity of United States residents to the United States-Mexico border.

Statistical analysis

We first estimated summary descriptive statistics for our sample of interest, including stratifying by non-prescription and prescription antibiotic users. For categorical variables, we presented proportions and frequencies and used chi-squared tests to identify any significant differences between the strata. For continuous variables, data were presented in mean ± standard deviation (SD) format and we used t-tests to identify strata differences. We also presented the odds ratios of responses for each component of the healthcare system distrust scale for our overall sample, United States participants only, and Mexico participants only. A correlation matrix of Pearson Correlation Coefficients was presented to demonstrate how the components of the distrust scale were related.

To assess the possible relationship between healthcare system distrust and non-prescription antibiotic use, we used unadjusted and adjusted logistic regression models to estimate the odds (with 95% confidence intervals) of non-prescription antibiotic use in each distrust quartile with the lowest quartile acting as our reference group. Our fully adjusted model included the variables chosen a priori, described above. We also included a partially adjusted model, only including covariates that were significant in our fully adjusted model.

We conducted a sensitivity analysis to test the robustness of our partially adjusted model by redefining our inclusion criteria and rerunning all models. The survey did not have a question to limit the sample to strictly oral or injectable antibiotic users in the last 3 years, even though that was how antibiotic use was defined in the non-prescription antibiotic use question. In the primary model, we limited the sample to all oral and injectable antibiotic users, assuming that this use was recent. To account for this assumption, in our first sensitivity analysis we limited the sample to individuals who had used antibiotics the year before when they completed their survey. This included anyone who answered “In the last year”, "In the last 6 months", "Within the past 3 months", or "Within the past month" to the question "When was the last time you took oral antibiotics outside of a hospital setting?" We used the same covariates as our primary analysis.

We also ran two more sensitivity analyses where we redefined our outcome variable, non-prescription antibiotic use, using just one question instead of two. For our first analysis, non-prescription antibiotic users were classified as anyone who answered "True" to the question "I have bought non-prescription oral or injectable antibiotics within the past 3 years" and anyone who answered "False" was classified as a prescription antibiotic user. Our second analysis used the question "I have asked my friends or family for leftover oral or injectable antibiotics within the past 3 years," with anyone answering "True" classified as a non-prescription antibiotic user.

To test for interaction between healthcare system distrust and race, we fit our partially adjusted model with an interaction term to test for effect modification. Using the same method, we tested for interaction between healthcare system distrust and ethnicity. We also analyzed a sub-sample limited to just our United States data by running our partially adjusted model. For our adjusted model, we used the same covariates as our primary analysis and proceeded to fit an interaction term to test whether proximity to the border modifies the effect of healthcare system distrust on non-prescription antibiotic use.

We assessed the assumptions of logistic regression: independence and linearity in the log odds for continuous variables. All statistical analyses performed in this study used SAS OnDemand for Academics.[61]

RESULTS

Figure 2. Flowchart of participants included in primary statistical analysis

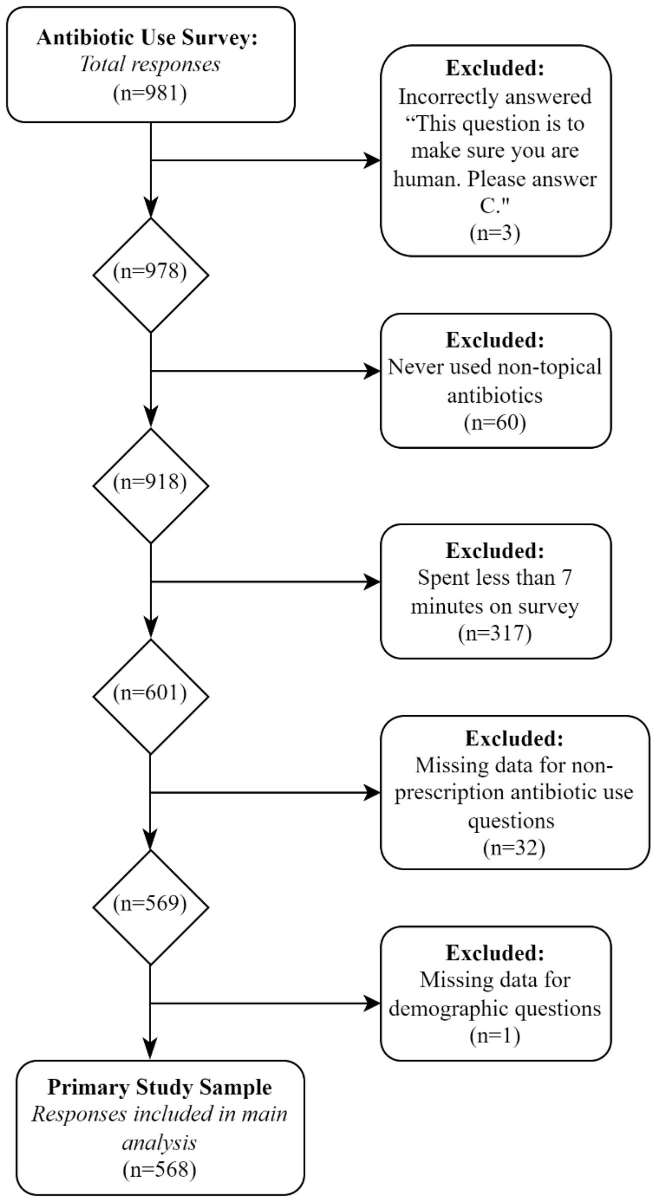


Table 1. Characteristics of the primary study sample: non-prescription vs. prescription antibiotic users in the United States and Mexico (n=568)

Characteristic	Total (n=568)	Non-Prescription (n=276)	Prescription (n=292)	p-value
	n (%)	n (%)	n (%)	χ^2-test
Gender				0.57
Male	310 (54.6)	154 (49.7)	156 (50.3)	
Female	258 (45.4)	122 (47.3)	136 (52.7)	
Age				<0.01
18-24	28 (4.9)	15 (53.8)	13 (46.4)	
25-34	229 (40.3)	132 (57.6)	97 (42.4)	
35-44	189 (33.3)	87 (46.0)	102 (54.0)	
45-54	66 (11.6)	24 (36.4)	42 (63.6)	
55+	56 (9.9)	18 (32.1)	38 (67.9)	
Education level				<0.01
High school diploma or less	120 (21.1)	44 (36.6)	76 (63.3)	
High school diploma or more	448 (78.9)	232 (51.8)	216 (48.2)	
Income[a]				0.02
Low	51 (9.0)	26 (51.0)	25 (49.0)	
Middle	301 (53.0)	161 (53.5)	140 (46.5)	
High	216 (38.0)	89 (41.2)	127 (58.8)	
Political views				<0.01
Very left wing/liberal	55 (9.7)	15 (27.3)	40 (72.7)	
Left wing/liberal	107 (18.8)	51 (47.7)	56 (52.3)	
Center left/slightly liberal	52 (9.2)	23 (44.2)	29 (55.8)	
Middle of the road	113 (19.9)	40 (35.4)	73 (64.6)	
Center right/slightly conservative	63 (11.1)	29 (46.0)	34 (54.0)	
Right wing/conservative	135 (23.8)	89 (65.9)	46 (34.1)	
Very right wing/conservative	43 (7.6)	29 (67.4)	14 (32.6)	
Ethnicity				0.15
Hispanic / Latinx	185 (32.6)	98 (53.0)	87 (47.0)	
Non-Hispanic / Latinx	383 (67.4)	178 (46.5)	205 (53.5)	
Race				<0.01
White	399 (70.3)	180 (45.1)	219 (54.9)	
American Indian or Alaskan Native	11 (1.9)	6 (54.6)	5 (45.5)	
Asian	24 (4.2)	9 (37.5)	15 (62.5)	
Black or African American	79 (13.9)	58 (73.4)	21 (26.6)	
Native Hawaiian or Pacific Islander	6 (1.1)	6 (100.0)	0 (0.0)	
Mixed race	20 (3.5)	6 (30.0)	14 (70.0)	
Other	29 (5.1)	11 (37.9)	18 (62.1)	
Country of primary residence				0.62
United States	475 (83.6)	233 (49.0)	242 (51.0)	
Mexico	93 (16.4)	43 (46.2)	50 (53.8)	
Proximity to the US-Mex border				0.82
Zip code ≤100km	58 (10.2)	29 (50.0)	29 (50.0)	
Zip code >100km	510 (89.8)	247 (48.4)	263 (51.6)	
	mean (±SD)	mean (±SD)	mean (±SD)	t-test
Antibiotic knowledge[b]	5.11 (±3.0)	3.6 (±2.5)	6.5 (±2.8)	<0.01
Healthcare system distrust[c]	28.3 (±6.7)	30.6 (±6.1)	26.1 (±6.8)	<0.01

[a]Low income: <$20,000 (US) / <$10,000 (pesos) (MX) | Middle: $20-60,000 (US) / $10-30,000 (pesos) (MX) | High: $60,000+ (US) / $30,000 (pesos) (MX) | [b]Scores possible: 0-10, higher scores=more antibiotic knowledge | [c]Scores possible: 10-50, higher scores=more healthcare system distrust | SD = standard deviation

For our primary analysis, 568 participants were included from the 983 original responses after our exclusion criteria were applied (**Figure 2**). In general, our sample was younger, had at least a high school diploma, white, and middle/high income. Most were not Hispanic/Latinx or of Spanish Origin (67.4%) and had a primary residence in the United States (83.6%). Our total sample had 10.2% of participants living within 100 kilometers of the United States-Mexico border. We had an even distribution of political affiliations and only slightly more men than women. The mean antibiotic knowledge score was 5.11 out of 10. Complete summary statistics are shown in **Table 1**.

In our sample, non-prescription antibiotic use was significantly different by age, with younger individuals more likely to use non-prescription antibiotics. Those with a high school diploma or higher were more likely to use non-prescription antibiotics ([n, %]: 232, 51.8%) than someone without a high school diploma (44, 36.6%). Individuals with a high income were less likely to use non-prescription antibiotics (89, 41.2%) compared to low (26, 51.0%) or middle income (161, 53.5%). There were fewer individuals who were more left-wing/liberal who used non-prescription antibiotics compared to those more right-leaning / conservative. There was a slight difference among ethnicities, with Hispanic / Latinx (98, 53.0%) individuals more likely to use non-prescription antibiotics than non-Hispanic / Latinx individuals (178, 46.5%). Black or African American individuals showed a higher proportion of non-prescription antibiotic use (58, 73.4%) than white individuals (180, 45.1%). Our other racial categories were much more sparse, but American Indian or Alaskan Native (6, 54.6%), Native Hawaiian or Pacific Islander (6, 100.0%) were more likely to use non-prescription antibiotics, while racial categories such as Asian (9, 37.5%), mixed-race (6, 30.0%), or anyone who classified as “other” (11, 37.9%) were less likely to be in the non-prescription category. Lower antibiotic knowledge scores were seen in non-prescription antibiotic use as well as higher healthcare system distrust scores, highlighted in **Table 2.**

Table 2. Characteristics of the primary study sample: non-prescription vs. prescription antibiotic users in the United States and Mexico (n=568)

Characteristic	Total (n=568)	Non-Prescription (n=276)	Prescription (n=292)	*p*-value
	n (%)	n (%)	n (%)	χ^2-test
Healthcare System Distrust - categorical				<0.01
Quartile 1 (lowest scores)		39 (27.3)	104 (72.7)	
Quartile 2		55 (38.2)	89 (61.8)	
Quartile 3		102 (61.1)	65 (38.9)	
Quartile 4 (highest scores)		80 (70.2)	34 (29.8)	
		mean (±SD)	mean (±SD)	t-test
Healthcare System Distrust[a] - continuous		30.6 (±6.1)	26.1 (±6.8)	<0.01

[a]Scores possible: 10-50, higher scores=more healthcare system distrust | SD = standard deviation

The assumptions for our primary analysis logistic regression models were met. The observations were independent and there was linearity between the Antibiotic Knowledge Scale, our only continuous predictor, and our outcome, non-prescription antibiotic use. See **Appendix 3** for details on our assessments of model assumptions.

As shown in **Table 3**, before adjusting for potential confounding we found that as someone's healthcare system distrust increases, the odds of non-prescription antibiotic use also increase. More specifically, the odds of someone in quartile 2 using non-prescription antibiotics is 1.65 times that of someone in quartile 1, the lowest distrust quartile (95% Confidence Interval [CI]: 1.0, 2.7). The odds of someone in quartile 3 using non-prescription antibiotics is 4.19 (95% CI: 2.6, 6.8) times that of someone in quartile 1, and the odds of someone in quartile 4 are 6.23 (95% CI: 3.6, 10.8) times that of someone in quartile 1. After adjusting for all potential confounders, we saw a similar relationship, whereas the quartile of distrust increased, and so did the odds of non-prescription antibiotic use. Someone in quartile 2 had 1.33 (95% CI: 0.8, 2.3) times the odds of using non-prescription antibiotics, quartile 3 had 2.10 (95% CI: 1.2, 3.6) times the odds, and quartile 4 had 3.20 (95% CI: 1.8, 6.1) times the odds compared to quartile 1. The significant confounders that we included in our partially adjusted model included race and antibiotic knowledge scores. We also included political views in this model since it was only marginally insignificant in our fully adjusted model (95% CI: 1.0, 2.4). Our partially adjusted model yielded similar results to our unadjusted and fully adjusted models, with non-prescription antibiotic use increasing with the level of healthcare system distrust. Quartile 2 had 1.34 (95% CI: 0.8, 2.4) times the odds of using non-prescription antibiotics compared to quartile 1, quartile 3 had 2.36 (95% CI: 1.4, 4.0) times the odds, and quartile 4 had 3.51 (95% CI: 1.9, 6.5) times the odds. All three of these models are also visualized in **Figure 3**.

Table 3. Results of primary logistic regression analysis for non-prescription antibiotic use with healthcare system distrust as a predictor (n=568)

	Unadjusted OR (95% CI)	Fully Adjusted[a] OR (95% CI)	Partially Adjusted[b] OR (95% CI)
Healthcare system distrust score[c]			
Quartile 1 (lowest)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quartile 2	1.65 (1.0, 2.7)	1.33 (0.8, 2.3)	1.34 (0.8, 2.4)
Quartile 3	4.19 (2.6, 6.8)	2.10 (1.2, 386)	2.36 (1.4, 4.0)
Quartile 4 (highest)	6.23 (3.6, 10.8)	3.20 (1.8, 6.1)	3.51 (1.9, 6.5)
Gender			
Male	--	1.00 (ref)	--
Female	--	1.09 (0.7, 1.6)	--
Age			
18-34	--	1.00 (ref)	--
35+	--	0.72 (0.5, 1.1)	--
Education level			
High school diploma or more	--	1.00 (ref)	--
High school diploma or less	--	0.83 (0.5, 1.4)	--
Income[d]			
High	--	1.00 (ref)	--
Low / middle	--	1.45 (0.9, 2.2)	--
Political views			
Liberal / middle of the road	--	1.00 (ref)	1.00 (ref)
Conservative	--	1.56 (1.0, 2.4)	1.39 (0.9, 2.1)
Ethnicity			
Not Hispanic/Latinx or of Spanish origin	--	1.00 (ref)	--
Hispanic/Latinx or of Spanish origin	--	1.16 (0.7, 2.0)	--
Race			
Non-black / African American	--	1.00 (ref)	1.00 (ref)
Black / African American	--	2.34 (1.3, 4.3)	2.48 (1.4, 4.5)
Country of primary residence			
United States	--	1.00 (ref)	--
Mexico	--	1.40 (0.7, 2.9)	--
Proximity to the US-Mex border			
Zip code >100km	--	1.00 (ref)	--
Zip code ≤100km	--	1.27 (0.6, 2.6)	--
Antibiotic knowledge[e]	--	0.75 (0.7, 0.8)	0.75 (0.7, 0.8)

OR = odds ratio, CI = confidence interval

[a]Adjusted for: gender, age, education level, income, political views, ethnicity, race, country of primary residence, proximity to US-MEX border, antibiotic knowledge level

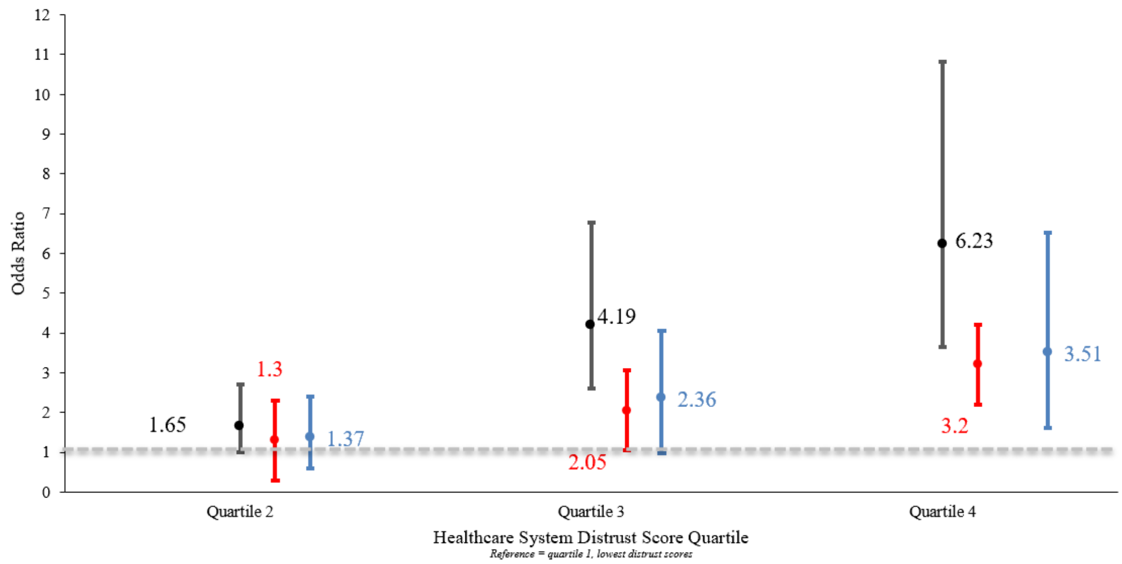
[b]Adjusted for only significant covariates: race, political views, antibiotic knowledge

[c]Scores possible: 10-50, higher scores=more healthcare system distrust

[d] Low / middle income: <$60,000 (US) / <$30,000 (pesos) (MX) | High: $60,000+ (US) / $30,000 (pesos) (MX)

[e]Scores possible: 0-10, higher scores=more antibiotic knowledge

Figure 3. Odds of using non-prescription antibiotics by healthcare system distrust score quartile (n=568)



Unadjusted Model
Fully Adjusted Model: adjusted for age, sex, country of primary residence, ethnicity, race, education level, and proximity to US-Mex border, antibiotic knowledge
Partially Adjusted Model: (only significant covariates included) adjusted for: race, antibiotic knowledge

After breaking down our distrust score into its components, we saw that transparency of blood tests (OR=1.65) was the component that showed the largest effect of distrust on non-prescription antibiotic use. Transparency of medical ingredients (OR=1.49), transparency of medical errors (OR=1.43) and privacy of medical records (OR=1.39) also showed larger effects. Privacy of medical records (OR=0.92) and prioritization of medical needs (OR=1.01) showed the smallest effect of distrust on non-prescription use. The effects of each component are highlighted in **Table 4.** In the sample that was United States participants only, the effects we saw were consistent with our entire sample. Transparency of blood tests (OR=1.71), transparency of medication ingredients (OR=1.53), transparency of medical errors (OR=1.47), and the privacy of medical records (OR=1.43) were the components with the largest effects, while privacy of medical records (OR=0.89) and prioritization of medical needs (OR=0.96) showed the smallest effects. For our Mexico sample, the largest effects we saw were due to deaths due to medical errors (OR=1.66), quality of medical care (OR=1.64), transparency of blood tests (OR=1.59), and transparency of medical errors (OR=1.49). The smallest effects were from privacy of medical records

(OR=0.98) and profit versus quality of care (OR=1.12). A correlation matrix is shown in **Table 5** demonstrating how the different component of the healthcare system distrust score are related. **Appendix 4** gives details on the distribution of how each component was answered.

Table 4. Results of adjusted logistic regression, individual distrust components as a predictor

Distrust Component	Adjusted OR[a] (95% CI) Entire Sample (n=568)	Adjusted OR[a] (95% CI) US only (n=475)	Adjusted OR[a] (95% CI) Mexico only (n=93)
1. Transparency of medical experiments	1.23 (1.0, 1.4)	1.30 (1.1, 1.6)	1.13 (0.8, 1.7)
2. Privacy of medical records	0.92 (0.8, 1.1)	0.89 (0.7, 1.1)	0.98 (0.6, 1.6)
3. Deaths due to medical errors	1.23 (1.0, 1.5)	1.26 (1.0, 1.5)	1.66 (0.9, 2.9)
4. Transparency of blood tests	1.65 (1.4, 2.0)	1.71 (1.4, 2.1)	1.59 (0.9, 2.9)
5. Transparency of medical errors	1.43 (1.2, 1.7)	1.47 (1.2, 1.8)	1.49 (0.9, 2.4)
6. Privacy of medical records	1.39 (1.2, 1.7)	1.43 (1.2, 1.7)	1.26 (0.8, 2.1)
7. Profit versus quality of care	1.15 (1.0, 1.4)	1.18 (1.0, 1.4)	1.12 (0.7, 1.8)
8. Quality of medical care	1.21 (1.0, 1.5)	1.13 (0.9, 1.4)	1.64 (1.0, 2.7)
9. Prioritization of medical needs	1.01 (0.8, 1.2)	0.96 (0.8, 1.2)	1.35 (0.8, 2.2)
10. Transparency of medication ingredients	1.49 (1.2, 1.8)	1.53 (1.3, 1.9)	1.17 (0.7, 1.9)

OR = odds ratio, CI = confidence interval

[a]Adjusted for antibiotic knowledge, race, political affiliation, and ethnicity

Table 5. Pearson Correlation Coefficients of distrust scale components (n=568)

	1.	**2.**	**3.**	**4.**	**5.**	**6.**	**7.**	**8.**	**9.**	**10.**
1. Transparency of medical experiments	1.00	0.12	0.31	0.63	0.46	0.61	0.40	-.01	-.12	0.48
2. Privacy of medical records	0.12	1.00	-.02	0.06	0.07	0.23	0.05	0.33	0.32	0.09
3. Deaths due to medical errors	0.31	-.02	1.00	0.32	0.50	0.30	0.41	0.08	0.03	0.34
4. Transparency of blood tests	0.63	0.06	0.32	1.00	0.49	0.62	0.40	0.01	-.12	0.58
5. Transparency of medical errors	0.46	0.07	0.50	0.49	1.00	0.49	0.49	0.16	0.08	0.47
6. Privacy of medical records	0.61	0.23	0.30	0.62	0.49	1.00	0.43	-.01	-.11	0.49
7. Profit versus quality of care	0.40	0.05	0.41	0.40	0.49	0.43	1.00	0.25	0.17	0.39
8. Quality of medical care	-.01	0.33	0.08	0.01	0.16	-.01	0.25	1.00	0.62	0.05
9. Prioritization of medical needs	-.12	0.32	0.03	-.12	0.08	-.11	0.17	0.62	1.00	-.05
10. Transparency of medication ingredients	0.48	0.09	0.34	0.58	0.47	0.49	0.39	0.05	-.05	1.00

As shown in **Table 6**, the results of our first sensitivity analysis, which restricted our partially adjusted model to recent oral antibiotic users only, we saw similar trends as we saw in our primary analysis. After redefining our exclusion criteria, our sample consisted of 378 responses. We saw an increase in odds of using non-prescription antibiotics as the quartile of healthcare system distrust scores increased, consistent with our original findings.

Table 6. Results of primary logistic regression analysis to sensitivity analysis, restricted to recent antibiotic users only

	Primary Analysis (n=568)	**Sensitivity Analysis (n=378)**
	Adjusted OR[a] (95% CI)	Adjusted OR[a] (95% CI)
Healthcare system distrust score[b]		
Quartile 1 (lowest)	1.00 (ref)	1.00 (ref)
Quartile 2	1.34 (0.8, 2.4)	1.91 (1.0, 3.8)
Quartile 3	2.36 (1.4, 4.0)	2.53 (1.3, 4.9)
Quartile 4 (highest)	3.51 (1.9, 6.5)	3.29 (1.5, 7.0)
Political views		
Liberal / middle of the road	1.00 (ref)	1.00 (ref)
Conservative	1.39 (0.9, 2.1)	1.36 (0.8, 2.3)
Race		
Non-black / African American	1.00 (ref)	1.00 (ref)
Black / African American	2.48 (1.4, 4.5)	1.66 (0.9, 3.2)
Antibiotic knowledge[c]	0.75 (0.7, 0.8)	0.75 (0.7, 0.8)

OR = odds ratio, CI = confidence interval
Recent antibiotic users = individuals who answered: "In the last year", "In the last 6 months", "Within the past 3 months", or "Within the past month" to the question "When was the last time you took oral antibiotics outside of a hospital setting?"
[a]Adjusted for only significant covariates: race, political views, antibiotic knowledge
[b]Scores possible: 10-50, higher scores=more healthcare system distrust
[c]Scores possible: 0-10, higher scores=more antibiotic knowledge

As shown in **Table 7**, our results in our second and third sensitivity analyses reveal that the magnitude of the effect varies depending on whether "non-prescription antibiotic use" is defined as buying non-prescription antibiotics or borrowing non-prescription antibiotics from a family member or friend. When it is defined as buying non-prescription antibiotics, the odds ratios are smaller. Using this definition, someone in quartile 2 has 1.23 (95% CI: 0.7, 2.2) times the odds of using non-prescription antibiotics compared to quartile 1, someone in quartile 3 has 1.65 (95% CI: 0.9, 2.9) times the odds, and someone in quartile 4 has 1.97 (95% CI: 1.1, 3.6) times the odds. However, when "non-prescription antibiotic use" is defined as borrowing non-prescription antibiotics from a family member or friend, someone in quartile 2 has 2.56 (95% CI: 1.2, 5.3) times the odds of using non-prescription antibiotics compared to quartile 1, someone in quartile 3 has 3.33 (95% CI: 1.7, 6.7) times the odds, and someone in quartile 4 has 5.95 (95% CI: 2.8, 12.5) times the odds.

Table 7. Results of sensitivity analyses: relationship between healthcare system distrust and non-prescription antibiotic use, non-prescription antibiotic use redefined (n=568)

	Bought Non-Prescription Antibiotics[a] (n=568)	**Borrowed Non-Prescription Antibiotics[b] (n=568)**
	Adjusted OR[c] (95% CI)	Adjusted OR[c] (95% CI)
Healthcare system distrust score[d]		
Quartile 1 (lowest)	1.00 (ref)	1.00 (ref)
Quartile 2	1.23 (0.7, 2.2)	2.56 (1.2, 5.3)
Quartile 3	1.65 (0.9, 2.9)	3.33 (1.7, 6.7)
Quartile 4 (highest)	1.97 (1.1, 3.6)	5.95 (2.8, 12.5)
Political views		
Liberal / middle of the road	1.00 (ref)	1.00 (ref)
Conservative	0.92 (0.6, 1.4)	2.20 (1.4, 3.4)
Race		
Non-black / African American	1.00 (ref)	1.00 (ref)
Black / African American	2.79 (1.7, 4.7)	1.72 (1.0, 3.0)
Antibiotic knowledge[e]	0.78 (0.7, 0.8)	0.75 (0.7, 0.8)

OR = odds ratio, CI = confidence interval
[a]Non-prescription antibiotic use redefined: "True" for the question "I have bought non-prescription oral or injectable antibiotics within the past 3 years"
[b]Non-prescription antibiotic use redefined: "True" for the question "I have asked my friends or family for leftover oral or injectable antibiotics within the past 3 years"
[c]Adjusted for only significant covariates: race, political views, antibiotic knowledge
[d]Scores possible: 10-50, higher scores=more healthcare system distrust
[e]Scores possible: 0-10, higher scores=more antibiotic knowledge

As shown in **Table 8,** we saw a main effect of race in our partially adjusted model. Ethnicity wasn't included in our original partially adjusted model, so we also ran an adjusted model including ethnicity to observe its main effects. Being black / African American resulted in 2.48 (95% CI: 1.4, 4.5) times the odds of non-prescription antibiotic use in our original partially adjusted model, and being Hispanic / Latinx resulted in 1.34 (95% CI: 0.9, 2.2) times the odds of non-prescription antibiotic use in our partially adjusted model with the ethnicity variable included. After fitting the partially adjusted model with a race interaction term, we did not see significant race effect modification (OR: 0.95, 95% CI: 0.5, 1.6). Similarly, after fitting the partially adjusted model with the ethnicity variable included, we did not see any significant ethnicity effect modification (OR: 0.94, 95% CI: 0.6, 1.4). The full details of these interaction models are highlighted in **Table 9.**

Table 8. Partially adjusted logistic regression models showing the main effects in the relationship between healthcare system distrust and non-prescription antibiotic use (n=568)

	Significant Covariates	**Significant Covariates + Ethnicity**
	Adjusted OR[a] (95% CI)	Adjusted OR[a] (95% CI)
Healthcare system distrust score[b]		
Quartile 1 (lowest)	1.00 (ref)	1.00 (ref)
Quartile 2	1.37 (0.8, 2.4)	1.34 (1.3, 3.8)
Quartile 3	2.36 (1.4, 4.1)	2.21 (1.3, 3.8)
Quartile 4 (highest)	3.51 (1.9, 6.5)	3.35 (1.8, 6.2)
Political views		
Liberal / middle of the road	1.00 (ref)	1.00 (ref)
Conservative	1.39 (0.9, 2.1)	1.45 (1.0, 2.2)
Ethnicity		
Non-Hispanic / Latinx	--	1.00 (ref)
Hispanic / Latinx	--	1.34 (0.9, 2.2)
Race		
Non-black / African American	1.00 (ref)	1.00 (ref)
Black / African American	2.48 (1.4, 4.5)	2.57 (1.4, 4.7)
Antibiotic knowledge[c]	0.75 (0.7, 0.8)	0.75 (0.7, 0.8)

OR = odds ratio, CI = confidence interval
[a]Adjusted for only significant covariates: race, political views, antibiotic knowledge
[b]Scores possible: 10-50, higher scores=more healthcare system distrust
[c]Scores possible: 0-10, higher scores=more antibiotic knowledge

Table 9. Results of logistic regression analysis for non-prescription antibiotic use with healthcare system distrust as a predictor, investigating race and ethnicity as potential effect modifiers (n=568)

	Race Interaction	**Ethnicity Interaction**
	Adjusted OR[a] (95% CI)	Adjusted OR[a] (95% CI)
Healthcare system distrust score[b]		
Quartile 1 (lowest)	1.00 (ref)	1.00 (ref)
Quartile 2	1.39 (0.8, 2.4)	1.36 (0.8, 2.4)
Quartile 3	2.40 (1.4, 4.2)	2.29 (1.3, 4.1)
Quartile 4 (highest)	3.59 (1.9, 6.9)	3.53 (1.7, 7.2)
Political views		
Liberal / middle of the road	1.00 (ref)	1.00 (ref)
Conservative	1.39 (0.9, 2.1)	1.46 (1.0, 2.2)
Ethnicity		
Hispanic / Latinx	--	1.00 (ref)
Non-Hispanic / Latinx	--	1.57 (0.5, 5.0)
Race		
Non-black / African American	1.00 (ref)	1.00 (ref)
Black / African American	2.84 (0.7, 11.9)	2.58 (1.4, 4.7)
Antibiotic knowledge[c]	0.75 (0.7, 0.8)	0.75 (0.7, 0.8)
Race*Distrust	0.95 (0.5, 1.6)	--
Ethnicity*Distrust	--	0.94 (0.6, 1.4)

OR = odds ratio, CI = confidence interval
[a]Adjusted for only significant covariates: race, political views, antibiotic knowledge
[b]Scores possible: 10-50, higher scores=more healthcare system distrust
[c]Scores possible: 0-10, higher scores=more antibiotic knowledge

Figure 4. Flowchart of participants included in secondary statistical analysis

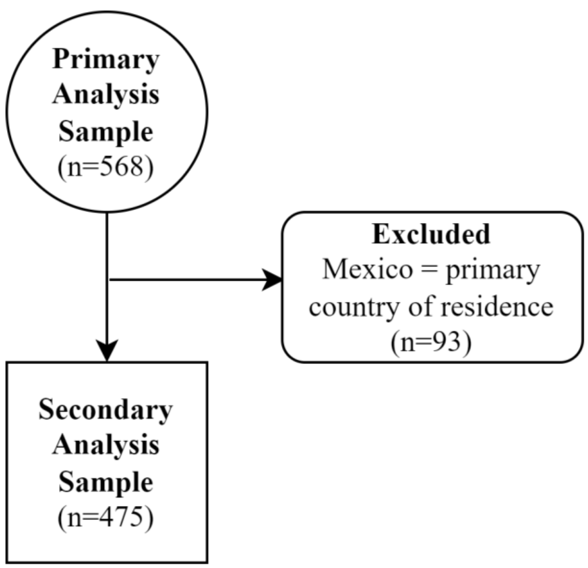


Table 10. Results of logistic regression analysis for non-prescription antibiotic use with healthcare system distrust as a predictor, investigating proximity to the United States-Mexico border as a potential effect modifier (n=475)

	Proximity to Border Interaction
	Adjusted OR[a] (95% CI)
Healthcare system distrust score[b]	
Quartile 1 (lowest)	1.00 (ref)
Quartile 2	1.13 (0.6, 2.1)
Quartile 3	2.34 (1.3, 4.3)
Quartile 4 (highest)	3.61 (1.8, 7.3)
Political views	
Liberal / middle of the road	1.00 (ref)
Conservative	1.76 (1.1, 2.8)
Race	
Non-black / African American	1.00 (ref)
Black / African American	2.91 (1.6, 5.4)
Proximity to the US-Mex border	
Zip code >100km	1.00 (ref)
Zip code ≤100km	1.25 (0.3, 6.2)
Antibiotic knowledge[c]	0.77 (0.7, 0.8)
Border region*Distrust	1.06 (0.6, 2.0)

OR = odds ratio, CI = confidence interval
[a]Adjusted for: age, sex, country of primary residence, antibiotic knowledge
[b]Scores possible: 10-50, higher scores=more healthcare system distrust
[c]Scores possible: 0-10, higher scores=more antibiotic knowledge

When limiting our sample to United States participants only, we were left with 475 responses, highlighted in **Figure 4.** Proximity to the border was not originally included in our partially adjusted model due to lack of statistical significance but was included to observe potential interaction. As shown in **Table 10**, we did not observe an interaction between proximity to the border and healthcare system distrust (OR: 1.06, 95% CI: 0.6, 2.0).

DISCUSSION

This study demonstrated that individuals with high levels of healthcare system distrust have higher odds of using non-prescription antibiotics compared to those with lower levels of healthcare system distrust. Redefining our exclusion criteria to recent antibiotic users only confirmed these findings. However, when redefining "non-prescription antibiotic use" to either buying non-prescription antibiotics or borrowing them from a family member or friend, we found that the effect of healthcare system distrust on non-prescription antibiotic use is greater for those who borrowed from a family member or friend. "Transparency of medical records" was the most distrust component that showed the largest effect on non-prescription antibiotic use. We also found that the relationship between healthcare system distrust and non-prescription antibiotic use did not appear to be modified by race or ethnicity. We did, however, observe a main effect of race and ethnicity, where those who were black or Hispanic had a higher odds of using non-prescription antibiotics than those who were non-black or non-Hispanic. The relationship between healthcare system distrust and non-prescription antibiotic use in the United States did not appear to be modified by proximity to the United States-Mexico border. In all our interaction models, however, we saw very wide confidence intervals, which indicates we may not have had high enough power to adequately power these models, and interpretation of these results should bear that in mind.

Although we did not observe interaction due to race or ethnicity, we did observe main effects that should be taken into consideration when evaluating the relationship between healthcare system distrust and non-prescription antibiotic use. We know that black and Hispanic children are less likely to be prescribed antibiotics, specifically broad-spectrum antibiotics, compared to white children.[49,52] We also know that racial and ethnic minorities show higher levels of distrust in the healthcare system.[33,35,46] If someone who is black or Hispanic knows they are less likely to be prescribed antibiotics and their distrust in the healthcare system is higher, there is potential that the relationship between their healthcare system distrust and non-prescription antibiotic use is stronger. Due to the discrepancy, we observe among black and Hispanic groups, having community-based antimicrobial stewardship programs that consider contextual differences by race and ethnicity is an important step in increasing equity of appropriate antibiotic use.

We observed a difference in non-prescription antibiotic use between the United States and Mexico in our descriptive analysis. We saw that people who considered Mexico as their primary country of residence were less likely to use non-prescription antibiotics. However, this could be due to the differences in prescribing practices and could potentially have limited our results. As previously mentioned, even though Mexico passed a law in 2010 to limit antibiotic sales to prescription-only, physician consultation offices within pharmacies have served as a major loophole and antibiotics are not necessarily more difficult to access even with the new law in place.[21] In our analysis, the meaning of "non-prescription antibiotics" held a different weight in Mexico compared to the United States. We also know that there are many pharmacies along the United States-Mexico border where antibiotics can be accessed very easily.[53] It is possible that the variation in what was considered "non-prescription antibiotic use" could have affected our border region interaction model. We did not observe a significant main effect of living along the United States-Mexico border and non-prescription antibiotic use or effect modification due to living in the border region. However, the high availability of prescription antibiotics along the border could have introduced noise to our model. Further research should be done to explore what effect the physician consultation offices are having on overall antibiotic use along the United States-Mexico border.

A limitation of this study was our exclusion criteria. The wording of our outcome variable included individuals who had taken oral or injectable antibiotics in the last 3 years. Ideally, we would have limited our study sample to participants who matched this criterion so that the only component we would be comparing would be whether the oral or injectable antibiotic used was non-prescription or prescription. However, there was no question on our survey that asked whether someone had taken oral injectable antibiotics in the past 3 years. Instead, we limited our study sample to participants who had *ever* taken oral or injectable antibiotics. This could have misclassified individuals who used non-prescription oral or injectable antibiotics without a prescription, however, if they did not do this in the past 3 years they would be classified as a prescription antibiotic user only. To address this limitation, our sensitivity analysis was limited to oral antibiotic users in the past year. This also did not match the criteria outlined in the questions we utilized for our outcome variable, however, the added time component allowed us to examine the robustness of our findings from our primary model.

Another limitation of this study was our race variable in our effect modification analysis. Due to sparse cells, we had to collapse our racial groups into two categories: black and non-black. Classifying individuals as "non-black" is problematic in that it homogenizes a group of individuals that are very much heterogeneous. To address this issue, we left our racial categories uncollapsed for other descriptive summary statistics and only used the collapsed version of this variable for our logistic regression models. Since our categories included "black or African American", a group that has been and still is discriminated against, we left the opportunity to identify possible effects of historic and current marginalization on health care system distrust. However, we acknowledge that some individuals in our "non-black" category could also have been discriminated against in the healthcare system, which could have biased our results towards the null. As the relationship between healthcare system distrust and non-prescription antibiotic use continues to be studied, having a larger and more diverse sample would allow us to better understand the implications of healthcare system distrust among a wider variety of racial groups.

Our recruitment strategies potentially acted as a further limitation. Our survey was solely online, which could have excluded individuals without access to the internet. Our sample was mostly from the United States, and it is possible that MTurk, the website we used to distribute the survey, is more popular and well-utilized in the United States. Along the border, we distributed flyers at health clinics and COVID-19 testing sites which could have resulted in selection bias, since everyone along the border who took the survey was utilizing the healthcare system. We could have been recruiting individuals with lower levels of healthcare system distrust than the general population in the border region since those with higher levels of distrust would be less likely to be utilizing their healthcare system.[34]

As far as we know, this study was the first of its kind in identifying antibiotic use and practices on this scale. Many prior non-prescription antibiotic use studies have focused on specific populations,[26,62–65,66(p),67,68] however this study was much more generalizable. It was one of the first to examine the motivations behind non-prescription antibiotic use which is information that can be leveraged to further the reach of antimicrobial stewardship programs. The cross-sectional design allowed this study to be conducted relatively quickly and inexpensively. The binational nature of this study was also a strength. Since antibiotic resistance is a global health problem, it is important that the research surrounding it is not siloed and that we continue the global collaboration. Seeing how practices in Mexico are impacting the United States, and vice versa, allows us to treat this issue more broadly.

It is important that antimicrobial stewardship programs are meeting people where they are, regardless of beliefs or healthcare practices. The relationship between healthcare system distrust and non-prescription antibiotic use reveals how important it is that appropriate antibiotic use messaging and AMR education are not solely limited to clinical settings. Community-based programming is an important step in bridging the gap between antimicrobial stewardship programs and non-prescription antibiotic use. Antimicrobial stewardship programs need to acknowledge that people make decisions outside of the healthcare system, and that trust is a big driver of this practice. We must avoid relying on language such as “talk to your provider” when delivering education on antibiotic use and antibiotic resistance. It is also important to take into account contextual differences in antibiotic use and prescribing practices by race and ethnicity when designing these programs. Further research should be done to assess how community-based programming might be leveraged to most effectively improve our antimicrobial stewardship programs.

Further research is needed to fully understand why individuals choose to access antibiotics outside of the medical system. While this study revealed that healthcare system distrust is a potential motivator, this is a complex and nuanced issue that cannot be fully addressed with a single cross-sectional study. Diversifying the populations we are studying will help us develop a more well-rounded understanding of how non-prescription antibiotic use is affecting antibiotic resistance globally and how motivations differ or are similar across different cultures and regions of the world. Our healthcare system distrust scale was more relevant for the United States healthcare system, so developing a distrust scale that is more appropriate for the Mexican healthcare system is important for fully understanding how distrust is motivating non-prescription antibiotic use outside of the United States.

AMR is a complex and important issue that needs to be addressed. Inappropriate and excessive use is one driver of resistance and although antimicrobial stewardship programs address this on a clinical level, developing our understanding of non-prescription use will further address the issue of overuse. This study reveals that healthcare system distrust is a potential motivator for seeking out antibiotics outside of the medical system, especially when individuals are borrowing non-prescription antibiotics from a family member or friend. Antimicrobial stewardship programs should include community-based programming and take into account racial and ethnic minorities' experiences with the healthcare system and antibiotic use. The experience along the United States-Mexico border is not fully understood due to the ease of accessing prescription antibiotics in pharmacies with physician consultation offices on the Mexican side of the border. Further research should be done to further understand the complexities of healthcare system distrust and non-prescription antibiotic use as well as the development and implementation of community-based antimicrobial stewardship programs.

APPENDIX 1: HEALTHCARE SYSTEM DISTRUST SCALE

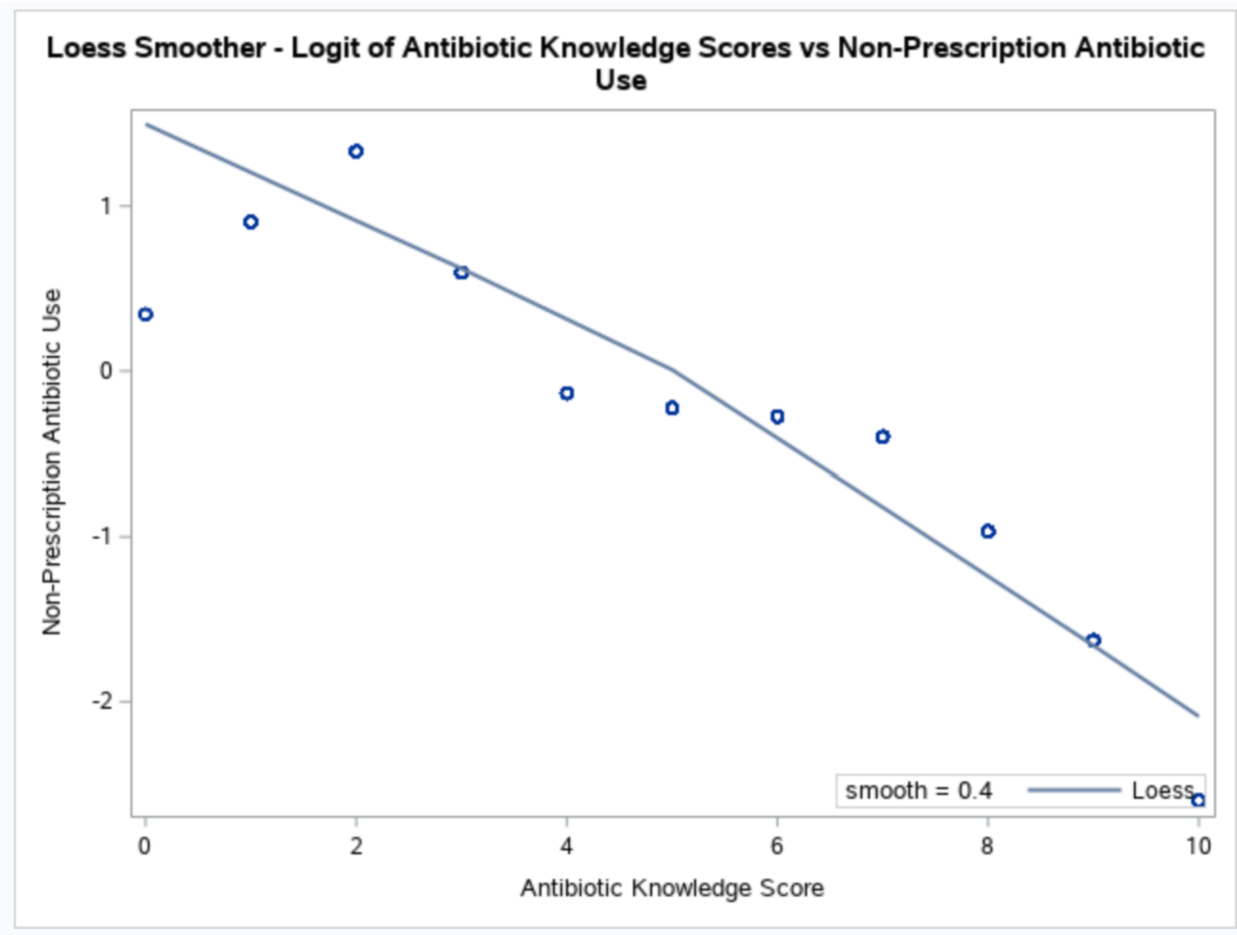
Question	Response / Scoring				
	Strongly Agree	Agree	Not Sure	Disagree	Strongly Disagree
Medical experiments can be done on me without my knowing about it.	+5	+4	+3	+2	+1
My medical records are kept private.	+1	+2	+3	+4	+5
People die every day because of mistakes by the health care system.	+5	+4	+3	+2	+1
When they take my blood, they do tests they don’t tell me about.	+5	+4	+3	+2	+1
If a mistake were made in my health care, the health care system would try to hide it from me.	+5	+4	+3	+2	+1
People can get access to my medical records without my approval.	+5	+4	+3	+2	+1
The health care system cares more about holding costs down than it does about doing what is needed for my health.	+5	+4	+3	+2	+1
I receive high-quality medical care from the health care system.	+1	+2	+3	+4	+5
The health care system puts my medical needs above all other considerations when treating my medical problems.	+1	+2	+3	+4	+5
Some medicines have things in them that they don’t tell you about.	+5	+4	+3	+2	+1

APPENDIX 2: ANTIBIOTIC KNOWLEDGE SCALE

Question	Response / Scoring				
	Strongly Agree	Agree	Not Sure	Disagree	Strongly Disagree
Antibiotics should never be saved for the next time you get sick.	+1	+1	+0	+0	+0
When I have a cold, antibiotics help me to get better more quickly.	+0	+0	+0	+1	+1
When I have a cold, I should take antibiotics to prevent getting a more serious illness	+0	+0	+0	+1	+1
It is okay to borrow antibiotics from friends or family	+0	+0	+0	+1	+1
In the big picture of antibiotic resistance, my personal use doesn't matter	+0	+0	+0	+1	+1
As soon as you are feeling better, you should stop taking antibiotics	+0	+0	+0	+1	+1
Antibiotic resistance is only a problem for those who take antibiotics regularly	+0	+0	+0	+1	+1
Skipping or forgetting a dose of antibiotics does not contribute to antibiotic resistance	+0	+0	+0	+1	+1
There is no connection between taking antibiotics and the development of resistant bacteria	+0	+0	+0	+1	+1
Bacteria that are resistant to antibiotics can be spread from person to person	+1	+1	+0	+0	+0

APPENDIX 3: ASSESSMENT OF MODEL ASSUMPTIONS

Linearity in logit of Antibiotic Knowledge Scale (continuous variable)



APPENDIX 4 : HEALTHCARE SYSTEM DISTRUST COMPONENTS

Healthcare System Distrust Components, primary sample (n=568)

	Highest Distrust (5), %	High Distrust (4), %	Not Sure (3), %	Low Distrust (2), %	Lowest Distrust (1), %
Transparency of medical experiments	10.7	19.4	15.3	30.5	24.1
Privacy of medical records	2.1	6.3	19	45.3	27.3
Deaths due to medical errors	16.2	45.8	20.8	14.6	2.6
Transparency of blood tests	6.3	18.8	19.7	33.6	21.5
Transparency of medical errors	14.1	26.8	29.1	22.9	7.2
Privacy of medical records	10.6	20.4	21.7	28.5	18.8
Profit versus quality of care	18.5	29.2	23.8	23.9	4.6
Quality of medical care	4.1	10.9	21.3	48.8	15
Prioritization of medical needs	7	17.4	24.8	38.7	12
Transparency of medication ingredients	12.9	27.5	24.5	23.4	11.8

Red = higher proportions, green = lower proportions

Healthcare System Distrust Components, United States participants only (n=475)

	Highest Distrust (5), %	High Distrust (4), %	Not Sure (3), %	Low Distrust (2), %	Lowest Distrust (1), %
Transparency of medical experiments	10.7	20.8	13.9	31.8	22.7
Privacy of medical records	2.1	6.3	16	47.6	28
Deaths due to medical errors	16	46.7	20	14.5	2.7
Transparency of blood tests	7.2	20.2	18.5	33.5	20.6
Transparency of medical errors	12.6	25.9	28.9	24.8	7.8
Privacy of medical records	12	20.4	17.9	31.2	18.5
Profit versus quality of care	16.6	29.3	23.6	25.5	5.1
Quality of medical care	2.7	9.9	19.2	51.8	16.4
Prioritization of medical needs	5.9	15.6	22.7	42.5	13.3
Transparency of medication ingredients	13.5	27.8	23.4	23.4	12

Red = higher proportions, green = lower proportions

Healthcare System Distrust Components, Mexico participants only (n=93)

	Highest Distrust (5), %	High Distrust (4), %	Not Sure (3), %	Low Distrust (2), %	Lowest Distrust (1), %
Transparency of medical experiments	10.8	11.8	22.6	23.7	31.2
Privacy of medical records	2.2	6.5	34.4	33.3	23.7
Deaths due to medical errors	17.2	40.9	24.7	15.1	2.2
Transparency of blood tests	2.2	11.8	25.8	34.4	25.8
Transparency of medical errors	21.5	31.2	30.1	12.9	4.3
Privacy of medical records	3.2	20.4	40.9	15.1	20.4
Profit versus quality of care	28	29	24.7	16.1	2.2
Quality of medical care	10.8	16.1	32.3	33.3	7.5
Prioritization of medical needs	12.9	26.9	35.5	19.4	5.4
Transparency of medication ingredients	9.7	25.8	30.1	23.7	10.8

Red = higher proportions, green = lower proportions

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