New Insights into *Neisseria gonorrhoeae* (NG)*:*

Geographic heterogeneity in Black-White disparities and spatiotemporal trends among US females and the role of azithromycin use for STI treatment in antibiotic resistance

Emily Rowlinson

A dissertation
submitted in partial
fulfillment of the requirements for the degree of

Doctor of Philosophy

University of Washington
2022

Reading committee
Matthew R. Golden, Chair
Christine M. Khosropour
James P. Hughes

Program Authorized to Offer Degree:
Public Health – Epidemiology

University of Washington

New Insights into *Neisseria gonorrhoeae* (NG)*:*

Geographic heterogeneity in Black-White disparities and spatiotemporal trends among US females and the role of azithromycin use for STI treatment in antibiotic resistance

Abstract

Emily Ellen Rowlinson

Chair of the Supervisory Committee:
Matthew R. Golden
Department of Medicine

Gonorrhea (caused by the *Neisseria gonorrhoeae* (NG) bacterium) is the second most-commonly reported sexually transmitted infection (STI) in the United States (US) and can cause serious, permanent reproductive sequalae in females. Gonorrhea rates have increased rapidly in the US throughout the last 3 decades, while profound racial disparities have stubbornly persisted with non-Hispanic Black (NHB) populations experiencing the greatest burden of disease. In geographic depictions of gonorrhea rates, the US Southeast is highlighted as the area of highest morbidity. Concerningly, NG has developed antimicrobial resistance (AMR) to nearly all drugs historically used for treatment. AMR NG is more common among men who have sex with men (MSM), which may be related to the more frequent use of antibiotics for STI treatment in this population.

While racial disparities in gonorrhea rates are well-described, our understanding of variation in the magnitude of these disparities within the US is lacking. Reduction of racial disparities is a

core goal of the 2021-2015 US National Strategic Plan for STIs; it is therefore imperative that national and local public health programs know where such disparities are greatest for interventions to have greatest impact. Similarly, national data demonstrating increases in gonorrhea rates among females may obscure informative variation in localized trends. Areas with later or earlier increases in gonorrhea rates, with high or low rates of disease, may share characteristics influential in gonorrhea epidemiology. There is also currently conflicting evidence about the role of individual-level antibiotic use on the development of AMR gonorrhea. A study of Dutch clinic attendees identified an association between AZM use and AZM resistance, while two reviews of surveillance data from the UK found no such association. In this dissertation, we sought to fill these gaps in our knowledge of gonorrhea epidemiology through several related but distinct analyses. First, we examined the geographic variation in county-level gonorrhea rates among NHB and non-Hispanic White (NHW) females using national gonorrhea surveillance data obtained from the US Centers for Disease Control and Prevention. We created a series of maps to depict the spatial distribution of within- and between-race disparities (relative and absolute) in gonorrhea rates. We then used group-based trajectory models to identify and characterize distinct groups of counties with similar trajectories of NG rates in these populations separately. Lastly, we examined the association between individual-level receipt of AZM for sexually transmitted infection treatment and subsequent NG infection with reduced susceptibility to AZM among attendees of the Public Health Seattle-King County Sexual Health Clinic (SHC).

We found that nearly all US counties had NHB female gonorrhea rates ≥3x those in NHW females, with NHB females in most highly populated counties experienced ≥9-fold difference in gonorrhea rates. Additionally, NHB females in counties in the south had lower rates of gonorrhea compared to NHB females in the Midwest and West. In our analysis of county-level spatiotemporal gonorrhea trends, we identified 9 distinct gonorrhea trajectories for NHB, 3 of which experienced declines in case rates from 2003-2018; conversely, all 7 identified trajectories among NHW females were characterized by stable or increasing rates of gonorrhea. Furthermore, counties with similar gonorrhea trajectories were sometimes, but not always, in close proximity. Finally, we found evidence for an association between receipt of AZM in the prior 30 days and having an AMR NG infection among SHC attendees.

Our first analysis highlights pervasive yet variable racial disparities in gonorrhea; further, these disparities are often greater outside the US south. These findings counter damaging regional stereotypes, provide evidence to refocus prevention efforts to areas of highest disparities, and suggest that monitoring racial disparities can function as an actionable public health metric. Our second analysis confirmed that national data do obscure a highly heterogenous gonorrhea epidemic for both NHW and NHB females. These two exploratory analyses should prompt further analysis into the differential drivers of gonorrhea morbidity. Lastly, our finding of an association between AZM use and AZM-resistance underscore the timeliness of updated STI treatment guidelines that reduce the utilization of AZM in populations at high risk for AMR NG.

Table of Contents

Chapter 1. Introduction

Gonorrhea (caused by the *Neisseria gonorrhoeae* (NG) bacterium) is the second most-commonly reported sexually transmitted infection (STI) in the United States (US)[1]. NG can infect the male and female urogenital tracts, the rectum, and the oropharynx. Male urogenital infections commonly cause male urethritis, and major complications of cervicovaginal infections include chronic pelvic pain, secondary infertility, and ectopic pregnancy[2]. NG infection during pregnancy can cause intrauterine inflammation and result in low birth weight [3] and preterm birth[4].

Concerningly, the gonococcus has progressively developed resistance to nearly all drugs historically used for treatment[5]. MSM experience a higher burden of antimicrobial resistant (AMR) NG than heterosexuals; in 2020, 9.2% of NG isolates from a US sample of MSM had reduced susceptibility to azithromycin (AZM), compared to 4.3% of isolates from a comparable sample of men who have sex with women exclusively[1]. The disparity in rates of AMR between MSM and heterosexual populations may be driven by the higher frequency of antimicrobial therapy for bacterial STIs (including NG and *Chlamydia trachomatis* [CT]*)* among MSM[6]. An analysis of clinical data from the Public Health Seattle-King County (PHSKC) Sexual Health Clinic (SHC) found that AZM is the most prescribed antibiotic for MSM, who received on average 1 dose every 2 years from 2016-2018[7]. Many of these doses are given as epidemiologic therapy after contact to a partner(s) with NG or CT infection before confirming the patient has either infection[8]. The exceptionally long half-life of AZM[9] exposes both NG and commensal *Neisseria* species (which can transfer resistance determinants to NG[10,11]) to subtherapeutic levels, leading to selective pressure for emergence of resistant strains.

There is currently conflicting evidence regarding the relationship between individual-level AZM exposure and subsequent AZM resistance in persons with NG infection. *In vitro* studies have demonstrated that exposure to erythromycin (a similar macrolide) induces high-level macrolide resistance in NG strains with low-level resistance[12], and there have been isolated case reports of *de novo* selection for AZM resistance in individuals receiving NG treatment[13,14]. However, population-level and clinical studies have demonstrated mixed results, with 1 study demonstrating a positive association between the AZM use in the previous 30 days and higher AZM minimum inhibitory concentrations (MIC) and 2 others demonstrating no association between having an AZM-resistant infection and AZM use in the prior 6 months[15] or 3 years[16] (inferred from STI surveillance records). Understanding the relationship between individual-level antibiotic therapy and AMR NG has implications for the current clinical model of frequent testing and antibiotic treatment of STIs in MSM.

In addition to the emergence of AMR NG, gaps in our knowledge of the population-level epidemiology of NG challenge our ability to effectively prioritize areas and populations with highest morbidity for intensive control and prevention. Among US females, gonorrhea rates have increased rapidly in almost all populations throughout the last decade, and profound racial disparities have persisted[17]. However, geographic variation in the magnitude of these disparities are poorly described. Current maps of NG morbidity provide an outsize focus on geographic space[18,19], obscuring important distinctions in the distribution of population-level morbidity, while race- and sex-stratified maps do not explicitly depict racial disparities. More comprehensive maps incorporating underlying population size and the magnitude of racial disparities will allow public health to focus on areas with highest morbidity and generate opportunities to identify and address social determinants of health creating the epidemiologic contexts driving racial disparities in NG rates[20–23].

Similarly, spatiotemporal trends in female NG morbidity have only inconsistently assessed beyond the state and national level. Although NG rates have increased for all race/ethnicity groups[1], it is not known whether all areas of the US experienced these increases concurrently. Understanding localized heterogeneity in these trends may be key to identifying group-level factors most influential in NG epidemiology such as socioeconomic or population characteristics, or effective local public health programs and policies. Uncovering these spatiotemporal patterns may also inform our understanding of population-level transmission dynamics.

To fill these gaps in our knowledge of NG epidemiology, we propose a set of analyses to evaluate the association between individual-level receipt of AZM for STI treatment and subsequent NG infection with AZM reduced susceptibility (Chapter 2), describe the geographic heterogeneity of within and between-race disparities in NG among non-Hispanic White and non-Hispanic Black US females (Chapter 3), and characterize the spatiotemporal epidemiology of NG among US females by classifying and mapping counties based on their trajectories of NG morbidity among non-Hispanic Black and non-Hispanic White females (Chapter 4). To conclude, we will discuss the implications of our findings for clinical management of persons at high risk for AMR NG and provide recommendations for future work building on our findings that may inform strategic approaches to NG control and prevention.

Chapter 2. “It’s not just the Southeast - geographically pervasive racial disparities in *Neisseria gonorrhoeae* between Non-Hispanic Black and White US females”

Abstract

Background: Spatial analyses of gonorrhea morbidity among females often highlight the southeastern US but may not provide information on geographic variation in the magnitude of racial disparities; such maps also focus on geographic space, obscuring underlying population characteristics. We created a series of visualizations depicting both county-level racial disparities in female gonorrhea diagnoses and variations in population size.

Methods: We calculated county- and region-level race-specific relative rates (RelR) and between-race rate differences (RD) and rate ratios (RR) comparing gonorrhea case rates in non-Hispanic Black (NHB) vs non-Hispanic White (NHW) females. We then created proportional symbol maps with color representing counties’ RelR/RD/RR category and symbol size representing counties’ female population.

Results: Gonorrhea rates among NHB females were highest in the Midwest (718.7/100,000) and West (504.8), rates among NHW females were highest in the West (74.1) and Southeast (72.1). RDs were highest in the Midwest (654.3 excess cases/100,000) and West (430.7), while RRs were highest in the Northeast (12.4) and Midwest (11.2). Nearly all US counties had NHB female rates ≥3x those in NHW females, with NHB females in most highly populated counties experiencing ≥9-fold difference in gonorrhea rates.

Conclusions: Racial disparities in gonorrhea were not confined to the Southeast; both relative and absolute disparities were equivalent or larger in magnitude in areas of the Northeast, Midwest, and West. Our findings help counter damaging regional stereotypes, provide evidence to refocus prevention efforts to areas of highest disparities, and suggest a useful template for monitoring racial disparities as an actionable public health metric.

Introduction

Racial disparities are a well-described and persistent hallmark of gonorrhea epidemiology among females in the US, where non-Hispanic Black [NHB] females experience the highest rates of infection[24,25]. Racial disparities in rates of gonorrhea and other STIs in the US are fueled by social and sexual network factors that create contexts of higher risk for NHB females[21–23,26,27]. In response to these long-standing inequities, the US Department of Health and Human Services established the reduction of STI-related racial disparities as a core goal of the 2021-2025 STI National Strategic Plan[28].Achieving these goals will require focused efforts designed to reach specific populations experiencing the highest burden of disease, which in turn requires a comprehensive understanding of the geographic distribution of cases and where racial inequities in disease rates are greatest.

The 2021-2025 Strategic Plan also includes the reduction of NG rates in the US South as a key indicator among their disparities goals. However, prior analyses have revealed that rates of gonorrhea [29,30] and other STIs[31,32] are higher outside the South. Spatial visualizations of gonorrhea morbidity, which the Centers for Disease Control and Prevention's (CDC) annual Sexually Transmitted Disease surveillance reports have routinely included, represent geographic distribution at the state or county level with color scales to represent the rate or count of gonorrhea cases[33], which draws attention to the Southeastern US as the area with the highest concentration of counties with the highest rates of gonorrhea. However, these maps focus attention primarily on geographic space[18,19] and tend to obscure the size and composition of the underlying population to which these metrics apply. Counties with similar rates but vastly different population sizes are depicted in the same color, potentially obscuring important distinctions in the distribution of population-level morbidity. Proportional symbol maps are one way to potentially overcome this limitation by using variations in the size, color, and/or shape of symbols to depict multiple dimensions of the underlying data, with symbol size representing underlying population size and color representing burden of disease. The CDC has recently made race- and sex-stratified county-level maps of gonorrhea rates available through a web application, which allows comparison of rates among different groups in a geographic area[33]. However, these maps do not depict variation in the magnitude of disparities between race groups.

We attempt to enhance the current view of NG morbidity by more fully visualizing the geographic heterogeneity of county-level absolute and relative disparities in NHB and NHW female gonorrhea cases in the US. We focus on gonorrhea among females because the reproductive sequalae are more severe in cisgender females as compared to males, and rates in males may be more sensitive to the local epidemiology of gonorrhea in MSM[34] as well as the geographic heterogeneity of the MSM population[35]. These maps depict the number and geographic distribution of NHB and NHW females experiencing differential rates of reported gonorrhea cases in the US and highlight locations where intensive control and prevention measures may have the largest impact on reducing racial disparities.

Methods

We used surveillance data on rates of reported gonorrhea cases in females of all ages reported to the National Notifiable Disease Surveillance System (NNDSS) from all 50 US states for years 2015-2018 as of September 25, 2019, stratified by age and race and aggregated by month at the county level[1]. The number of cases in stratified cells for which age and/or county/state of residence were missing were excluded from the analysis (22,766; 2.7%). Because a substantial proportion of cases (19%) were reported with missing race and/or ethnicity (hereafter referred to as race/ethnicity) data, we redistributed cases in stratified cells missing this information using a missing at random assumption based on that county's distribution of known age group and race/ethnicity data for female cases reported that year (single imputation). Previous work evaluating gonorrhea cases reported to the CDC's STD Surveillance Network (SSuN), a supplemental surveillance system that collects detailed demographic information on a random

---

[1] County-level aggregate case data were obtained from the Division of STD Prevention, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, US Centers for Disease Control (CDC) under an approved Data Use Agreement.

sample of gonorrhea cases in participating jurisdictions, found relatively minor differences in the racial/ethnic distribution of fully ascertained cases vs those reported to NNDSS[36].

Metrics for total and race-specific county-level gonorrhea morbidity

We calculated annual county-level rates of reported gonorrhea cases among NHW and NHB females per 100,000 population using the US Census Bureau's population estimates[37] as denominators. Rates were reweighted to the age/sex/race distribution of the 2010 Decennial US Population to adjust for differential age distributions across counties, as rates of STIs are typically highest in adolescents and young adults. County-level annual rates were averaged over the 2015-2018 period to stabilize the estimates.

We calculated race-specific county- and regional-level relative rates (RelRs) for NHW and NHB females using the county and regional-level female race-specific rate as the numerator and the national female race-specific rate as the denominator. Relative rates were assigned to one of the following RelR categories: <0.50, 0.50-0.74, 0.75-0.89, 0.90-1.09 (approximately equal to the national rate), 1.10-1.24, 1.25-1.49, 1.5+. We then created two race-specific proportional symbol maps, with the color of the circle representing relative rate category and the size representing the total number NHW or NHB female residents in that county.

To assess the extent to which areas with relatively high female gonorrhea rates in NHW also experienced relatively high rates of gonorrhea in NHBs, we calculated the female-population Spearman's rank correlation coefficient[38] between county-level gonorrhea race-specific rates in NHW and NHB females, stratified by US region (Northeast, Southeast, Midwest, and West[25]) and weighted by counties' female population. We also created a scatterplot of county-level race-specific relative rates with NHW RelRs on the x-axis and NHB RelRs on the y-axis to visually depict, using color to denote the county's region and point size to represent the county's female population. This scatterplot provides a visualization of the proportion and distribution of counties that are of higher/lower relative risk for both race groups simultaneously.

We also evaluated measures of both absolute and relative disparity in rates of reported gonorrhea between NHW and NHB females, considering both metrics to be important measures of health equity[39–41]. We calculated the absolute disparity in gonorrhea rates by subtracting the county-level 4-year average gonorrhea rate in NHW females from the 4-year average gonorrhea rate in NHB females to obtain a rate difference (RD). We calculated the relative disparity by calculating the rate ratio (RR) of the 4-year average gonorrhea rate in NHB females divided by the 4-year average gonorrhea rate in NHW females. County-level RDs were assigned to 1 of 6 groups: <-25.0 per 100,000 population (indicating higher rates among NHW females compared to NHB females), -25.0 - 24.0 (approximately equal rates in both groups), and quartiles for RDs >25/100,000 (25-174, 175-314, 315-489, 490+). Similarly, county-level RRs were assigned to 1 of 6 groups as follows: <0.80 (higher rates among NHW females), 0.80-1.19 (indicating approximately equal rates in both groups), and quartiles for relative rates >1.20 (1.20-3.64, 3.65-5.74, 5.75-8.99, 9.0+). If there were no cases among NHB or NHW females in a county, we imputed a small rate (0.25/100,000) to enable calculation of racial disparities metrics. These RD and RR disparity categories were mapped using the approach described above, with circle color representing each county's RD/RR category and circle size representing the NHB female population of each county. We plotted the NHB female population to depict the population most affected by disparities in gonorrhea rates.

Finally, we calculated NHW and NHB-specific RelRs, RDs, and RRs in each of the 4 US regions (Northeast, Southeast, Midwest, and West).

Data suppression

Counties that met any of the following criteria for >1 year 2015-2018 were excluded: 1) counties with total female population <100 or <100 NHW and/or NHB females for all metrics and 2) counties with >50% of reported female gonorrhea cases missing race/ethnicity for race-stratified metrics.

Statistical Analysis and Software

All data management and statistical analysis was performed in SAS version 9.4. Maps were created in R using the *urbnmapr*[42] package.

Results

Geographic and Population distribution of race-specific female gonorrhea morbidity

The overall national rate of reported gonorrhea cases among females during 2015-2018 was 124.7 per 100,000 population, varying substantially by region, from 150.2 in the Southeast to 75.8 in the Northeast. As described in prior reports[25], national rates also varied by race, with rates of 495.9 and 64.1 among NHB and NHW females, respectively (Table 1). However, these estimates obscure regional variations in race-specific gonorrhea epidemiology. Among NHW females, the highest rates occurred in the West (74.2) and Southeast (72.1), the rate in the Midwest was somewhat lower (64.1), and the lowest rate occurred in the Northeast (28.8). Among NHB females, the rate of gonorrhea was highest in the Midwest (718.7) and second highest in the West (504.8), with lower rates in the Southeast (464.6) and Northeast (357.8).

Reflecting region-specific rates, highly populated counties in the West had NHW-specific rates that were higher relative to the US rate (depicted as orange to red circles) (Figure 1). Counties in and around San Francisco, Portland, Oregon, and southeast of Seattle had higher relative morbidity compared to the US rate for NHW females compared to counties in the Los Angeles area. Most counties in the Southeast had higher morbidity relative to the US rate among NHW females, but this was not consistently observed in the most populated counties; for example, the Miami-Dade, Houston, Raleigh-Durham, and Atlanta metro areas all had lower relative morbidity while Dallas-Fort Worth, Oklahoma City, and Nashville had high relative morbidity. Midwestern counties were similarly mixed, with the areas around Chicago, Detroit, and Minneapolis having lower NHW-specific relative rates compared to the US rate than Indianapolis, Columbus, Cleveland, and Kansas City. In contrast, highly populated counties along the Northeastern seaboard were almost universally categorized as having lower relative race-specific morbidity for NHW females (depicted as blue circles).

A map of county-level relative gonorrhea rates among NHB females demonstrated both similarities and differences from the map of rates in NHW females. Major urban areas of the Southeast, including the Atlanta metropolitan area, Houston, Dallas-Fort Worth, and nearly all counties in southeast Florida, had lower or equivalent morbidity relative to the US rate for NHB females, though Baltimore, New Orleans, and Memphis had high levels of relative morbidity. Less populated Southeastern counties were a mix of both higher and lower than US NHB-specific relative rates. In contrast, most counties in the Midwest had higher than average relative morbidity for NHB females regardless of population size, with most of the NHB female population residing in metropolitan areas with high relative morbidity (Chicago, Detroit, Indianapolis and Cleveland, Cincinnati, and St. Louis). There was a notable concentration of high NHB female-specific relative morbidity counties, of varying population size, both along the Mississippi River from northern Louisiana to Illinois and north through the Midwest, as well as in states along the Ohio River Valley, including Indiana, Michigan, and Ohio. Most counties in the Northeast had lower than average relative morbidity for NHB female residents, apart from urban centers in Western New York and Pennsylvania.

Figure 2 presents a scatterplot of county-level NHW- and NHB-specific rates relative to the US average race-specific rates. The diagonal dashed line denotes counties with equal race-specific relative rates of gonorrhea among NHB and NHW females relative to national rates in these groups (i.e., relative local race-specific rates are higher or lower than national race-specific rates by comparable proportions). The scatterplot is divided into four quadrants denoting whether counties had higher/lower female NHW- and

NHB specific rates relative to race-specific US rates; for example, counties in the upper righthand quadrant had relative rates ≥1.0 for both NHW and NHB females, while those in the lower righthand quadrant had relative rates ≥1.0 for NHB females and <1.0 for NHW females. Most Northeastern counties had race-specific relative rates <1.0 for both NHB and NHW females. The majority of Western and Southeastern counties had higher race-specific relative rates in NHW females compared to NHB females, denoted as circles mainly above the diagonal line of equal race-specific relative rates. In contrast, many Midwestern counties had higher race-specific relative rates in NHB females than in NHW females. The population-weighted Spearman's correlation coefficient between female NHW- and NHB-specific relative rates for all US counties was 0.56 (p<0.01), regional population-weighted correlation coefficients were highest in the West (0.66), lowest in the Northeast (0.53), and 0.58 and 0.57 in the Southeast and Midwest, respectively. County-level race-specific average rates and relative rate categories and NHW/NHB female populations can be found in Supplemental Table 1.

County-level Absolute and Relative Disparities between NHW, and NHB females

Nationally, NHB females experienced an excess of 431.8 cases/100,000 over the rate in NHW females (Table 1). The absolute disparity in gonorrhea rates between NHW and NHB females was high in all areas of the US but was highest in the Midwest (654.6 excess cases/100,000) and West (430.6) and lowest in the Northeast (329.0) and Southeast (392.5).

The proportional symbol map of county-level rate differences illustrates our finding that highly populated Midwestern counties generally had the largest absolute disparities (490+) in the US (Figure 3A). However, counties with the largest absolute disparities were identified in all US regions, including the Northeast and West. Northern Virginia, Georgia, and southeastern Florida had lower than average absolute differences in gonorrhea rates, though the rate differences were still all larger than 25 excess cases per 100,000 population.

Relative disparities in gonorrhea diagnoses were high nationally, with NHB females experiencing a rate that was 7.7-fold the rate among NHW females. In contrast to absolute disparities, NHB-NHW rate ratios were highest in the Northeast (12.4); this reflected the very low relative rate of gonorrhea in NHW females in the region vs. the relative rate in NHB females (0.45 vs. 0.72) (Table 1). Rate ratios were also high in the Midwest (11.2); here the difference was driven by the very high relative rate in NHB (1.45), while the rate in NHWs was identical to that observed nationally. Rate ratios were lower in the Southeast (6.4) and West (6.8). The geographic distribution of counties with the highest relative disparities was somewhat different than those with the highest absolute disparities; notably, a higher proportion of counties in the Northeast and Southeast with comparatively lower absolute disparities had relative disparities ≥9.0 (e.g., parts of Virginia, the New York City metro area, and Massachusetts). In contrast, some areas with larger absolute disparities experienced smaller relative disparities, notably the Dallas-Fort Worth metro area and counties comprising the Los Angeles and San Francisco metro areas. As with absolute disparities, almost all counties in the US had NHB female gonorrhea rates ≥3.7 times the rate experienced by NHW females, with NHB females in most metro areas experiencing ≥5.8-fold difference in rates.

Discussion

In this analysis, we examined the epidemiology of gonorrhea among women using detailed visualizations of between- and within-race disparities in county-level average case rates in NHW and NHB females. We found that profound disparities by race were ubiquitous, perhaps reflecting the pervasiveness of structural racism, social, and network factors that leave Black women structurally more vulnerable to high rates of STIs[26,27]. However, our findings also demonstrate the heterogeneity of these disparities and challenges a view of the Southeast as somehow distinct from other parts of the US[28,43].

Although the absolute burden of NG cases among NHB and NHW females is indeed highest in the Southeast, that reality does not owe to unique patterns of disparities or outsized race-specific rates, but rather is influenced by the region’s concentration of persons often subject to the same race-associated vulnerabilities pervasive throughout the US. Indeed, we found that absolute disparities were highest in the Midwest and West, driven in large measure by rates of gonorrhea among NHB women that were higher than other regions. In contrast, relative disparities were highest in the Northeast, where rates in both NHW and NHB females were lowest, but where the relative rate in NHW females (compared to the US NHW rate) was lower than that in NHB females. These results are similar to analyses of NHB-NHW disparities in HIV[32] and syphilis diagnoses[31] among US females, which found the highest relative disparities of both infections in the Northeast, but higher absolute disparities and NHB female-specific rates outside of the Midwest, which may indicate differences in social determinants most influential in these infections compared to gonorrhea.

We chose to examine both relative and absolute racial disparities to provide a more comprehensive and balanced picture of the burden of gonorrhea in both populations. Absolute disparity metrics incorporate the scale of the disease measure being compared and provide a better sense of overall rate of disease in the population[44]. This is best illustrated by the large absolute disparities we identified in Midwestern counties, which accurately reflect the high rates of gonorrhea among NHB females in this region. Conversely, relative disparity metrics are inherently scaleless and uninformative about underlying rates of disease. For example, we identified similarly high relative disparities in the Midwest and Northeast despite vastly different rates of disease among NHB females in these two regions. Previous work has demonstrated that a simultaneous increase in relative disparities and reduction in absolute disparities is often an interim stage as burden of disease declines in both populations[40,41]; as demonstrated in previous work, monitoring temporal changes in both metrics, along with group-specific rates of disease, is therefore critical to ensuring *both* groups progress towards reduced morbidity[41].

The maps produced in our analysis can offer two main advantages for visualizing racial disparities in gonorrhea and other conditions. First, these maps explicitly detail geographic patterns of multiple disparity metrics and allow for comparisons of geographic patterns by these different metrics.. Despite a laudable emphasis on reducing racial disparities, the 2021-2025 National STI Strategic Plan does not clearly define specific disparity measures and quantifiable targets[28]; we hope this work could contribute to setting such goals and help prioritize jurisdictions with highest disparities. Additionally, our maps provide a level of granularity that highlights the heterogeneity in disparities within regions along with population size, providing a more detailed characterization of the influence different geographic areas have on national and regional trends.

We had hoped to identify a subset of counties in which the rate of gonorrhea among NHB females was equal to, or less than, the rate among NHW females and explore characteristics of these counties in future analyses. However, such counties were rare and home to very few NHB females, suggesting that racial disparities are a ubiquitous feature of gonorrhea epidemiology in the US; as such, subsequent analyses will necessarily involve exploring factors influential in the *degree* rather than the *presence* of disparities. For example, segregation of communities by racial identity[45] has resulted in neighborhood conditions that sustain higher STI endemicity through inequitable access to education, economic opportunity, and housing, and sexual health care. The greater disparities for NHB females residing in the Northeast and Midwest revealed in our analysis may be a reflection of contexts created by highly racially segregated communities; of the 10 most racially segregated metropolitan areas in the US, all but one (Miami-Miami Beach-Kendall) are located in the Northeast or Midwest[46]. Given the large variation in social conditions within counties, analyses of the role of social determinants on STI disparities within smaller geographic units, such as the census tract or zip code, should also considered where data permits.

We acknowledge several potential limitations of our analysis. Assessment of race/ethnicity, gender, and sex is not standardized across reporting jurisdictions and may lead to systematic differences in ascertainment and inaccurate reflection of these identities. Data from suppressed counties were not included; however, this was a small proportion of reported cases (8%), and only 4% and 6% of the NHB and NHW population, respectively, lives in counties where data were suppressed. Virtually all laboratory-confirmed diagnoses are reported to public health departments given that gonorrhea is a nationally notifiable disease, but populations with lower access to screening are likely under-diagnosed. However, the United States Preventive Services Task Force recommends annual gonorrhea screening for sexually active females <24 years and females >25 years at increased risk for infection[47]. Finally, our depictions of geographic variation in within-race gonorrhea rates should not be used to compare morbidity between NHB and NHW given the large disparities observed.

In summary, our maps provide a more comprehensive geographic visualization of NG epidemiology among US females that contributes a novel perspective to previous work locating high NG morbidity outside of the US Southeast. Our findings can focus public health efforts on specific localities with highest morbidity and disparities, which exist in all US regions. Our results can also contribute to development of template for monitoring racial disparities as an explicit and actionable public health metric that is worthy of a detailed and comprehensive national roadmap to elimination. Finally, we hope that our work will prompt future efforts to uncover and address systemic sociocultural causes, mediating factors, and pathways underlying the large and ubiquitous disparities in STI morbidity and ultimately lead to increased health equity.

Tables and Figures

Figure 1: Map of average county-level relative *Neisseria gonorrhoeae* rates, 2015-2018, a) White, non-Hispanic county-level age-adjusted female rate relative to national rate among White females, b) Black, non-Hispanic female county-level age-adjusted rate relative to national rate among Black non-Hispanic females

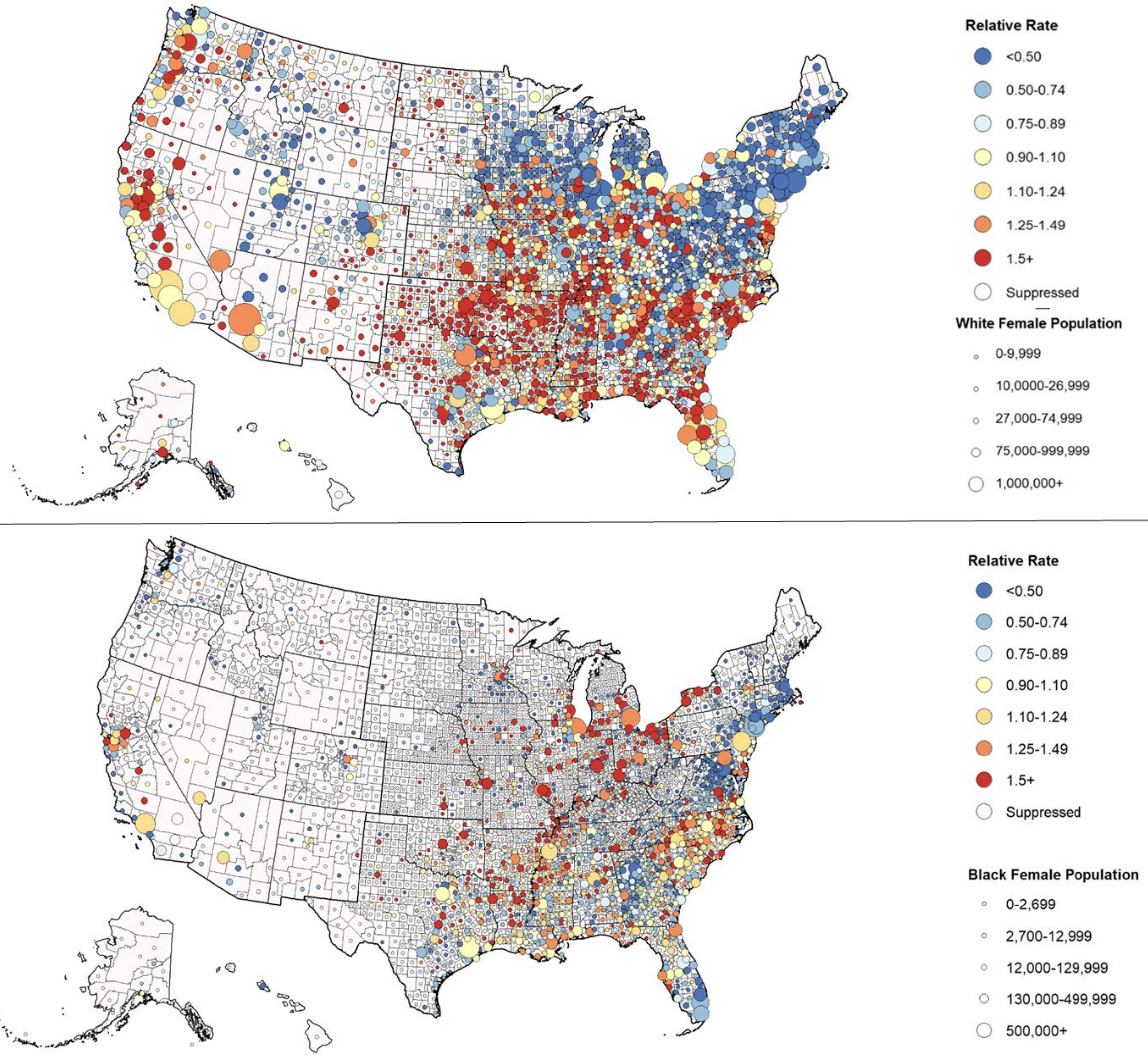
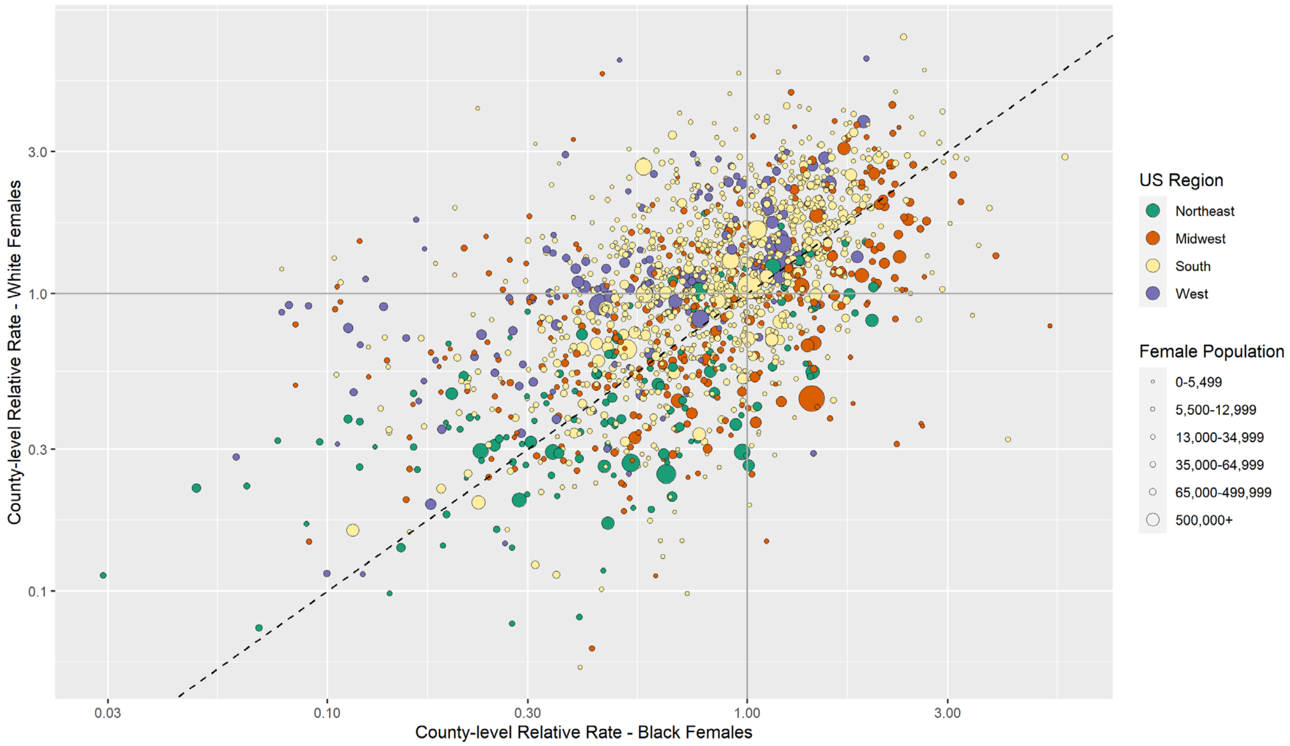


Figure 2. County-level Black Female NG Rate relative to the National NG Rate in Black, non-Hispanic Females with County-level White Female NG Rate relative to the National NG Rate in White, non-Hispanic Females



*Counties falling on diagonal have the same level of race-specific relative NG rates; this does not imply NG rates in both groups are equal

Includes only counties with non-suppressed data for both White, non-Hispanic and Black, non-Hispanic females

Figure 3. Maps of A) County-level Black Female-White Female Rate Difference B) County-level Black Female-White Female Rate Ratio

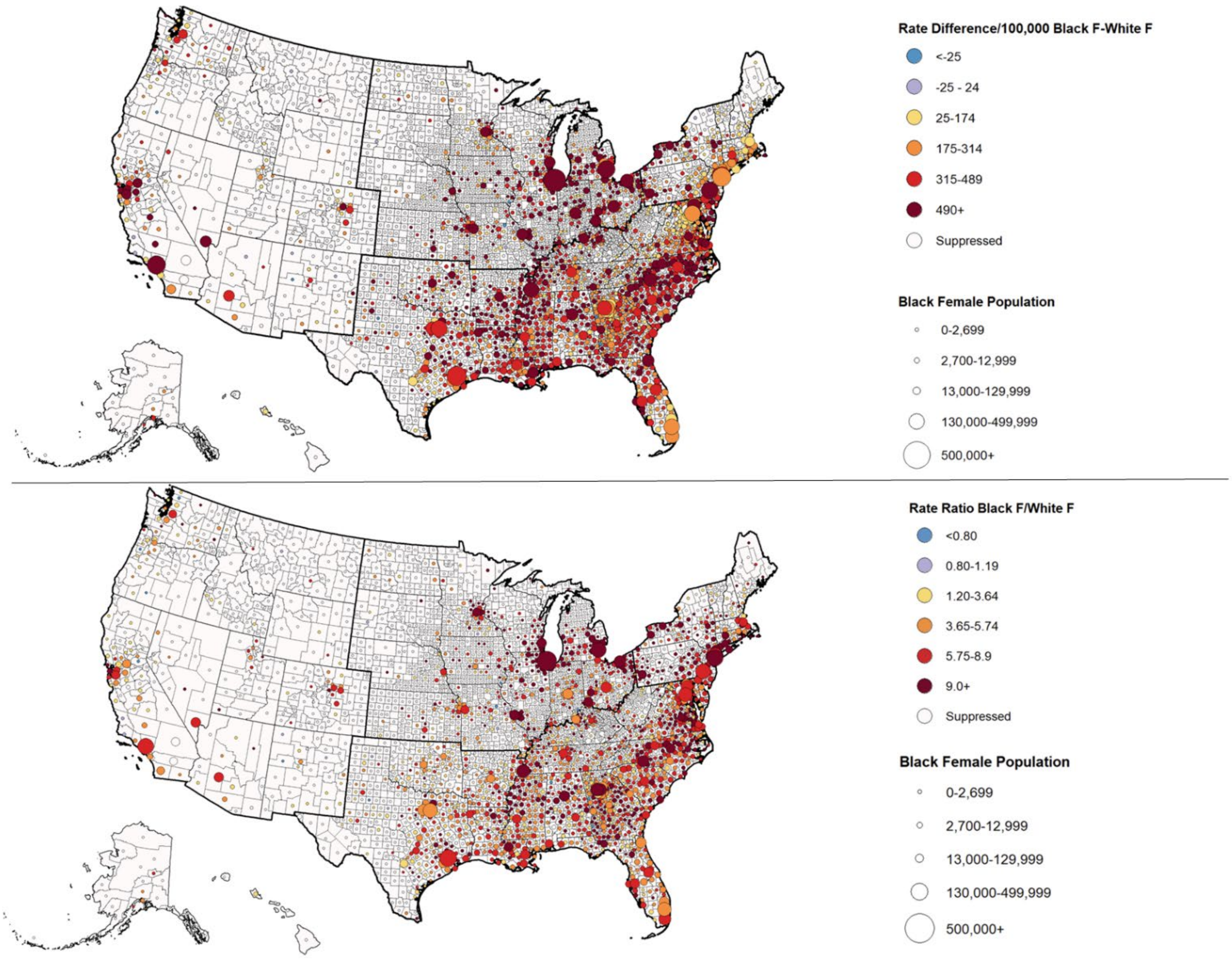


Table 1. Average US and regional gonorrhea population, cases, rates in non-Hispanic Black (NHB) and non-Hispanic White (NHW) females, 2015-2018

	United States	Midwest	Northeast	Southeast	West
NHW Female Population	100,240,314	26,173,392	18,900,982	35,755,361	19,410,579
NHB Female Population	21,079,157	3,690,971	3,334,123	12,331,994	1,722,070
NHW Female gonorrhea cases	62,394	16,766	5,230	25,796	14,402
NHB Female gonorrhea cases	104,522	26,541	11,931	57,347	8,703
NHW Female gonorrhea Rate[1]	64.1	64.1	28.8	72.1	74.2
NHB Female gonorrhea Rate[1]	495.9	718.7	357.8	464.6	504.8
NHB Female-NHW Female Rate Difference[2]	431.8	654.6	329.0	392.5	430.6
Regional NHB Female-NHW Female Rate Ratio[3]	7.7	11.2	12.4	6.4	6.8
NHW Relative rate compared to US rate[4]	-	1.00	0.45	1.12	1.16
NHB Relative rate compared to US rate[5]	-	1.45	0.72	0.94	1.02

[1] Rates calculated from 4-year average population and reported cases may differ slightly from rates presented below, which are the average of 4 single-year rates

[2] Rate Difference= NHB female gonorrhea rate – regional NHW female gonorrhea rate

[3] Rate Ratio= NHB female gonorrhea rate/regional NHW female gonorrhea rate

[4] NHW female gonorrhea rate/US NHW female gonorrhea rate

[5] NHB female gonorrhea rate/US NHB female gonorrhea rate

Chapter 3. Diverging Neisseria gonorrhoeae morbidity in NHW and NHB non-Hispanic females: Application of group-based trajectory modeling to trends in county-level morbidity 2003-2018

Abstract

Introduction

National trends in gonorrhea rates may obscure local variations in morbidity. We used Group-based Trajectory Models to identify groups of counties with similar gonorrhea rate trajectories among Non-Hispanic White (NHW) and Non-Hispanic Black (NHB) females.

Methods

Using county-level data on gonorrhea cases in US NHW and NHB females 2003-2018, we used group-based trajectory models to estimate rate trajectories separately for NHB and NHW females. We assessed models with 1-15 groups and selected final models based on fit statistics and identification of divergent trajectory groups with distinct intercepts and/or slopes. We mapped counties by assigned trajectory group and examined the association of county characteristics with group membership.

Results

We identified 7 distinct trajectory groups for NHW females and 9 distinct groups for NHB females. All identified groups for NHW female morbidity experienced increasing gonorrhea rates; trajectories of NHB female morbidity were diverse and included 3 groups with a net decline in gonorrhea rates. Counties with higher NHW female morbidity had lower male:female adult sex ratios, lower health insurance coverage, and lower marital rates. Counties with higher NHB female morbidity were more urban, experienced higher rates of poverty, and lower rates of marriage.

Conclusion

National data obscure a highly heterogenous gonorrhea epidemic for both NHW and NHB females. Morbidity patterns did not always follow geographic proximity, which could be explained by variation in social determinants of health. This exploratory analysis should prompt further analysis into the differential drivers of gonorrhea morbidity.

Introduction

Gonorrhea (caused by the *Neisseria gonorrhoeae* [NG] bacterium) is the second most-commonly reported sexually transmitted infection (STI) in the US[25]. Among females, NG infection is associated with serious reproductive sequalae[3,4,48]. Between 2015-2020, the NG rate among US females increased from 106.3 to 172.7 cases per 100,000 females[1,49], the highest level since 1991[24], with all US states experienced varying levels of increased rates[49]. During this same period, NG rates among non-Hispanic White (NHW) females increased 70%, while rates among non-Hispanic Black (NHB) females increased 21%. The extent to which these increases affected all areas of the US simultaneously versus affecting different areas at different times is uncertain. Identification of areas with heterogenous trends could help identify macro-level factors that influence NG epidemiology and perhaps identify spatiotemporal patterns in how gonorrhea epidemics spread.

While there is a robust body of work on individual-level behavioral risk factors for NG, social determinants of risk[26,27,50,51] , and disparities in subpopulations defined by race[52,53], age[54], and sexual orientation[25,55,56], there is considerably less published research characterizing heterogeneity and correlates of population-level spatiotemporal trends. In part, this reflects difficulty summarizing large-scale variation in such trends with traditional descriptive methods. Group-based trajectory models (GBTM) are a class of finite mixture models that can identify and define groups of individuals following similar trajectories of a characteristic over time[57]. These models are increasingly recognized as a powerful tool for group-level longitudinal epidemiologic data and have recently been used for county-level analyses of trends in all-cause mortality[58] and SARS-CoV-2 infection[59] in the US. To our knowledge, GBTM has not been used to characterize such trends in NG or other STIs.

In this exploratory analysis, we used GBTMs to characterize the spatiotemporal epidemiology of NG among US females by classifying and mapping counties based on their trajectories of NG morbidity among NHB and NHW females. We chose to compare these two populations because NHB females experience the highest rates of NG, while NHW females constitute the largest racial group in the US and have historically experienced far lower rates of NG [1,55]. We then sought to identify and characterize areas where trends in race-specific female NG morbidity anticipated or diverged from national trends during the period examined. This stratified approach also allowed us to assess how trends varied between NHB and NHW.

Methods

NG is a nationally notifiable condition, and all laboratories and medical providers are required by law to report diagnoses to local health departments, which subsequently report to state STI control programs and finally to the National Electronic Telecommunications System for Surveillance (NETSS) at the US Centers for Disease Control and Prevention (CDC). We used surveillance data on NG cases reported for years 2003-2018 as of September 25, 2019, aggregated by year at the county level and stratified by race and ethnicity[2]. We initially examined trends in NG epidemiology among all females; however, we found that the racial composition of counties' population was the strongest predictor of identified group membership by a factor of >5 (results not shown).

For each race-stratified model, we used data from counties that 1) reported ≥1 NHW or NHB female NG case each year and/or 2) reported an average of ≥2 NHW or NHB female NG cases annually to retain counties with substantial but inconsistent morbidity. County-level NHW and NHB female-specific rates per 100,000 were calculated using the total number of NHW or NHW female residents each year as the denominator; population data was obtained from the US Census[37]. County-level NHB and NHW female NG rates were log-transformed due to a highly skewed distribution (NHW females: median 80.7/100,000, mean 121.3, range 0.6-3,039.3; NHB females: median 462.3/100,000, mean 627.4, range 1.6-8,792.6).

We used the SAS *Proc Traj*[60] procedure to estimate county-level rate trajectories separately for NHB and NHW females. This procedure estimates a discrete mixture model to identify and cluster individual time-series data into groups with similar trajectories[61]. Unlike hierarchical or latent growth analysis, GBTM does not assume that the underlying trajectories within a population follow a continuous distribution. For each race-stratified procedure we estimated a model with 1 group with a cubic trend and sequentially increased the number of groups by 1 until reaching 15 groups, assessing Bayesian Information Criteria (BIC), Akaike's Information Criteria (AIC), log-likelihood, percentage of group membership, and average posterior probabilities of group membership (AvePP[57]) as indications of model fit. The AvePP is the mean posterior probability of counties' membership in each of *n* groups. After the addition of each group, the model was assessed for fit; if the cubic term of any group(s) was not statistically significant (α=0.05), a model including quadratic and linear terms only for those group(s) was estimated and compared to the previous model; if the quadratic term of that group was not statistically significant, a model with a linear

---

[2] County-level aggregate case data were obtained from the Division of STD Prevention, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, US Centers for Disease Control (CDC) under an approved Data Use Agreement.

term only was estimated for that group and if no terms were significant, an intercept-only trajectory for that group was estimated[62]. Final model selection was based on fit statistics and identification of divergent groups with distinct intercepts and/or slopes.

We mapped counties by assigned trajectory group using the *urbnmapr* package[42] in R to examine their geospatial distribution. We then calculated the number of NHB and NHW female NG cases each identified group of counties contributed to the national annual total and the 2018 NHW and NHB female population residing in counties comprising each identified group.

Finally, we examined the association of county-level characteristics with trajectory group membership separately for the NHW and NHB female models. We obtained the following characteristics from the US Census American Community Survey (ACS) 5-year estimates covering the period of 2008-2018: 1) % of NHW/NHB adults with income <100% of the Federal Poverty Level (FPL), 2) % of NHW/NHB persons age ≥15 who are married, 3) % NHW/NHB adults without health insurance, and 4) income inequality as measured by Gini coefficient. We elected to use the 5-year ACS estimates because: 1) 5-year estimates are available for all counties regardless of population size and because our goal was to understand the effect of general social/economic conditions represented by these characteristics on the trajectory of female NG morbidity. We also examined the ratio of males to females (age ≥15) for NHW/NHB adults, derived from Census population estimates. For ACS and population characteristics, we examined both the average value of each variable over all 5-year estimates and the percent change in each characteristic between the earliest and most recent estimates. We also included the 1990, 2006 and 2013 county urbanicity from the National Center for Health Statistics' Urban-Rural Classification Scheme for Counties[63] as a weighted average of these three estimates (0.1875*1990 estimate), (0.4375*2006 estimate) and (0.375*2013 estimate), and as a % change in the county's urbanicity classification between these years.

For each race-stratified model, we constructed two multinomial logistic regression models to estimate adjusted odds ratios (aORs) and 95% confidence intervals for the effect of these county-level covariates on trajectory group membership relative to membership in the trajectory group most resembling the national average trajectory for that race group. aORs were reported as a function of a change in 1 standard deviation (SD) in each covariate. In both models, we controlled for the proportion of the population that was NHW and NHB.

Results

NHW female model

We selected a model with 7 distinct trajectory groups for county-level NHW female NG rates in 1,785 counties with sufficient data for inclusion in the analysis. Excluded counties (N=1,360) reported an average of 0.76 cases annually; 123 counties (3.9%) reported no female NG cases 2003-2018. Model fit continued to improve with increasing numbers of groups (Supplemental Table 1); however, we were unable to obtain convergence for models with >13 groups. The inclusion of an eighth or more groups produced only roughly parallel additional groups, with little emergent difference between group intercepts and slopes (Supplemental Figure 1). The AvePP for all 7 groups was higher than Nagin's suggested criteria of ≥0.70[57] (Table 1A).

The NHW model with 7 groups included a distinctive group of counties that experienced stable NG rates from 2003-2008 followed by a >500% increase in rates between 2008-2018 (Group 6 in Figure 1B). The rise in NG rates in this group – which comprised only 2.5% (N=79) of included counties and 4% of reported NHW female cases in 2018 (Table 2) - antedated a roughly simultaneous increase in groups 3, 4, 5, and 7. Group 7 counties experienced the highest morbidity until 2015, after which it was overtaken by group 6. Group 6 counties were located primarily in the Southeast and Mississippi river delta, California, New Mexico, and WA State, and were often located adjacent to the more numerous and populous group 7 counties (Figure 1A). However, this pattern of adjacency was not consistently observed in WA State or northern California. Despite being home to only 17% of the NHW female population in the US, counties in these 2 groups contributed 35% of all reported cases among NHW females in 2018.

Counties in 6 of identified 7 groups experienced increases in the NG rate among NHW females, but the size of this increase varied dramatically, from 46% (group 1) to 352 (group 6); in absolute terms, these changes varied from 3.7 to 141 cases per 100,000 (Table 1A). Groups 3, 4, 5, and 7 experienced roughly parallel trajectories of NG morbidity. Although we observed some geographic clustering of counties by trajectory group (e.g., group 7 included clusters of counties along the Mississippi, in the Carolinas, and in California and group 2 and 3 counties were clustered in the northeast), many groups included counties were widely dispersed across different regions of the U.S. For example, counties in the largest group (group 5), comprising 17% of all US counties and home to 29% of NHW females, were located throughout all US regions. We identified a small group of counties (group 1, N=23) with very low rates that contributed <1% of all cases among NHW females in 2018. Counties in group 1 were mainly located in rural areas of the Northeast and mountain West. One other group with stably low rates (group 2) was identified and counties in this group were clustered in the Northeast and Midwestern states.

NHB female model

We selected a model with 9 distinct trajectory groups for county-level NHB female gonorrhea rates in 1,265 counties with sufficient data. Excluded counties (N=1,878) reported an average of 0.45 cases; 850 counties (27%) reported no NG cases among Black females. Model fit continued to improve with increasing numbers of groups (Supplemental Table 2) up to 15 groups. The inclusion of a tenth or more groups produced only roughly parallel additional groups, with little emergent difference between group intercepts and slopes (Supplemental Figure 1). The AvePP for all 9 groups was higher than Nagin's suggested criteria of ≥0.70[64] (Table 1B).

The trajectories observed among NHB females were more diverse that those observed for NHW, though as in NHW, most groups experienced increases in gonorrhea rates between 2015-2018. The identified groups fell into three general patterns. In the first pattern, two groups had initially stable rates that later increased (groups 6 and 7, Figure 2B). These groups experienced the largest relative and absolute changes in gonorrhea rates over the 15-year period of observation. Counties in these groups were distributed throughout the Southeast, West, and Midwest. Group 6 was small but distinctive with a low initial rate in 2003 that increased >150% between 2009-2018 (Figure 2B) and comprised 2.3% (N=30) of included counties and 0.4% of reported cases among NHB females in 2018 (Table 1B), with no obvious geographic pattern. Secondly, four groups (3, 5, 8, 9) experienced declines in NG rates between 2003-2015 followed by increases from 2015- 2018 (Table 1), with a net decline over the 15-year study period in three of these four groups. Group 9 counties, with consistently highest rates, were concentrated in the Midwest with a notable cluster at the juncture of Oklahoma, Texas, and Arkansas. Group 8, the largest group, comprised 12% of counties home to 35% of NHB females and contributed >40% of cases in 2018; counties in this group were concentrated in the Southeastern US. Finally, counties in groups 1, 2, and 4 had roughly stable rates 2003-2018, though rates in all 3 groups were >100/100,000 for all years observed and increased 13-37 cases/100,000 (Figure 2B). Most counties in group 2 (205-220/100,000 in all years) were clustered in the Northeast and Washington, DC metro area. A very small group of counties (group 1, N=37) had consistently low morbidity (115.8 to 146.3/100,000). Counties in group 1 were home to 2.2% of US NHB females and clustered in the Northeast but were also found in California, Washington state, Utah, and Florida (Figure 2).

NHB and NHW females residing in counties comprising each trajectory group

A cross-tabulation of the number of NHW and NHB females residing in each identified NHB and NHW trajectory groups are presented in Supplemental Table 3. The majority of the NHW female population residing in group 7 counties (the group with the highest morbidity among NHW females) was evenly distributed between the two groups of counties with highest NHB female morbidity (group 8 [43%] and group 9 [39%]). Similarly, over 30% of NHW females residing in group 1 (with the lowest morbidity for NHW females) were residents of the counties with lowest NHB female morbidity (groups 1 [22%] and 2 [10%]) and no NHW females residing in group 1 were residents of counties with high morbidity for NHB females (groups 6-9). However, NHW females in group 6, which experienced a similar rate of increase as group 7, were more evenly distributed across all identified NHB trajectory groups; the same pattern was observed for groups 2-5. We observed a similar pattern of distribution for the NHB female population. 45% of NHB females residing in group 9 (with the highest morbidity in NHB females) were residents of counties in the group with highest NHW female morbidity (group 7), and 36% were residents of counties in NHW group 5 (with the third highest morbidity among NHW females by 2018). No NHB females residing in the counties with lowest NHB morbidity (groups 1 and 2) were residents of the groups with highest NHW female morbidity (groups 6 and 7).

Logistic models of county-level characteristics associated with group membership

Figures 3A and 3B plot the adjusted ORs (aORs) and 95% confidence intervals for county characteristics significantly associated with membership in at least 1 identified NG trajectory group in the NHW female and NHB female models, respectively. Numerical results are shown in tabular format in Supplemental Tables 4 (NHW) and 5 (NHB).

In the NHW female model, aORs compare the odds of membership in each group relative to group 5 (the group closest to the national trajectory for NHW females). Factors associated with membership in groups with lower morbidity in NHWs included a higher average ratio of adult NHW males to NHW females and a smaller proportion of the population being uninsured. Rural counties were more likely to be members of groups with higher morbidity. County-level income inequality and poverty among NHW adults were not associated with NHW trajectory group membership (Supplemental Table 3). In the NHB female model, aORs compare the odds of membership in each group relative to group 8 (the group closest to the national trajectory in NHB females). Counties in group 9 (the highest morbidity counties) were characterized by greater urbanicity, a higher proportion of Black adults with incomes below the federal poverty line, and a lower percentage of married Black adults. Conversely, counties in group 1 (the lowest morbidity group), were characterized by a low proportion of Blacks lacking health insurance but higher income inequality.

Discussion

In this analysis, we used GBTM to describe the spatiotemporal variation in NG rates among US NHW and NHB females between 2003 and 2018. Our findings highlight the profound geographic heterogeneity in trends in gonorrhea rates, and how these trends may vary at the local level between NHB and NHW women. Among NHWs, rates increased in almost all groups defined by our model, though the relative and absolute magnitude of that increase was highly variable. Rate trajectories among NHBs were more diverse than among NHWs, with 3 groups of counties experiencing a net decline in female case rates between 2003-2018. While we observed instances of geographic clustering of trajectory groups, with most counties in the low morbidity groups located in the northeastern and midwestern states, we also found that counties experiencing similar trajectory patterns were often widely distributed. Several factors associated with county membership in high or low morbidity clusters, including male to female ratios, poverty, and insurance status, highlight the potential role of social determinants of health in shaping gonorrhea epidemiology.

The geographic patterns we observed among trajectory groups should generate new hypotheses about the drivers of NG epidemiology. Counties with similar trajectories may have linked epidemics, epidemiologically separate but parallel epidemics shaped by shared social determinants, or separate epidemics driven by distinct causes. For example, in the NHW model, the increasing rates in group 6 counties predated a similar rate of increase in frequently geographically adjacent group 7 counties by 6 years. This may suggest that increased transmission in group 6 counties fueled the subsequent rise in adjacent group 7 counties; alternatively, higher transmission in group 7 counties may have spilled over into adjacent group 6 counties. This pattern is supported by previous work showing that areas of concentrated NG transmission may drive morbidity in geographically proximate areas[65]. However, the wide distribution of counties in the same trajectory group could alternatively be explained by economic or other connections to more distal high morbidity areas[66]We also observed that much of the NHW population of high morbidity NHW counties were also residents of high NHB counties, and vice versa. This may indicate that NG transmission networks are not as racially assortative as those previously identified in studies of HIV transmission networks[67].

Given national trends of increasing NG morbidity in both NHW and NHB females, the identification of trajectory groups with decreasing or stably low rates among both groups was somewhat unexpected and likely points to underlying geographic heterogeneities in upstream factors influential in STI epidemiology. Some of these, such as marital rates[68,69], poverty[22,70,71], and health insurance coverage[72], are supported by previous work. However, a number of associations we identified were surprising. For example, rural counties were more likely to have higher morbidity for NHW females, while urban counties had higher morbidity for NHB females, indicative of multiple, possibly disparate, population-level determinants of NG risk. We also found that low adult sex ratios were not significantly associated with high NG morbidity in the NHB female model, despite multiple studies that have linked lower male to female ratios with higher rates of STIs among persons of Black race in the US[73,74]. Similarly, we found that income inequality was inversely associated with membership in the lowest morbidity trajectory for NHB females, contradicting previously described associations between income inequality and STIs for both NHW and NHB persons[75–77]. However, a 2013 study of NG rates in US metropolitan areas found the association between income inequality and NG rates was attenuated after controlling for racial geographic segregation[78], a factor we were unable to account for. We should emphasize that our analysis of county-level factors associated with group membership was ecological in nature and does not imply a causal, temporal relationship between changes in these characteristics and NG morbidity. However, the goal of our analysis was to examine the general socioeconomic conditions associated with identified NG trends, which is more salient as our view of STI risk broadens from individual-level factors to the social context in which individuals exist.

We acknowledge several limitations that may have affected our analysis. Surveillance does not capture all NG infections, particularly asymptomatic and extragenital (i.e., pharyngeal and rectal) infections which are less likely to be diagnosed and reported. However, because NG is a nationally notifiable condition, we expect that data captured a large proportion of infections. Because current gender is inconsistently collected across jurisdictions reporting NG case data, female sex may not reflect the gender identity of persons within the data. We also note several important strengths of our analysis. We are not aware of prior publications using GBTM to characterize spatiotemporal trends in the morbidity of NG or any other STI in the US. We believe this approach provides a unique insight into spatiotemporal trends in NG rates that are not apparent when viewing a series of static maps with sequential annual rates. We utilized a nationally representative dataset comprising virtually all reported cases of NG among females and representative of over 97% of all NHW and NHB female NG cases reported during the period examined. Furthermore, the results of our logistic models of group association generally reflect prior work linking social determinants of health with NG morbidity, giving us confidence in our findings.

Conclusions

In this analysis, we have shown that the gonorrhea epidemic in US NHW and NHB females is highly heterogenous. This heterogeneity did not consistently follow patterns of geographic proximity, which points to variation in the social determinants of health driving inequities in STI morbidity. Our results should also generate further research into the factors shaping shared epidemic trajectories across multiple geographies.

Tables and Figures

Table 1. Model trajectories, number and percent of assigned counties, and average posterior probabilities and rates per 100,000 in counties assigned to a) each of 9 groups for non-Hispanic White females, and b) each of 7 groups for non-Hispanic Black females

Model for White Female County-level morbidity (7 groups)

Trajectory	Average Posterior Probability	Counties N (%)		White Female Population 2018		Cases 2003 N (%)		Cases 2018 N (%)		Rate 2003	Rate 2018	Absolute Rate Difference 2003-2018	% Rate Change 2003-2018
1	91.5	23	0.7%	1,583,207	1.6%	100	0.3%	222	0.3%	7.9	11.6	+3.7	+46.6%
2	78.4	125	4.0%	7,846,150	7.8%	2,410	6.7%	2,509	3.3%	30.4	31.4	+0.9	+3.0%
3	91.7	243	7.7%	16,227,450	16.2%	2,506	7.0%	4,911	6.4%	16.4	36.4	+20.0	+121.7%
4	85.5	424	13.5%	21,291,177	21.3%	4,581	12.7%	14,437	18.9%	23.1	84.5	+61.4	+266.4%
5	88.6	534	17.0%	29,155,695	29.1%	12,799	35.5%	25,281	33.1%	44	99.1	+53.2	+115.7%
6	80.9	79	2.5%	2,009,678	2.0%	703	2.0%	3,139	4.1%	40	181.0	+141.0	+352.5%
7	92.5	357	11.4%	15,365,112	15.3%	12,152	33.8%	23,742	31.1%	82.9	183.3	+99.3	+119.8%
No Data	-	1,357	43.2%	6,638,996	6.6%					-	-	-	-
Total	-	3,145	100%	100,117,465	100.0%	36,008	100%	23742	100%	35.6	76.3	+40.7	+114.3%

Model for Black Female County-level morbidity (9 groups)

Trajectory	Average Posterior Probability	Counties N (%)		Black Female Population 2018		Cases 2003 N (%)		Cases 2018 N (%)		Rate 2003	Rate 2018	Absolute Rate Difference 2003-2018	% Rate Change 2003-2018
1	92.4	37	1.2%	468,672	2.2%	424	0.4%	682	0.6%	115.8	146.3	+30.5	+26.3%
2	76.5	63	2.0%	929,456	4.4%	1,375	1.2%	2,038	1.8%	205.9	219.0	+13.1	+6.3%
3	78.8	64	2.0%	365,115	1.7%	1,119	1.0%	1,100	1.0%	526.3	358.8	-167.5	-31.8%
4	78.2	209	6.6%	3,437,789	16.1%	9,392	8.5%	9,841	8.7%	336.5	373.5	+37.1	+11.0%
5	76.9	157	5.0%	2,016,848	9.5%	8,816	8.0%	7,987	7.1%	522.3	413.2	-109.1	-20.9%
6	84.5	30	1.0%	165,063	0.8%	128	0.1%	504	0.4%	172.1	497.9	+325.7	+189.3%
7	77.6	220	7.0%	2,432,153	11.4%	9,906	9.0%	12,165	10.8%	439.5	615.7	+176.1	+40.1%
8	86.4	372	11.8%	7,546,352	35.4%	42,587	38.7%	46,860	41.5%	685.8	708.8	+23.1	+3.4%
9	90.6	113	3.6%	3,681,157	17.3%	36,398	33.0%	31,095	27.5%	1037.4	966.0	-71.4	-6.9%
No Data	-	1,877	59.7%	283,557	1.3%					-	-	-	-
Total	-	3,145	100%	21,326,162	100.0%	110145	100%	113010	100%	586.3	529.9	-66	-11.3%

Figure 1. *Spatial distribution of White Female NG Rate Trajectory Groups and Average county-level White female NG rate by group*

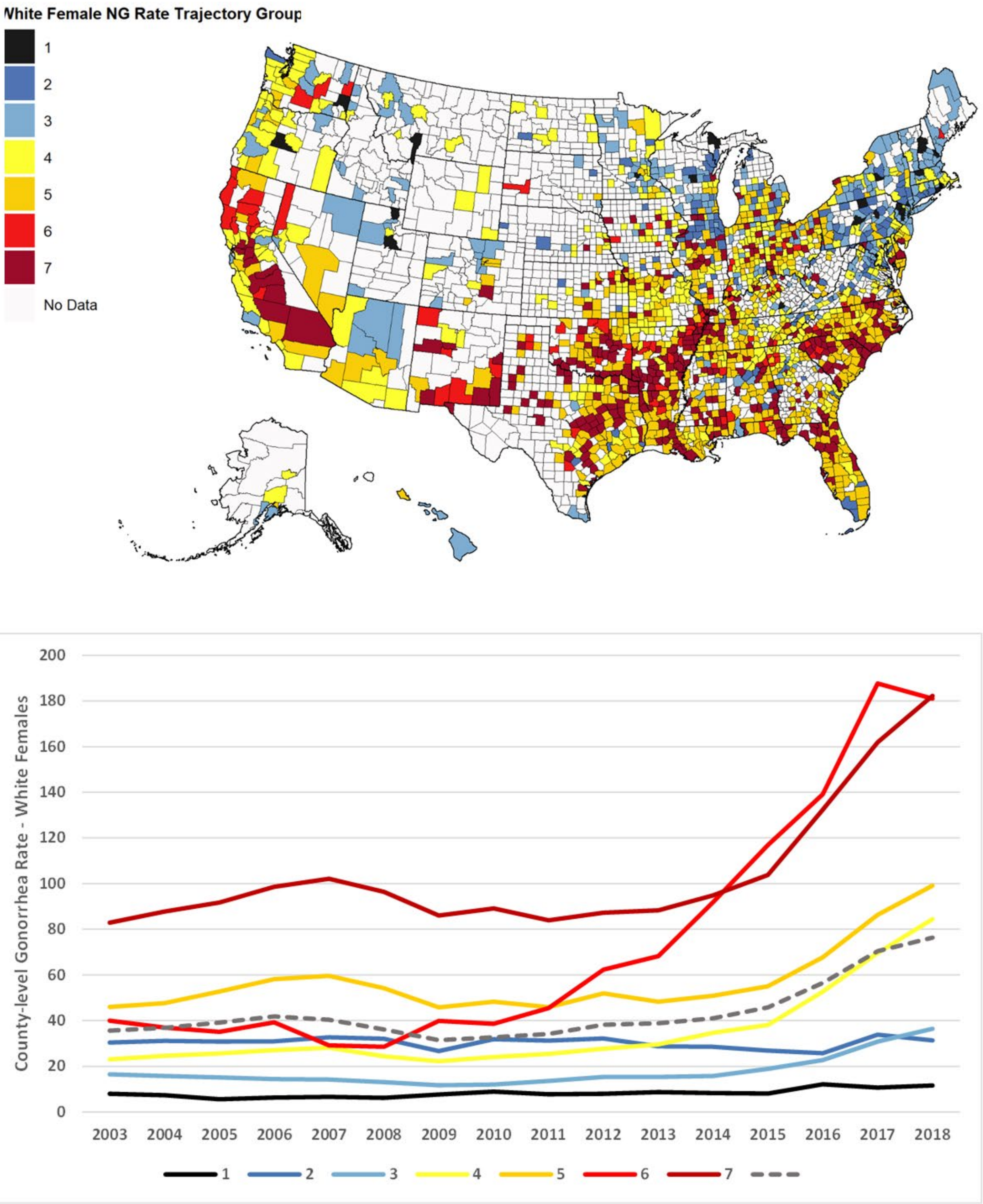


Figure 2. *Spatial distribution of Black Female NG Rate Trajectory Groups and Average county-level Black female NG rate by group*

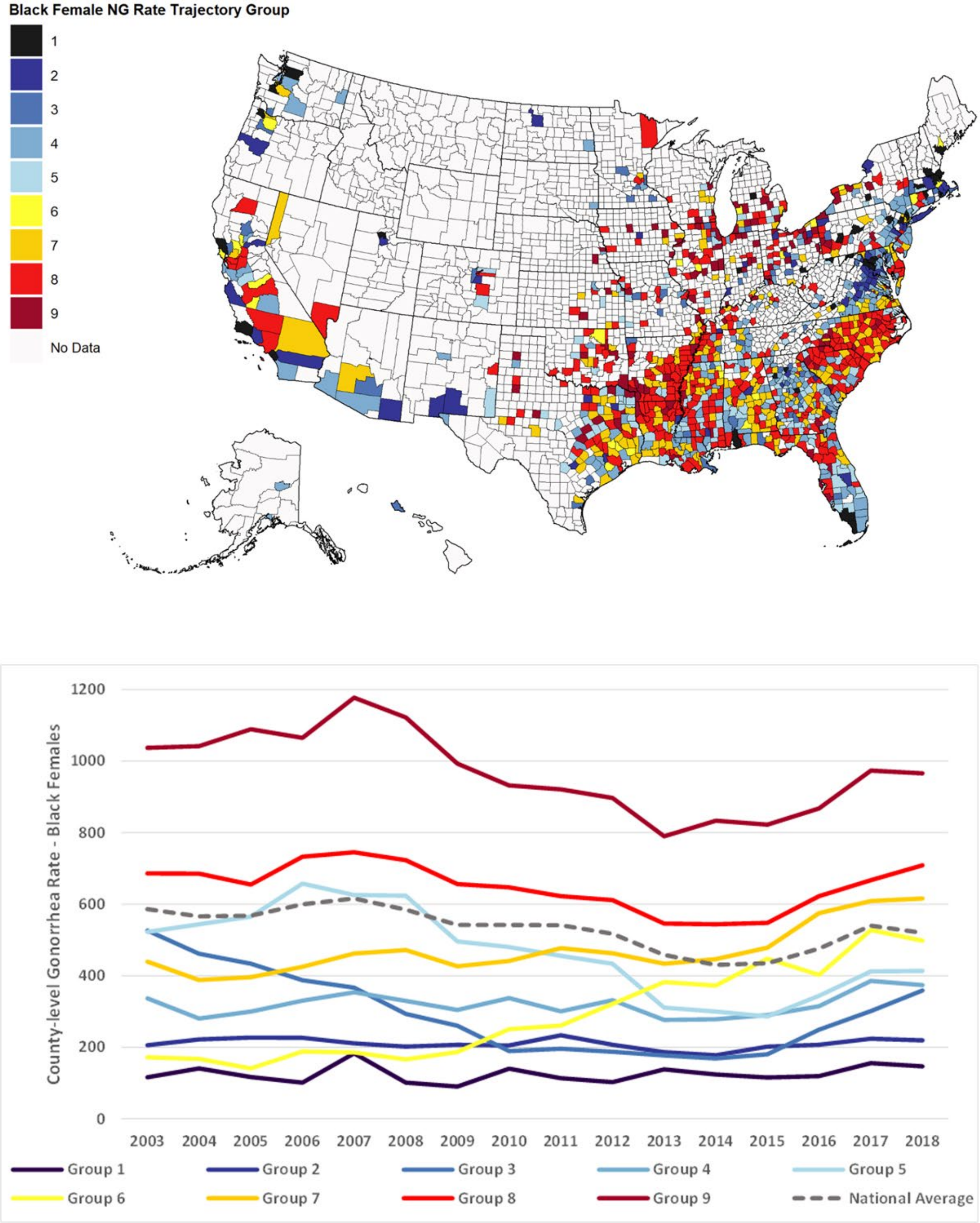
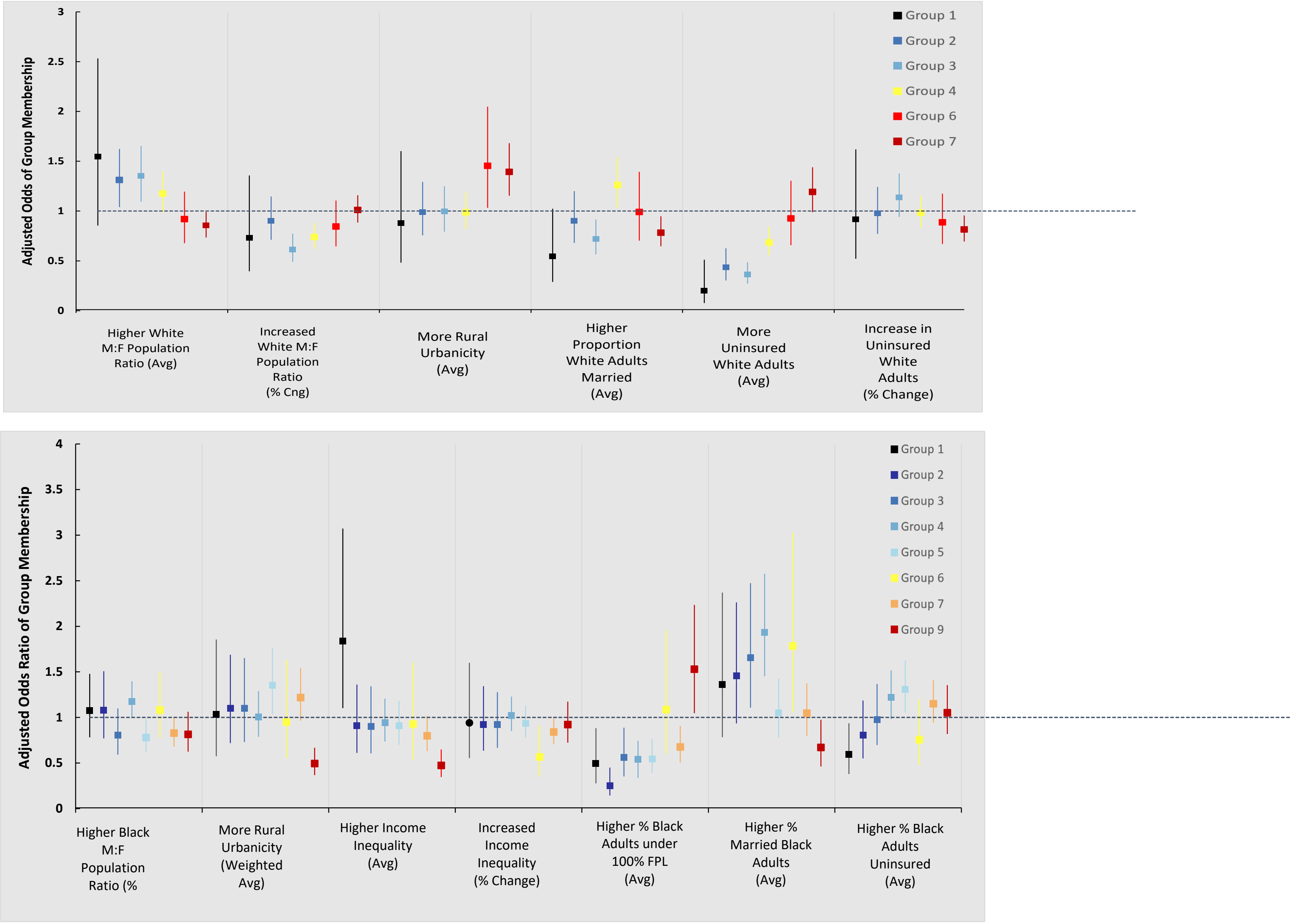


Figure 3. Adjusted odds ratios (aORs) of a) White Female NG Rate trajectories[a] and b) Black Female NG Rate trajectories[b] and 95% confidence intervals (CI) for demographic and socioeconomic variables significantly associated with group membership in each model[d]



[a] ORs are for a 1 standard deviation increase in the covariate, [b] ORs compare odds relative to that of the trajectory group closest to the national average rate trajectory for NHW females (group 5), [c] ORs compared odds relative to that of the trajectory group closest to the national average rate trajectory for NHB females (group 8), [t]Avg: Mean value 2003-2018; [d]% Change: Percent Change in value from 2003 to 2018

Supplemental Table 1. Parameters, BIC, and AIC for models with 1-15 groups

	Black Females			**White Females**		
Groups	AIC	BIC	Δ BIC	AIC	BIC	Δ BIC
1	-19536.9	-19549.8	.	-32380.4	-32394.1	
2	-16777.9	-16803.6	2746.14	-27728.6	-27756.0	4631.44
3	-15972.3	-16010.9	792.76	-26311.3	-26352.5	1396.94
4	-15577.2	-15628.7	382.19	-25800.5	-25855.4	490.44
5	-15402.1	-15466.4	162.29	-25589.5	-25658.1	190.68
6	-15308.6	-15385.7	80.67	-25570.6	-25636.5	22.92
7	-15296.5	-15371.1	14.64	-25434.3	-25513.9	115.95
8	-15226.4	-15306.1	64.95	-25248.5	-25341.8	165.41
9	-15145.8	-15246.1	60.01	-25217.9	-25316.7	22.5
10	-15117.6	-15230.7	15.39	-25099.7	-25209.4	101.91
11	-15119.3	-15229.9	0.8	-25187.4	-25297.1	-87.67
12	-15091.7	-15215.1	14.78	-25252.6	-25359. 6	-61.12
13	-15114.3	-15224.9	-9.72	-24919.0	-25097.4	227.65
14	-15124.3	-15237.4	-12.54		-	
15	-15111.7	-15232.5	4.87		-	

Supplemental Table 2A. % counties per group for Non-Hispanic White Females models with 1-13 Groups, 2B. % counties per group for Non-Hispanic Black Females models with 1-15 groups,

Model **2A.**	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8	Group 9	Group 10	Group 11	Group 12	Group 13	Group 14	Group 15
2 Group	44.90%	55.10%	.	.	.	.	.	.	.	.	.	.	.	.	.
3 Group	17.90%	44.10%	37.90%	.	.	.	.	.	.	.	.	.	.	.	.
4 Group	10.90%	31.50%	35.50%	22.10%	.	.	.	.	.	.	.	.	.	.	.
5 Group	6.70%	18.90%	31.10%	30.40%	12.90%	.	.	.	.	.	.	.	.	.	.
6 Group	1.50%	13.80%	23.10%	8.60%	19.90%	33.20%	.	.	.	.	.	.	.	.	.
7 Group	1.40%	7.70%	13.30%	23.40%	5.00%	19.70%	29.50%	.	.	.	.	.	.	.	.
8 Group	1.00%	7.30%	10.60%	17.00%	4.80%	24.90%	24.50%	9.90%	.	.	.	.	.	.	.
9 Group	0.80%	4.60%	6.80%	18.00%	6.30%	4.60%	24.10%	24.90%	9.90%	.	.	.	.	.	.
10 Group	0.60%	3.90%	3.20%	10.90%	6.10%	12.30%	23.60%	5.20%	24.00%	10.10%	.	.	.	.	.
11 Group	0.50%	1.00%	4.60%	6.50%	17.60%	6.30%	22.90%	4.30%	4.00%	8.80%	23.40%	.	.	.	.
12 Group	0.50%	1.00%	2.70%	3.90%	7.30%	20.80%	4.30%	5.60%	5.00%	21.90%	2.20%	24.70%	.	.	.
13 Group	2.20%	5.00%	6.90%	12.40%	8.50%	4.30%	1.90%	4.60%	17.40%	19.00%	1.40%	6.90%	9.60%	.	.
2B.															
2 Group	38.8%	61.2%	.	.	.	.	.	.	.	.	.	.	.	.	.
3 Group	18.1%	45.6%	36.3%	.	.	.	.	.	.	.	.	.	.	.	.
4 Group	5.4%	27.4%	43.1%	24.1%	.	.	.	.	.	.	.	.	.	.	.
5 Group	3.8%	19.7%	31.8%	33.9%	10.9%	.	.	.	.	.	.	.	.	.	.
6 Group	3.4%	16.2%	14.1%	19.6%	35.0%	11.9%	.	.	.	.	.	.	.	.	.
7 Group	2.9%	6.5%	15.3%	30.3%	6.6%	29.3%	9.2%	.	.	.	.	.	.	.	.
8 Group	2.7%	5.7%	14.0%	16.3%	6.2%	15.2%	30.0%	9.7%	.	.	.	.	.	.	.
9 Group	2.8%	4.8%	2.6%	5.3%	17.8%	15.7%	28.4%	13.4%	9.2%	.	.	.	.	.	.
10 Group	2.8%	4.5%	2.4%	4.8%	19.6%	14.8%	9.1%	15.9%	18.1%	8.0%	.	.	.	.	.
11 Group	2.7%	4.1%	2.8%	18.5%	6.0%	12.1%	18.3%	12.6%	10.6%	9.8%	2.5%	.	.	.	.
12 Group	2.5%	3.0%	6.7%	4.3%	5.3%	11.7%	14.0%	8.6%	12.4%	18.7%	10.4%	2.4%	.	.	.
13 Group	0.6%	2.3%	2.6%	6.2%	6.0%	3.9%	10.0%	11.8%	14.8%	9.6%	5.1%	3.6%	23.4%	.	.
14 Group	0.6%	2.3%	2.9%	2.7%	6.0%	9.1%	6.4%	9.5%	14.1%	9.8%	8.4%	5.9%	18.9%	3.4%	.
15 Group	0.5%	1.2%	2.6%	5.3%	1.5%	8.8%	2.6%	13.9%	5.2%	11.8%	5.8%	9.5%	18.8%	10.1%	2.4%

Supplemental Table 3. White Non-Hispanic Female (WNH) Population Residing in WNH and Black Non-Hispanic (BNH) Female Trajectory Group Counties

		White Female Population by Trajectory Group															
		White Female Trajectory Group															
		No Data		**1**		**2**		**3**		**4**		**5**		**6**		**7**	
	White Female Population	N=6,638,996		N=1,583,207		N=7,846,150		N=16,227,450		N=21,291,177		N=29,155,695		N=2,009,678		N=15,365,112	
Black Female Trajectory Group	**Black Female Population**	White Female Population (Col %)	Black Female Population (Row %)	White Female Population (Col %)	Black Female Population (Row %)	White Female Population (Col %)	Black Female Population (Row %)	White Female Population (Col %)	Black Female Population (Row %)	White Female Population (Col %)	Black Female Population (Row %)	White Female Population (Col %)	Black Female Population (Row %)	White Female Population (Col %)	Black Female Population (Row %)	White Female Population (Col %)	Black Female Population (Row %)
No Data	283,157	93%	27%	59%	3%	15%	5%	35%	24%	24%	25%	5%	10%	25%	3%	1%	3%
1	468,672	0%	1%	22%	6%	3%	4%	18%	74%	7%	16%	0%	0%	0%	0%	0%	6%
2	929,456	0%	1%	10%	3%	5%	9%	11%	34%	14%	43%	2%	9%	2%	0%	0%	3%
3	365,115	1%	7%	0%	0%	4%	7%	7%	35%	6%	38%	2%	11%	6%	1%	0%	0%
4	3,437,789	2%	3%	0%	0%	11%	2%	17%	25%	24%	32%	13%	32%	25%	1%	3%	0%
5	2,016,848	1%	3%	8%	9%	25%	38%	4%	5%	4%	8%	8%	27%	5%	0%	6%	9%
6	165,063	0%	4%	0%	0%	0%	4%	3%	18%	3%	64%	0%	2%	8%	7%	0%	0%
7	2,432,153	2%	4%	0%	0%	3%	1%	4%	13%	10%	18%	17%	49%	15%	1%	7%	0%
8	7,546,352	1%	1%	0%	0%	20%	4%	1%	1%	7%	6%	37%	56%	14%	1%	43%	0%
9	3,681,157	0%	0%	0%	0%	14%	18%	0%	0%	1%	1%	15%	36%	0%	0%	39%	0%

Supplemental Table 4. Logistic Model of County Group Membership compared to Group 5 – White Female Model

Covariate	Group	Unit (1 SD)	Adjusted Odds Ratio	95% CI	
White Adult Sex Ratio (M:F) Average 2003-2018	1	5.9%	1.743	1.03	2.951
	2		1.3	1.046	1.616
	3		1.381	1.129	1.69
	4		1.204	1.013	1.431
	6		0.897	0.668	1.204
	7		0.83	0.713	0.965
White Adult Sex Ratio (M:F) % Change 2003-2018	1	2.8%	0.732	0.395	1.357
	2		0.903	0.712	1.146
	3		0.616	0.491	0.773
	4		0.74	0.621	0.881
	6		0.845	0.645	1.106
	7		1.012	0.885	1.158
County Urbanicity (1=Urban Metro, 6=Noncore/Rural) Average 2003-2018	1	1.43	0.878	0.482	1.602
	2		0.989	0.756	1.292
	3		0.995	0.793	1.249
	4		0.987	0.821	1.188
	6		1.455	1.033	2.049
	7		1.394	1.155	1.682
County Urbanicity (1=Urban Metro, 6=Noncore/Rural) Difference 2003-2018	1	0.55	1.138	0.647	2.001
	2		1.021	0.822	1.269
	3		0.933	0.779	1.119
	4		1.095	0.952	1.259
	6		1.128	0.878	1.451
	7		0.956	0.837	1.093
Income Inequality (GINI) Average 2003-2018	1	0.03	1.622	0.875	3.008
	2		1.114	0.84	1.479
	3		1.131	0.887	1.44
	4		0.856	0.7	1.048
	6		0.822	0.571	1.184
	7		0.883	0.73	1.068
Income Inequality (GINI) % Change 2003-2018	1	5.3%	0.877	0.5	1.538
	2		1.131	0.893	1.433
	3		0.984	0.801	1.21
	4		1.088	0.932	1.272
	6		1.136	0.884	1.46
	7		1.014	0.883	1.166
% White Adults Earning <100% Federal Poverty Level Average 2003-2018	1	4.4%	0.56	0.228	1.379
	2		0.809	0.547	1.196
	3		0.758	0.554	1.037
	4		1.233	0.97	1.567
	6		1.438	0.982	2.105
	7		0.917	0.726	1.158
	1	2.6%	1.055	0.688	1.618

% White Adults Earning <100% Federal Poverty Level % Change 2003-2018	2		0.98	0.741	1.296
	3		1.173	0.955	1.44
	4		0.984	0.813	1.19
	6		1.046	0.811	1.35
	7		1.054	0.902	1.232
% White Adults Married Average 2003-2018	1	4.7%	0.544	0.289	1.024
	2		0.903	0.68	1.2
	3		0.719	0.565	0.915
	4		1.262	1.031	1.544
	6		0.991	0.704	1.394
	7		0.783	0.646	0.948
% White Adults Married % Change 2003-2018	1	6.5%	0.626	0.355	1.103
	2		1.009	0.789	1.291
	3		0.959	0.766	1.202
	4		1.014	0.852	1.207
	6		0.87	0.656	1.153
	7		0.941	0.817	1.085
% White Adults without Health Insurance Average 2003-2018	1	3.7%	0.199	0.077	0.512
	2		0.436	0.303	0.627
	3		0.363	0.271	0.486
	4		0.684	0.554	0.844
	6		0.926	0.658	1.305
	7		1.192	0.988	1.439
% White Adults without Health Insurance % Change 2003-2018	1	17.1%	0.918	0.521	1.62
	2		0.979	0.771	1.242
	3		1.139	0.941	1.378
	4		0.983	0.835	1.157
	6		0.887	0.669	1.175
	7		0.815	0.694	0.956

Supplemental Table 5. Logistic Model of County Group Membership compared to Group 8 – Black Female Model

Covariate	Group	Unit (1 SD)	Adjusted Odds Ratio	95% CI	
Black Adult Sex Ratio (M:F) Average 2003-2018	1	0.45	1.423	0.98	2.065
	2		1.025	0.687	1.53
	3		1.201	0.897	1.608
	4		1.201	0.974	1.48
	5		0.979	0.777	1.233
	6		1.2	0.808	1.784
	7		0.985	0.804	1.206
	9		0.817	0.595	1.12
Black Adult Sex Ratio (M:F) % Change 2003-2018	1	12.3%	1.075	0.782	1.479
	2		1.078	0.77	1.508
	3		0.807	0.592	1.099
	4		1.028	0.845	1.249
	5		0.781	0.621	0.983
	6		1.082	0.777	1.506
	7		0.829	0.68	1.009
	9		0.816	0.626	1.063
County Urbanicity (1=Urban Metro, 6=Noncore/Rural) Weighted Average 2003-2018	1	1.51	1.033	0.575	1.856
	2		1.101	0.719	1.688
	3		1.123	0.753	1.673
	4		1.008	0.788	1.289
	5		1.354	1.038	1.766
	6		0.95	0.553	1.632
	7		1.219	0.964	1.543
	9		0.496	0.368	0.668
County Urbanicity Difference (1=Urban Metro, 6=Noncore/Rural) Change 2003-2018	1	0.59	0.811	0.432	1.523
	2		0.986	0.7	1.389
	3		0.827	0.635	1.078
	4		0.923	0.773	1.102
	5		0.996	0.821	1.208
	6		1.296	0.902	1.862
	7		1.043	0.877	1.241
	9		0.859	0.681	1.083
Income Inequality (GINI) Average 2003-2018	1	3.2%	1.84	1.102	3.072
	2		0.912	0.611	1.361
	3		0.902	0.607	1.341
	4		0.943	0.736	1.207
	5		0.911	0.702	1.183
	6		0.928	0.535	1.608
	7		0.8	0.63	1.016
	9		0.967	0.714	1.309
Income Inequality (GINI) % Change 2003-2018	1	5.7%	0.942	0.554	1.6
	2		0.924	0.635	1.343

	3		0.923	0.667	1.278
	4		1.023	0.852	1.23
	5		0.936	0.777	1.129
	6		0.568	0.354	0.912
	7		0.841	0.706	1.001
	9		0.922	0.724	1.174
% Black Adults Earning <100% Federal Poverty Level Average 2003-2018	1	9.9%	0.495	0.278	0.883
	2		0.254	0.144	0.451
	3		0.561	0.354	0.889
	4		0.541	0.394	0.744
	5		0.548	0.392	0.766
	6		1.088	0.605	1.957
	7		0.677	0.505	0.907
	9		1.53	1.047	2.235
% Black Adults Earning <100% Federal Poverty Level % Change 2003-2018	1	34.2%	1.012	0.703	1.457
	2		0.986	0.73	1.331
	3		1.201	0.93	1.552
	4		0.919	0.749	1.127
	5		0.997	0.799	1.245
	6		1.13	0.786	1.627
	7		0.898	0.731	1.102
	9		1.09	0.816	1.458
% Black Adults Married Average 2003-2018	1	6.9%	1.364	0.785	2.37
	2		1.455	0.935	2.263
	3		1.655	1.108	2.473
	4		1.935	1.453	2.576
	5		1.053	0.778	1.426
	6		1.785	1.054	3.024
	7		1.047	0.798	1.374
	9		0.672	0.463	0.975
% Black Adults Married % Change 2003-2018	1	26.2%	0.784	0.487	1.264
	2		1.181	0.907	1.538
	3		1.185	0.942	1.489
	4		0.85	0.674	1.071
	5		1.11	0.932	1.322
	6		1.107	0.76	1.612
	7		0.907	0.746	1.104
	9		1.012	0.804	1.273
% Black Adults without Health Insurance Average 2003-2018	1	4.7%	0.596	0.379	0.936
	2		0.808	0.551	1.186
	3		0.977	0.698	1.368
	4		1.221	0.982	1.517
	5		1.308	1.054	1.625
	6		0.756	0.476	1.203
	7		1.151	0.942	1.408
	9		1.053	0.819	1.355
	1	53.1%	1.205	0.903	1.608

% Black Adults without Health Insurance % Change 2003-2018	2		1.021	0.618	1.686
	3		1.115	0.841	1.479
	4		1.227	0.95	1.583
	5		0.987	0.688	1.416
	6		1.228	0.904	1.666
	7		1.238	0.975	1.571
	9		0.931	0.617	1.406

Chapter 4. Prior exposure to azithromycin and azithromycin resistance among persons diagnosed with *Neisseria gonorrhoeae* infection at a Sexual Health Clinic 2012-2019

Abstract

Background

There is conflicting evidence on whether prior azithromycin (AZM) exposure is associated with reduced susceptibility to AZM (AZM^{RS}) among persons infected with *Neisseria gonorrhoeae* (NG).

Methods

The study population included Public Health-Seattle & King County Sexual Health Clinic (SHC) patients with culture-positive NG infection at ≥1 anatomic site whose isolates were tested for AZM susceptibility 2012-2019. We used multivariate logistic regression to examine the association of time since last AZM prescription from the SHC in ≤12 months with subsequent diagnosis with AZM^{RS} NG (minimum inhibitory concentration [MIC] ≥2.0 µg/ml) and used linear regression to assess the association between number of AZM prescriptions in ≤12 months and AZM MIC level, controlling for demographic, behavioral, and clinical characteristics.

Results

A total of 2,155 unique patients had 2,828 incident NG infections, 156 (6%) of which were caused by AZM^{RS} NG. AZM^{RS} NG was associated with receipt of AZM from the SHC in the prior 29 days (adjusted odds ratio [aOR] 6.76, 95% CI 1.76-25.90), but not with receipt of AZM in the prior 30-365 days. Log AZM MIC level was not associated with the number of AZM prescriptions within ≤12 months (Adjusted correlation [aCor] 0.0004, 95% CI -0.04, 0.037), but was associated with number of prescriptions within <30 days (adjusted coefficient [aCoef] 0.56, 95% CI 0.13-0.98)

Conclusion

Recent individual-level AZM treatment is associated with subsequent AZM^{RS} gonococcal infections. The long half-life and persistence of subtherapeutic levels of AZM may result in selection of resistant NG strains in persons with recent AZM use.

Introduction

Neisseria gonorrhoeae (NG) has progressively developed resistance to all antimicrobials previously used for its treatment,[5], leading the US Centers for Disease Control and Prevention (CDC) to declare antimicrobial resistant (AMR) NG an urgent health threat[79]. In December 2020[80], the US CDC changed its treatment recommendation for uncomplicated gonorrhea from a two-drug regimen of ceftriaxone 250mg and 1gm of azithromycin (AZM) to ceftriaxone 500mg monotherapy. This change was prompted by surveillance data demonstrating an increase in the percentage of Gonococcal Isolate Surveillance Project (GISP) isolates with an AZM minimum inhibitory concentrations (MICs) ≥2.0 µg/ml (indicating reduced susceptibility to AZM [AZM^{RS}] from 0.6% in 2013 to 5.1% in 2019; among 2019 isolates from men who have sex with men (MSM), 8.8%[49] had an elevated MIC to AZM. Current British guidelines have similarly dropped the inclusion of AZM as a second agent in treating gonorrhea[81], though European[82] and Australian[83] guidelines continue to recommend AZM-inclusive regimens.

Currently, there is conflicting evidence regarding the relationship between individual-level AZM exposure and subsequent AZM resistance in persons with NG infection. Exposure to erythromycin *in vitro* induces high-level macrolide resistance in NG strains with low-level resistance[12], and there have been numerous case reports of *de novo* selection for AZM resistance during NG treatment[13,14]. A study of STI clinic patients in the Netherlands found that NG isolates from persons who had received AZM in the preceding 30 days had higher AZM MICs than isolates from patients who received AZM 31-60 days prior to diagnosis and persons with no exposure to AZM in the preceding 60 days[84]. These findings are at odds with two UK studies which evaluated the association of prior NGU, CT, or NG diagnoses [15], or NG alone[16] – proxies for AZM exposure – and AZM^{RS} in persons with culture positive NG and found no such association.

We used data collected in the Public Health Seattle-King County (PHSKC) Sexual Health Clinic (SHC) to evaluate the association between individual-level receipt of AZM for STI treatment and subsequent NG infection with AZM^{RS}. We hypothesized that AZM treatment in ≤12 months preceding NG diagnosis would be associated with AZM^{RS} NG, and receipt of more courses of AZM would be associated with higher AZM MICs.

Methods

Study Design, Study Population, Clinical Protocols & Demographic and Behavioral Data

The study population included all patients from the PHSKC SHC with culture-positive NG at ≥1 anatomic site whose isolates were tested for AZM resistance between January 1, 2012, and December 31, 2019. Patients presenting to the clinic answered questions detailing demographic information, sexual history, and reason(s) for clinical visit using a computer assisted self-interview (CASI). During the visit, clinicians verified sexual histories and documented exam findings, testing and treatment. Throughout the study period, clinic policy recommended clinicians obtain specimens for culture from 1) persons with urethral discharge and diplococci detected on gram stain, 2) persons with symptoms of NG (cervicitis, PID, urethritis, proctitis, etc.), 3) persons reporting sexual contact to a partner with NG, or 4) persons who previously tested positive for NG on molecular tests and are returning for treatment.. Among men who have sex with men (MSM) evaluated as contacts to NG, clinicians collected culture specimens from all exposed anatomical sites. Among men who have sex with women exclusively (MSW) and women evaluated as contacts, from 2012-2016, clinicians collected only genital culture specimens; after 2016, cultures were collected from all exposed anatomic sites; after 2016, clinicians added pharyngeal cultures for individuals who reported performing oral sex in the past 2 months. In 2019, all MSW and women were screened at the oropharynx regardless of their report of oral sex.

AZM Susceptibility Data

AZM susceptibility testing was performed at the University of Washington Neisseria Reference Laboratory (NRL). From 2012–2016, urethral isolates were tested by agar dilution method[85], while isolates from extragenital and endocervical sites were tested using the Kirby-Bauer disk diffusion method using the CDC's protocol and azithromycin disk diffusion zone diameter breakpoints[86]. Isolates tested by Kirby-Bauer disk diffusion with AZM zone diameters ≤30 mm (equivalent to agar dilution AZM MIC ≥0.5–1 μg/mL) were also tested by agar dilution. We imputed a low AZM MIC (0.25) for cultures with AZM zone diameters >30mm. AZM susceptibility testing of isolates collected from 2017-2019 was performed by Etest[87]. Isolates were classified as having AZM^{RS} if the MIC was ≥2.0 μg/ml. If patients had a culture-positive infection at >1 anatomic site, we included the site with highest AZM MIC; if the MICs at multiple anatomic sites were equal, we randomly selected one anatomic site to include. Isolates were linked to patients' medical records by the PHSKC SHC data manager to create a de-identified dataset for analysis.

Statistical Analyses

We used a retrospective cohort study design comparing AZM use in the preceding 12 months between persons with NG infection with AZM^{RS} and without AZM^{RS}. Characteristics of patients with and without AZM^{RS} NG infections were compared using chi-square tests for categorical variables. We categorized timing of last prescription for 1g or 2g AZM from the SHC in the preceding 12 months into 1 of 5 categories: <30 days, 30-89 days, 90-179 days, 180-364 days, no AZM in past 365 days). We then examined the association of timing of last prescription with having an NG infection with AZM^{RS} using univariate and multivariate logistic regression for clustered outcomes to account for persons with >1 visit in the study period. We then examined the association between the number of 1 or 2g AZM prescriptions in the prior

12 months and log AZM MIC (due to the fact that MICs are a measured by dilution) using Spearman's rank correlation and multivariate partial Spearman's rank correlation[88] with robust standard errors. We examined the association between the number of AZM prescriptions in the prior <30 days and log AZM MIC using univariate and multivariate linear regression due to the abundance of ties produced by the smaller range of possible prescriptions in this time period in Spearman's rank correlation. Multivariate models adjusted for anatomic site of infection (penile urethral, cervicovaginal, rectal, or pharyngeal), number of sexual partners in ≤12 months (0, 1, 2-4, 5-9, ≥10, missing), self-reported HIV status, year (2012-2013, 2014-2015, 2015-2017, 2018-2019) and season of NG diagnosis (December-February, March-May, June-August, September-November)[89], race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic [any race], non-Hispanic Asian/Pacific Islander/Multiple Races, Declined/Missing/Unknown), patient's gender and sex of sex partner(s) (cisgender MSM, cisgender MSW, cisgender female, genderqueer/trans/non-binary), age in years, and number of clinic visits in the prior 12 months. We also repeated the univariate and multivariate models on restricted datasets of 1) only pharyngeal and rectal isolates and 2) penile urethral isolates, given the higher proportion of AZM^{RS} infections detected at extragenital sites[90]. As a sensitivity analysis, we also imputed higher (1.0) and lower (0.125) MIC values for isolates that did not meet the threshold for Kirby-Bauer disk diffusion for each linear regression model. Analyses were conducted using Stata software v15.1 (StataCorp, College Station, Texas). An α of 0.05 was considered significant.

Human Subjects Protection

The University of Washington's Human Subjects Division determined that all analyses were performed as part of gonorrhea surveillance and control activities and were thus non-human subject research as defined by federal and state regulations

Results

Study Population and Univariate Associations of Demographic and Clinical Characteristics with AZM^{RS} NG

Between 2012- 2019, 2,155 unique patients were diagnosed with 2,828 culture-positive NG infections, 156 (6%) of which had isolates with AZM^{RS}. Cisgender MSM, persons identifying as transgender, genderqueer and/or non-binary, and persons of Hispanic ethnicity were more likely to have an AZM^{RS} NG infection (Table 1). Isolates from the rectum and pharynx were more likely to be AZM^{RS} compared to penile urethral and cervicovaginal isolates. There were no significant differences between persons with AZM^{RS} and susceptible isolates by self-reported HIV status or age. Persons with an AZM^{RS} NG infection were more likely to report having ≥10 partners in the previous 12 months (35% vs 24%, p=0.02). The proportion of NG isolates with AZM^{RS} increased between 2012 and 2019, from 0% to 9% (p<0.001). However, there was no significant association between AZM^{RS} and season of diagnosis or the number of clinic visits or AZM prescriptions in the 12 months prior. The geometric mean of AZM MIC in persons with susceptible isolates was 0.24 (range 0.03-1.0) and the geometric mean in persons with AZM^{RS} isolates was 2.42 (range 2-256) (data not shown).

Univariate and Multivariate Regression Models

Of the 156 patients with AZM^{RS} NG infections, 115 (74%) had not received a prescription for AZM from the SHC in ≤365 days, 4 (2.6%) received a prescription in ≤29 days prior to a subsequent NG diagnosis, and 37 (24%) had received AZM in ≤30-364 days prior to NG diagnosis (Table 2). These proportions were similar when restricting to persons with extragenital vs penile urethral infections. In univariate analysis, diagnosis with AZM^{RS} NG was associated with prescription of AZM in <30 days (Odds Ratio [OR] 3.52, 95% Confidence Interval [CI] 1.32-9.38) compared to having no prescription for AZM in the previous 365 days (Table 2); this association was stronger after adjustment for clinical, demographic, and risk behavior characteristics (adjusted odds ratio [aOR] 6.76, 95% CI 1.76-25.90). Having a prescription for AZM in 30-

89 days, 90-179 days, or 180-364 days prior was not associated with having AZM^{RS} NG in either univariate or multivariate logistic regression. In the multivariate model restricted to persons with a rectal or pharyngeal infection, having an AZM prescription in the prior 30 days was associated with having an NG infection with AZM^{RS} compared to having no AZM prescription in the prior 365 days (aOR 5.40, 95% CI 1.24-23.43) (Table 2); having a prescription for AZM in 30-89 days, 90-179 days, or 180-364 days prior was not associated with having AZM^{RS} NG rectal or pharyngeal infection in either univariate or multivariate logistic regression. Although there was no association of AZM^{RS} penile urethral infection and receipt of AZM in the 30 days prior to diagnosis, we observed only 7 such infections and the aOR was similar to that observed for other anatomic sites (aOR 8.17, 95% CI 0.65-103.18).

Log AZM MIC was not associated with the number of AZM prescriptions from the SHC in the 12 months prior to NG diagnosis (adjusted correlation [aCorr] 0.0004, 95% CI -0.04, 0.037)(Table 3). This positive, non-significant relationship was also observed in the model restricted to rectal and pharyngeal infections (aCorr 0.049, 95% CI -0.011-0.11) (Table 3). For each additional AZM prescription in the past 30 days there was a 0.56 (95% C.I. 0.13-0.98) increase in the log AZM MIC in multivariate analysis (Table 4). This relationship was also significant when restricted to extragenital infections (a Coef 0.55, 95% CI 0.03-1.08), but not penile urethral infections alone (aCoef 0.52, 95% C.I. -0.27, 1.32). There were no substantial differences in the strength, direction, or significance of these associations when varying the imputed MIC for samples not meeting Kirby-Bauer disk diffusion threshold (data not shown).

Discussion

We found evidence for an association between recent (<30 days) receipt of AZM and subsequent AZM^{RS} NG infection. This relationship persisted when we restricted our analyses to extragenital infections. While the positive association between AZM receipt and NG infection with AZM^{RS} among persons with a penile urethral infection was not statistically significant, the similar effect size for this estimate along with wide confidence bounds may indicate we did not have sufficient statistical power to detect such an association if it exists. We also found a significant relationship between the number of exposures to AZM and increasing levels of resistance in NG infections acquired within 30 days, but not with the cumulative number of AZM exposures in the prior year. . These findings support our hypothesis of a relationship between recent AZM use and the development of AZM resistance in NG infections at an individual level.

Prior work has identified two potential mechanisms by which AZM resistance emerges; direct selection through exposure to AZM for STI infections (which this analysis was primarily designed to detect), and bystander selection through individual and community-level exposure to AZM for non-NG/STI infections[91]. Our results suggest that direct selection related to STI treatment occurs. AZM therapy could lead to selective pressure on chromosomal mutations conferring AZM^{RS} given the long half-life of AZM and intracellular persistence of subtherapeutic levels up to 20 days[9]. This period closely corresponds to the 30-day exposure period in which we observed a strong association with AZM^{RS}. These results, which are consistent with results of the aforementioned Dutch study that found an association between AZM^{RS} NG infection and AZM receipt in the same exposure period, provide strong evidence of a link between individual-level AZM use and emergence of AZM^{RS} in NG infections. Our results contradict two UK studies finding no association between AZM exposure and AZM resistance[15,16]. However, both these studies used surveillance data to infer AZM exposure from STI[15] or NG[16] diagnoses. This may have led to misclassification of AZM exposure categories, particularly when using only NG diagnoses.

Our findings may also point to the role of commensal bacterial species in development of resistance. NG is highly adept at acquiring resistance determinants due to its propensity for genome modification via passive uptake of exogenous genetic material. Exposure to macrolides can induce resistance mutations in commensal *Neisseria* and other bacterial species plentiful in the human oropharynx[10,92,93]. These mutations may then be acquired by NG during a subsequent infection via conjugal transfer[10,11]. Pharyngeal and rectal infections are often asymptomatic and can persist for longer periods of time, allowing a longer period of coexistence with commensals[94] and increase the chances of AMR gene transfer[95]. Additionally, previous work has demonstrated low concentrations of antibiotics used for NG treatment in the oropharynx[96], leading to suboptimal concentrations that allow for emergence and proliferation of resistant strains[97].

Despite the strong association of AZM exposure in the previous 30 days with AZM^{RS}, the majority of persons with an AZM^{RS} NG infection were not exposed to AZM in this time period. This suggests that AZM resistance arises from direct selection – in at least some instances as a result of STI treatment - and then spreads through transmission of clonal resistant strains. Whole genome sequencing (WGS) studies detected the emergence and spread of NG with high-level AZM^{RS} in Scotland as early as 2004[98]. In 2015, a cluster of NG with high-level AZM^{RS} was detected in Britain[99], and sustained transmission of this clonal strain was documented through at least 2018[100]; transmission of NG strains with high-level AZM^{RS} has been documented during the same period in Australia[101] and Canada[102]and later in the US[103]. The majority of resistant isolates included in our analysis occurred after 2017, which may indicate rapid proliferation of newly emergent clonal strains. Additionally, the densely connected sexual networks of MSM, in combination with frequent testing and treating, have been proposed as a mechanism by which AMR NG strains can emerge and quickly propagate[6,104].

The induction of resistant strains of NG may also result from an indirect bystander effect of population-level AZM exposure. High levels of AZM use for indications unrelated to STI could induce NG resistance in people with unidentified gonorrhea or who acquire gonorrhea shortly after receiving AZM. Some of the strongest evidence for the role of population-level selective pressure comes from an ecological study linking population-level seasonal macrolide use with seasonal variation in AZM MICs in a nationally representative sample of NG isolates[89]; we did not observe the same association between AZM^{RS} and seasonality in our results, possibly due to an incomplete assessment of AZM use from other clinical sources. Other ecological studies have demonstrated similar associations between country-level macrolide use and prevalence of AZM^{RS} NG[105,106]. We have previously demonstrated a marked increase in AZM use for epidemiologic and empiric treatment of STIs among PHSKC SHC attendees during the period examined, particularly among MSM[107],which may have contributed to high community-level selective pressure for AZM^{RS} determinants among this population. The documented increase in SHC AZM prescriptions closely correlates with the time periods in which AZM^{RS} infections were most commonly detected and year of infection was one of few covariates correlated with having an AZM^{RS} NG infection.

We acknowledge several limitations that may have impacted our analysis. Between 2013-2017, only extragenital isolates with AZM zone diameters ≤30mm on Kirby-Bauer disk diffusion were selected for agar dilution, and it is possible this method misclassified some extragenital isolates with lower-level (2 µg/mL) AZM^{RS}. We were limited to records of AZM episodes from a single sexual health clinic. Patients may have been prescribed AZM in other clinical settings, resulting in underestimates of total AZM use and misclassification of exposures, diminishing our statistical power. However, given that our clinic serves a population at high risk of bacterial STIs and provides regular screening and treatment, including quarterly screening for PrEP services, we believe our data captures a large proportion of total AZM use. Finally, we acknowledge that the sample size of patients exposed to AZM in the prior 30 days, the period of exposure for which we identified an association with AZM^{RS} NG, was relatively small (N=22). However, the strength of the association identified was very strong in both univariate and multivariate analysis, and our results align with the only other study to capture AZM prescriptions explicitly[84] rather than using STI diagnoses as proxy[15,16]. We also note that our study included over 2,800 anatomically diverse isolates with 156 AZM^{RS} isolates, making this one of the largest clinic-based analyses attempting to answer this question to date.

Conclusions

In conclusion, we found an association between recent receipt of AZM for STI treatment and AZM^{RS} NG infections among PHSKC SHC attendees. However, most persons with AZM^{RS} infections did not have AZM exposure in the previous year, suggesting transmission of clonal resistant strains and AZM use for non-STI indications also play an important role in the proliferation of AZM resistance. These findings underscore the timeliness of updated STI treatment guidelines that reduce the utilization of AZM in populations at high risk for NG and CT.

Tables and Figures

Table 1. Study Population Demographics, Sexual History, and Clinical characteristics by azithromycin minimum inhibitory concentration (MIC) of current infection

	AZM MIC <2.0 µg/mL	**AZM MIC ≥2.0 µg/mL**	***p***
	N=2,672 (94%)	N=156 (6%)	
	N (Col %)		
Gender/Sex of Sex Partners			
Cisgender Male who has Sex with Men (MSM)	2,190 (82%)	140 (90%)	0.005
Cisgender Male who has Sex with Females (MSW)	378 (14%)	9 (6%)	
Cisgender Female	67 (3%)	2 (1%)	
Transgender, Genderqueer, Non-binary	37 (1%)	5 (3%)	
Age in years			0.99
18-24	544 (20%)	32 (21%)	
25-29	838 (31%)	49 (31%)	
30-39	663 (25%)	37 (24%)	
40+	627 (23%)	38 (24%)	
Race/Ethnicity			0.008
Hispanic	352 (13%)	31 (20%)	
White	1,413 (53%)	90 (58%)	
Black	478 (18%)	13 (8%)	
Native American, Pacific Islander, Asian, Multiple races	345 (13%)	17 (11%)	
Unknown/Missing	84 (3%)	5 (3%)	
Living with HIV	367 (14%)	20 (13%)	0.75
Sexual partners in past 12 months			
0	698 (26%)	29 (19%)	0.02
1	63 (2%)	2 (2%)	
2-4	348 (13%)	20 (13%)	
5-10	365 (24%)	24 (15%)	
10+	633 (24%)	55 (35%)	
Missing partner info	565 (21%)	25 (4%)	0.02
Anatomic Site of Infection			0.04
Urethra	1,468 (55%)	72 (46%)	
Pharynx	486 (18%)	31 (20%)	
Rectum	675 (25%)	52 (33%)	
Cervicovaginal	43 (2%)	1 (0.6%)	
Year of Infection			
2012-2013	478 (18%)	0 (0;0)	<0.001
2014-2015	576 (22%)	25 (16%)	
2016-2017	748 (28%)	45 (29%)	
2018-2019	870 (33%)	86 (55%)	
Season			0.70
Dec-Feb	703 (26%)	46 (29%)	
Mar-May	653 (24 %)	39 (25%)	
June-Aug	668 (25%)	39 (25%)	
Sep-Nov	648 (24%)	32 (21%)	

# Prior Clinic Visits, 12 months			
0	1,212 (45%)	74 (47%)	0.93
1	521 (20%)	30 (19%)	
2-3	499 (19%)	26 (17%)	
4+	440 (16%)	26 (17%)	
Number of Azithromycin prescriptions in past 12 months			
0	1,821 (68%)	115 (74%)	0.44
1	561 (21%)	28 (18%)	
2	187 (7%)	7 (5%)	
3+	103 (4%)	6 (4%)	

IQR=interquartile range; HIV=human immunodeficiency virus

Table 2. Number and proportion of *Neisseria gonorrhoeae* infections with reduced azithromycin susceptibility and association of last azithromycin dose with azithromycin resistance (minimum inhibitory concentration [MIC] ≥2.0 μg/mL) in logistic regression

		Univariate			Multivariate		
	Persons with AZM^{RS} infection/Persons in azithromycin exposure category (%)	Odds Ratio	95% Confidence Interval	*p*	Odds Ratio	95% Confidence Interval	*p*
Any anatomic site of infection[a]							
No azithromycin in past 365 days (ref)	115/1,936 (6)	1.0	-	-	1.0	-	-
<30 days	4/22 (18)	3.52	1.32-9.38	0.01	6.76	1.76-25.90	0.005
30-89 days	9/216 (4)	0.69	0.34-1.39	0.30	0.75	0.35-1.61	0.46
90-179 days	10/301 (3)	0.54	0.28-1.05	0.07	0.51	-0.24-1.08	0.08
180-364 days	18/353 (5)	0.85	0.51-1.41	0.53	0.83	0.47-1.45	0.51
Pharyngeal or Rectal Infection[b]							
No azithromycin in past 365 days (ref)	60/860 (7)	1.0	-	-	1.0	-	-
<30 days	3/15 (20)	3.33	1.07-10.41	0.04	5.40	1.24-23.43	0.02
30-89 days	7/74 (8)	1.39	0.61-3.16	0.43	1.36	0.55-3.40	0.51
90-179 days	5/127 (4)	0.55	0.21-1.39	0.21	0.50	0.17-1.51	0.22
180-364 days	8/154 (5)	0.73	0.34-1.56	0.42	0.74	0.32-1.68	0.47
Urethral Infection[b]							
No azithromycin in past 365 days (ref)	54/1,030 (5)	1.0	-	-	1.0	-	-
<30 days	1/6 (17)	3.61	0.41-31.51	0.25	8.17	0.65-103.18	0.11
30-89 days	2/140 (1)	0.26	0.06-1.10	0.07	0.30	0.06-1.49	0.14
90-179 days	5/174 (3)	0.53	0.21-1.36	0.19	0.51	0.18-1.47	0.21
180-364 days	10/197 (5)	0.92	0.49-1.92	0.92	0.94	0.45-1.96	0.88

AZM^{RS}= reduced susceptibility to azithromycin

[a] Multivariate regression adjusted for anatomic site of infection (reference=penile urethral infection), number of sex partners in past 12 months, year of diagnosis (reference=2012/2013), self-reported HIV infection (reference=not HIV-positive), season (reference=summer [June-August]), race/ethnicity (reference=non-Hispanic White), gender/sex of sex partner(s) (reference=cisgender men who have sex with men), age, and number of clinic visits in past 12 months

[b] Multivariate regression adjusted for number of sex partners in past 12 months, self-reported HIV infection (reference=not HIV-positive), year of diagnosis (reference=2012/2013), season (reference=summer [June-August]), race/ethnicity(reference=non-

Hispanic White), gender/sex of sex partner(s) (reference=cisgender men who have sex with men), age, and number of clinic visits in past 12 months

Table 3. Association of azithromycin prescriptions in the past 365 days with log azithromycin minimum inhibitory concentration level µg/mL in univariate Spearman's rank correlation and multivariate partial Spearman correlation

	Univariate			Multivariate[a]		
	Coefficient		*p*	Coefficient	95% Confidence Interval	*p*
Any anatomic site of infection[a]	0.006	-0.03, 0.04	0.74	0.0004	-0.04, 0.037	0.98
Rectal or Pharyngeal infection[b]	0.019	-0.037, 0.075	0.51	0.049	-0.011-0.11	0.11
Urethral infection[b]	0.001	-0.049,0.051	0.97	-0.029	-0.078, 0.020	0.24

[a] Multivariate correlation adjusted for anatomic site of infection (reference=penile urethral infection), number of sex partners in past 12 months, year of diagnosis (reference=2012/2013), self-reported HIV infection (reference=not HIV-positive), season (reference=summer [June-August]), race/ethnicity (reference=non-Hispanic White), gender/sex of sex partner(s) (reference=cisgender men who have sex with men), age, and number of clinic visits in past 12 months

[b] Multivariate correlation adjusted for number of sex partners in past 12 months, year of diagnosis (reference=2012/2013), self-reported HIV infection (reference=not HIV-positive), season (reference=summer [June-August]), race/ethnicity (reference=non-Hispanic White), gender/sex of sex partner(s) (reference=cisgender men who have sex with men), age, and number of clinic visits in past 12 months

Table 4. Association of azithromycin prescriptions in the past <30 days with log azithromycin minimum inhibitory concentration level µg/mL in univariate linear regression and multivariate linear regression

	Univariate			Multivariate[a]		
	Coefficient	95% Confidence Interval	*p*	Coefficient	95% Confidence Interval	*p*
Any anatomic site of infection[a]	0.53	0.11-0.96	0.02	0.56	0.13-0.98	0.01
Rectal or Pharyngeal infection[b]	0.53	0.004-1.06	0.048	0.55	0.03-1.08	0.04
Urethral infection[b]	0.32	-0.38, 1.02	0.37	0.52	-0.27, 1.32	0.20

[a] Multivariate regression adjusted for anatomic site of infection (reference=penile urethral infection), number of sex partners in past 12 months, year of diagnosis (reference=2012/2013), self-reported HIV infection (reference=not HIV-positive), season (reference=summer [June-August]), race/ethnicity (reference=non-Hispanic White), gender/sex of sex partner(s) (reference=cisgender men who have sex with men), age, and number of clinic visits in past 12 months

[b] Multivariate regression adjusted for number of sex partners in past 12 months, year of diagnosis (reference=2012/2013), self-reported HIV infection (reference=not HIV-positive), season (reference=summer [June-August]), race/ethnicity (reference=non-Hispanic White), gender/sex of sex partner(s) (reference=cisgender men who have sex with men), age, and number of clinic visits in past 12 months

Chapter 5. Conclusion

In this dissertation, we have addressed several key gaps in our knowledge of NG epidemiology in the US. We have presented a more detailed and comprehensive view of NG epidemiology among females through a series of novel data visualizations. While our first two analyses are largely descriptive, they illuminate features of a highly heterogenous NG epidemic in US females that have not been fully described to date. We found that large disparities in NG rates within and between NHB and NHW females are pervasive throughout the US and rates in NHB females are often lower in southeastern states long assumed to experience the highest rates of disease. Our analysis also revealed previously undescribed geographic and temporal heterogeneity in NG trends among these two populations over the last 15 years. Finally, we have also provided strong evidence for a relationship between individual-level recent AZM use and AZM resistance.

Our finding of a relationship between AZM use and AZM resistance may challenge the current paradigm of frequent testing and antibiotic treatment of NG and CT in MSM, who have relatively low risk of reproductive sequalae but very high risk of AMR NG infections. One strategy for decreasing antibiotic usage in this population is to reserve antibiotic therapy for persons with confirmed NG or CT infection. Currently, the US CDC recommends treating persons who report exposure to a partner(s) with either infection concurrently with testing. However, a large proportion of these persons are uninfected, leading to unnecessary antibiotic use [8,108–113]. Until cost-effective point-of-care tests can be incorporated into routine clinical care, the next best option may be to delay treatment of asymptomatic contacts until infection is confirmed. An evaluation of this policy at a separate sexual health clinic in Australia found that 99% of asymptomatic contacts not treated at the time of evaluation who tested positive for NG/CT returned for treatment within a mean time of 5 days of receiving their test results, with a very low rate of new symptoms occurring between testing and treatment and serious sequalae[114]. Paradoxically, our ability to effectively treat future NG may require less treatment in the present time.

The results of our geographic analyses should generate new hypotheses about the macro-level drivers of NG morbidity in females. Our finding that counties experiencing similar trends in NG morbidity were often widely distributed could be explained by several could be explained by the presence of distally connected epidemics, separate epidemics shaped by shared social determinants of heightened risk, or parallel but separate epidemics each driven by unrelated factors. Elucidating these factors could be used to inform more effective prevention programs, which may very well fall outside the scope of traditional STI services to include economic development, social services programs, and/or increasing access to healthcare. It is clear from our analysis that reducing NG morbidity in females is contingent the elimination of racial disparities. We hope that these results can be used to explicitly monitor and focus interventions in areas with highest disparities *and* overall morbidity in pursuit of this goal.

In summary, we have provided a more comprehensive and nuanced view of the epidemic, and in the process challenged several long-held truisms in our understanding of population-level morbidity and antibiotic treatment practices. A reexamination of liberal antibiotic treatment among MSM is warranted given the risk of resistance. The geographic heterogeneity in burden of disease among females points to differences in upstream group-level factors shaping risk. Our results should prompt a renewed, multidisciplinary effort to uncover and intervene on the social determinants of health most influential in driving morbidity.

Acknowledgments

I am forever indebted to my mentors who have so generously provided their time, expertise, and guidance on this work. I am grateful for Dr. Matthew R. Golden's support and commitment to helping me become a more competent, confident, and experienced epidemiologist and for all his guidance in my career development. I would like to thank Dr. Christine M. Khosropour for encouraging me to embark on this journey and for providing endlessly patient advice and feedback on how to manage the transition to an academic environment. I am grateful to Dr. Lisa E. Manhart for her supportive mentorship and giving me an opportunity to be a part of her research team. I am incredibly lucky and thankful to have had the opportunity to be mentored by Dr. James P. Hughes before his retirement; I have learned so much from our discussions on methodology and this work would not have been possible without his guidance and expertise. I would like to also thank Dr. Lindley A. Barbee for including me on her work related to antibiotic use and antimicrobial resistance and her unwavering support through the dissertation process. I am also so thankful to Mr. Mark R. Stenger for facilitating the data use agreement that made this work possible and generously sharing his expertise in all things STI surveillance. I would also like to thank Dr. Isaac C. Rhew for graciously agreeing to share his time as GSR for this dissertation.

I would also like to acknowledge several organizations and individuals without whom this work would not have been possible. Dr. Olusegun Soge and the staff of the *Neisseria* Reference Laboratory at University of Washington performed all antibiotic sensitivity testing, and Ms. Christina Thibault pulled (and patiently re-pulled the clinical data) used for Aim 1. The University of Washington Institute for Translational Health Sciences (TR002318) and National Institutes of Health (1R03AI156261-01 to Lindley A. Barbee) granted funding critical to support this work. I would also like to acknowledge the Urban Institute's *urbnmapr* project for provision of open-source code for the creation of maps produced as part of this work. Finally, I would like to thank and acknowledge the contributions of patients and staff at the Public Health Seattle-

King County Sexual Health Clinic and all clinicians who work to test for, treat, and report STIs throughout the US, without whom this work would not exist.

I want to thank all the family and friends who supported me throughout my dissertation journey. Thank you to my parents, whose love and support I carry in my heart even though they are not here to see me reach this milestone, and to my stepfamily for unhesitatingly embracing me and this journey. Finally, words cannot express my gratitude and love for my biggest cheerleader and most enthusiastic supporter, my husband Omar Al-Hinai – thank you for always believing in me.

References

1. Sexually Transmitted Disease Surveillance, 2020. Accessed April 24, 2022. https://www.cdc.gov/std/statistics/2020/default.htm
2. Holmes KK. *Sexually Transmitted Diseases*. McGraw-Hill Medical; 2008.
3. Heumann CL, Quilter LAS, Eastment MC, Heffron R, Hawes SE. Adverse Birth Outcomes and Maternal Neisseria gonorrhoeae Infection: a Population-Based Cohort Study in Washington State. *Sex Transm Dis*. 2017;44(5):266. doi:10.1097/OLQ.0000000000000592
4. Gao R, Liu B, Yang W, et al. Association of Maternal Sexually Transmitted Infections With Risk of Preterm Birth in the United States. *JAMA Netw Open*. 2021;4(11):e2133413. doi:10.1001/JAMANETWORKOPEN.2021.33413
5. Unemo M, Shafer WM. Antimicrobial resistance in Neisseria gonorrhoeae in the 21st Century: Past, evolution, and future. *Clinical Microbiology Reviews*. 2014;27(3):587-613. doi:10.1128/CMR.00010-14
6. Fingerhuth SM, Bonhoeffer S, Low N, Althaus CL. Antibiotic-Resistant Neisseria gonorrhoeae Spread Faster with More Treatment, Not More Sexual Partners. Levin BR, ed. *PLOS Pathogens*. 2016;12(5):e1005611. doi:10.1371/journal.ppat.1005611
7. Rowlinson, Emily; Berzkalns, Anna; Thibault, Christina; Golden, Matthew R; Barbee LA. High incidence of antimicrobial use and overuse in cisgender MSM at high risk of bacterial STIs. In: *STI & HIV World Congress*. ; 2021.
8. Rowlinson, Emily; Golden, Matthew R; Berzkalns, Anna; Thibault, Christina; Barbee LA. Epidemiologic treatment of contacts to Neisseria gonorrhea and Chlamydia trachomatis infection in STD clinic patients in Seattle, WA 1994-2018. *Sexually Transmitted Diseases*. 2020;Publish Ah.
9. Horner P, Saunders J. Should azithromycin 1 g be abandoned as a treatment for bacterial STIs? The case for and against. *Sexually Transmitted Infections*. 2017;93(2):85-87. doi:10.1136/SEXTRANS-2015-052414
10. Wadsworth CB, Arnold BJ, Sater MRA, Grad YH. Azithromycin resistance through interspecific acquisition of an epistasis-dependent efflux pump component and transcriptional regulator in Neisseria gonorrhoeae. *mBio*. 2018;9(4). doi:10.1128/mBio.01419-18
11. Manoharan-Basil SS, Laumen JGE, Dijck C van, Block T de, Baetselier I de, Kenyon C. Evidence of Horizontal Gene Transfer of 50S Ribosomal Genes rplB, rplD, and rplY in Neisseria gonorrhoeae. *Frontiers in Microbiology*. 2021;12. doi:10.3389/FMICB.2021.683901
12. Chisholm SA, Dave J, Ison CA. High-level azithromycin resistance occurs in Neisseria gonorrhoeae as a result of a single point mutation in the 23S rRNA genes. *Antimicrob Agents Chemother*. 2010;54(9):3812-3816. doi:10.1128/AAC.00309-10

13. Soge OO, Harger D, Schafer S, et al. Emergence of Increased Azithromycin Resistance During Unsuccessful Treatment of Neisseria gonorrhoeae Infection With Azithromycin (Portland, OR, 2011). *Sex Transm Dis*. 2012;39(11):877. doi:10.1097/OLQ.0B013E3182685D2B

14. Young H, Moyes A, McMillan A. Azithromycin and erythromycin resistant Neisseria gonorrhoeae following treatment with azithromycin. *Int J STD AIDS*. 1997;8(5):299-302. doi:10.1258/0956462971920127

15. Clifton S, Town K, Furegato M, et al. Is previous azithromycin treatment associated with azithromycin resistance in Neisseria gonorrhoeae ? A cross-sectional study using national surveillance data in England. *Sexually Transmitted Infections*. Published online 2018. doi:10.1136/sextrans-2017-053461

16. Allen H, Merrick R, Ivanov Z, et al. Is there an association between previous infection with *Neisseria gonorrhoeae* and gonococcal AMR? A cross-sectional analysis of national and sentinel surveillance data in England, 2015–2019. *Sexually Transmitted Infections*. Published online March 4, 2022:sextrans-2021-055298. doi:10.1136/SEXTRANS-2021-055298

17. Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2018*.; 2019. doi:10.15620/cdc.79370

18. Speckmann A, Verbeek K. Necklace maps. *IEEE Transactions on Visualization and Computer Graphics*. 2010;16(6):881-889. doi:10.1109/TVCG.2010.180

19. Slocum TA, McMaster RB, Kessler FC, Howard HH. Thematic Cartography and Geovisualization. *Prentice Hall series in geographic information science*. Published online 2008:576. Accessed February 9, 2022. http://www.amazon.com/Thematic-Cartography-Geovisualization-3rd-Edition/dp/0132298341

20. Hogben M, Leichliter JS. Social determinants and sexually transmitted disease disparities. *Sex Transm Dis*. 2008;35(12 Suppl). doi:10.1097/olq.0b013e31818d3cad

21. Biello KB. Residential racial segregation and disparities in sexually transmitted disease risk in the United States: The growing evidence. *Sexually Transmitted Diseases*. 2013;40(6):444-446. doi:10.1097/01.olq.0000430673.76944.b8

22. Ibragimov U, Beane S, Friedman SR, et al. States with higher minimum wages have lower STI rates among women: Results of an ecological study of 66 US metropolitan areas, 2003-2015. *PLoS ONE*. 2019;14(10). doi:10.1371/journal.pone.0223579

23. Ibragimov U, Beane S, Friedman SR, et al. Police killings of Black people and rates of sexually transmitted infections: A cross-sectional analysis of 75 large US metropolitan areas, 2016. *Sexually Transmitted Infections*. 2019;96(6). doi:10.1136/sextrans-2019-054026

24. US Department of Health and Human Services, Centers for Disease Control and Prevention. CDC WONDER Online Database. Sexually Transmitted Disease Morbidity 1984-2014. Accessed January 27, 2022. http://wonder.cdc.gov/std-sex.html

25. Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2019*.; 2021.

26. Hogben M, Leichliter JS. Social determinants and sexually transmitted disease disparities. *Sex Transm Dis*. 2008;35(12 Suppl). doi:10.1097/olq.0b013e31818d3cad

27. Adimora AA, Schoenbach VJ. Social context, sexual networks, and racial disparities in rates of sexually transmitted infections. *Journal of Infectious Diseases*. 2005;191(SUPPL. 1):S115-S122. doi:10.1086/425280

28. US Department of Health and Human Services. *Sexually Transmitted Infections National Strategic Plan for the United States: 2021-2025*.; 2020.

29. Chesson HW, Kent CK, Owusu-Edusei K, Leichliter JS, Aral SO. Disparities in sexually transmitted disease rates across the "eight Americas." *Sexually Transmitted Diseases*. 2012;39(6):458-464. doi:10.1097/OLQ.0B013E318248E3EB

30. Farley TA. Sexually transmitted diseases in the Southeastern United States: Location, race, and social context. *Sexually Transmitted Diseases*. 2006;33(7 SUPPL.). doi:10.1097/01.olq.0000175378.20009.5a

31. Martin EG, Ansari B, Rosenberg ES, et al. Variation in Patterns of Racial and Ethnic Disparities in Primary and Secondary Syphilis Diagnosis Rates Among Heterosexually Active Women by Region and Age Group in the United States. *Sexually Transmitted Diseases*. 2022;49(5):330. doi:10.1097/OLQ.0000000000001607

32. McCree DH, Chesson H, Bradley ELP, Lima A, Fugerson AG. US Regional Changes in Racial/Ethnic Disparities in HIV Diagnoses Among Women in the United States, 2012 and 2017. *AIDS and Behavior*. 2020;24(4):1118-1123. doi:10.1007/S10461-019-02736-W/TABLES/1

33. AtlasPlus - Maps. Accessed February 29, 2020. https://gis.cdc.gov/grasp/nchhstpatlas/maps.html

34. Stenger M, Bauer H, Klingler E, et al. How Good Is Your Rule of Thumb? Validating Male-to-Female Case Ratio as a Proxy for Men Who Have Sex With Men Involvement in N. gonorrhoeae Incidence at the County Level. *Sexually Transmitted Diseases*. 2018;45(3):212-215. doi:10.1097/OLQ.0000000000000720

35. Grey JA, Bernstein KT, Sullivan PS, et al. Estimating the Population Sizes of Men Who Have Sex With Men in US States and Counties Using Data From the American Community Survey. *JMIR Public Health and Surveillance*. 2016;2(1):e14. doi:10.2196/publichealth.5365

36. Emerson B, Braxton J, Llata L, TorroneE, KlinglerE, TourdotL, Schumacher C, Wilson C, Hsu K, ToevsK, Madera R, Kohn R S, MR S. *How Missing and Misclassified Race and Hispanic Ethnicity Affect Reported Case Rates in the STD Surveillance Network (SSuN)*.; 2020.

37. National Center for Health Statistics. Vintage 2019 postcensal estimates of the resident population of the United States (April 1, 2010, July 1, 2010-July 1, 2019), by year, county, single-year of age (0, 1, 2, .., 85 years and over), bridged race, Hispanic origin, and sex.

38. Schober P, Schwarte LA. Correlation coefficients: Appropriate use and interpretation. *Anesthesia and Analgesia*. 2018;126(5):1763-1768. doi:10.1213/ANE.0000000000002864

39. Asada Y. On the Choice of Absolute or Relative Inequality Measures. *The Milbank Quarterly*. 2010;88(4):616. doi:10.1111/J.1468-0009.2010.00614.X

40. Moonesinghe R, Beckles GLA. Measuring health disparities: a comparison of absolute and relative disparities. *PeerJ*. 2015;3(11). doi:10.7717/PEERJ.1438

41. Chesson HW, Patel CG, Gift TL, Bernstein KT, Aral SO. Using Reported Rates of Sexually Transmitted Diseases to Illustrate Potential Methodological Issues in the Measurement of Racial and Ethnic Disparities. *Sex Transm Dis*. 2017;44(9):513. doi:10.1097/OLQ.0000000000000646

42. William, Sarah RBS, Kyle U, Aaron W, Murphy. urbnmapr R package. https://urbaninstitute.github.io/urbnmapr/

43. Learner ER, Kreisel K, Kirkcaldy RD, Schlanger K, Torrone EA. Gonorrhea Prevalence Among Young Women and Men Entering the National Job Training Program, 2000-2017. *Am J Public Health*. 2020;110(5):710-717. doi:10.2105/AJPH.2019.305559

44. Penman-Aguilar A, Talih M, Huang D, Moonesinghe R, Bouye K, Beckles G. Measurement of Health Disparities, Health Inequities, and Social Determinants of Health to Support the Advancement of Health Equity. *J Public Health Manag Pract*. 2016;22(Suppl 1):S33. doi:10.1097/PHH.0000000000000373

45. Jones CP. Levels of racism: a theoretic framework and a gardener's tale. *American Journal of Public Health*. 2000;90(8):1212. doi:10.2105/AJPH.90.8.1212

46. Logan JR, Stults Florida BJ. Metropolitan Segregation: No Breakthrough in Sight. Published online 2021.

47. US Preventive Services Task Force. Screening for Chlamydia and Gonorrhea: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2021;326(10):949-956. doi:10.1001/JAMA.2021.14081

48. Whelan J, Eeuwijk J, Bunge E, Beck E. Systematic Literature Review and Quantitative Analysis of Health Problems Associated with Sexually Transmitted Neisseria gonorrhoeae Infection. *Infect Dis Ther*. 2021;10(4):1887-1905. doi:10.1007/S40121-021-00481-Z

49. Prevention C for DC and. *Sexually Transmitted Disease Surveillance 2019*.; 2021.

50. Andreatos N, Grigoras C, Shehadeh F, et al. The impact of HIV infection and socioeconomic factors on the incidence of gonorrhea: A county-level, US-wide analysis. *PLoS ONE*. 2017;12(9). doi:10.1371/journal.pone.0183938

51. Du P, McNutt LA, O'Campo P, Coles FB. Changes in community socioeconomic status and racial distribution associated with gonorrhea rates: An analysis at the community level. *Sexually Transmitted Diseases*. 2009;36(7):430-438. doi:10.1097/OLQ.0B013E31819B8C2F

52. Thomas JC, Gaffield ME. Social structure, race, and gonorrhea rates in the southeastern United States. *Ethnicity & Disease*. 2003;13(3):362-368. Accessed February 22, 2022. https://europepmc.org/article/med/12894961

53. Chesson HW, Patel CG, Gift TL, Aral SO. Trends in Selected Measures of Racial and Ethnic Disparities in Gonorrhea and Syphilis in the United States, 1981–2013. *Sexually Transmitted Diseases*. 2016;43(11):661-667. doi:10.1097/OLQ.0000000000000518

54. Kaufman HW, Gift TL, Kreisel K, Niles JK, Alagia DP. Chlamydia and Gonorrhea: Shifting Age-Based Positivity Among Young Females, 2010-2017. *Am J Prev Med*. 2020;59(5):697-703. doi:10.1016/J.AMEPRE.2020.05.023

55. Newman LM, Dowell D, Bernstein K, et al. A tale of two gonorrhea epidemics: Results from the STD surveillance network. *Public Health Reports*. Published online 2012. doi:10.1177/003335491212700308

56. Weston EJ, Kirkcaldy RD, Stenger M, Llata E, Hoots B, Torrone EA. Narrative review: Assessment of neisseria gonorrhoeae infections among men who have sex with men in national and sentinel surveillance systems in the United States. *Sexually Transmitted Diseases*. 2018;45(4):243-249. doi:10.1097/OLQ.0000000000000740

57. Nagin DS. *Group-Based Modeling of Development*. (1, ed.). Harvard University Press; 2005.

58. Baltrus P, Malhotra K, Rust G, Levine R, Li C, Gaglioti AH. *Identifying County-Level All-Cause Mortality Rate Trajectories and Their Spatial Distribution Across the United States*. Vol 16. Centers for Disease Control and Prevention (CDC); 2019:180486. doi:10.5888/pcd16.180486

59. DuPre NC, Karimi S, Zhang CH, et al. County-level demographic, social, economic, and lifestyle correlates of COVID-19 infection and death trajectories during the first wave of the pandemic in the United States. *Sci Total Environ*. 2021;786. doi:10.1016/J.SCITOTENV.2021.147495

60. JONES BL, NAGIN DS, ROEDER K. A SAS Procedure Based on Mixture Models for Estimating Developmental Trajectories. *Sociological Methods & Research*. 2001;29(3):374-393. doi:10.1177/0049124101029003005

61. Jones BL, Nagin DS. Advances in group-based trajectory modeling and an SAS procedure for estimating them. *Sociological Methods and Research*. 2007;35(4):542-571. doi:10.1177/0049124106292364

62. Andruff H, Carraro N, Thompson A, Gaudreau P. Latent Class Growth Modelling: A Tutorial. *Tutorials in Quantitative Methods for Psychology*. 2009;5(1):11-24.

63. Center for Health Statistics N. *2013 NCHS Urban-Rural Classification Scheme for Counties Series 2, Number 166*.; 2013.

64. Nagin DS. *No Title*. Vol 65. S. Karger AG; 2014:205-210. doi:10.1159/000360229

65. Rothenberg R, Potterat JJ. Gonorrhea surveillance: The missing links. *Sexually Transmitted Diseases*. 2002;29(12):806-810. doi:10.1097/00007435-200212000-00012

66. Gesink DC, Sullivan AB, Norwood TA, Serre ML, Miller WC. Does core area theory apply to sexually transmitted diseases in rural environments? *Sex Transm Dis*. 2013;40(1):32-40. doi:10.1097/OLQ.0b013e3182762524

67. Oster AM, Wertheim JO, Hernandez AL, Ocfemia MCB, Saduvala N, Hall HI. Using molecular HIV surveillance data to understand transmission between subpopulations in the United States. In: *Journal of Acquired Immune Deficiency Syndromes*. Vol 70. Lippincott Williams and Wilkins; 2015:444-451. doi:10.1097/QAI.0000000000000809

68. Adimora AA, Schoenbach VJ, Bonas DM, Martinson FEA, Donaldson KH, Stancil TR. Concurrent sexual partnerships among women in the United States. *Epidemiology*. 2002;13(3):320-327. doi:10.1097/00001648-200205000-00013

69. Buot MLG, Docena JP, Ratemo BK, et al. Beyond race and place: Distal sociological determinants of HIV disparities. *PLoS ONE*. 2014;9(4):91711. doi:10.1371/journal.pone.0091711

70. Sales JM, Smearman EL, Swartzendruber A, Brown JL, Brody G, Diclemente RJ. Socioeconomic-related Risk and STI Infection among African-American Adolescent Females. *J Adolesc Health*. 2014;55(5):698. doi:10.1016/J.JADOHEALTH.2014.05.005

71. Hill A v., de Genna NM, Perez-Patron MJ, Gilreath TD, Tekwe C, Taylor BDP. Identifying Syndemics for Sexually Transmitted Infections Among Young Adults in the United States: A Latent Class Analysis. *J Adolesc Health*. 2019;64(3):319-326. doi:10.1016/J.JADOHEALTH.2018.09.006

72. Lee AJ, Montgomery MC, Patel RR, Raifman J, Dean LT, Chan PA. Improving insurance and healthcare systems to ensure better access to sexually transmitted disease testing and prevention. *Sex Transm Dis*. 2018;45(4):283. doi:10.1097/OLQ.0000000000000727

73. Adimora AA, Schoenbach VJ, Taylor EM, Khan MR, Schwartz RJ, Miller WC. Sex ratio, poverty, and concurrent partnerships among men and women in the United States: A multilevel analysis. *Annals of Epidemiology*. 2013;23(11):716-719. doi:10.1016/j.annepidem.2013.08.002

74. Pouget ER. Social determinants of adult sex ratios and racial/ethnic disparities in transmission of HIV and other sexually transmitted infections in the USA. *Philosophical Transactions of the Royal Society B: Biological Sciences*. 2017;372(1729). doi:10.1098/rstb.2016.0323

75. Harling G, Subramanian S v., Bärnighausen T, Kawachi I. Income inequality and sexually transmitted in the United States: who bears the burden? *Soc Sci Med*. 2014;102:174-182. doi:10.1016/J.SOCSCIMED.2013.11.025

76. Noah AJ, Yang TC, Wang WL. The Black-White Disparity in Sexually Transmitted Diseases During Pregnancy: How Do Racial Segregation and Income Inequality Matter? *Sex Transm Dis*. 2018;45(5):301-306. doi:10.1097/OLQ.0000000000000820

77. Holtgrave DR, Crosby RA. Social capital, poverty, and income inequality as predictors of gonorrhoea, syphilis, chlamydia and AIDS case rates in the United States. *Sexually Transmitted Infections*. 2003;79(1):62-64. doi:10.1136/sti.79.1.62

78. Pugsley RA, Chapman DA, Kennedy MG, Liu H, Lapane KL. Residential segregation and gonorrhea rates in US metropolitan statistical areas, 2005-2009. *Sex Transm Dis*. 2013;40(6):439-443. doi:10.1097/OLQ.0B013E31828C6416

79. CDC. *Antibiotic Resistance Threats in the United States, 2019.*; 2019.

80. st. Cyr S, Barbee L, Workowski KA, et al. Update to CDC's Treatment Guidelines for Gonococcal Infection, 2020. *MMWR Morbidity and Mortality Weekly Report*. 2020;69(50):1911-1916. doi:10.15585/mmwr.mm6950a6

81. Fifer H, Saunders J, Soni S, Sadiq ST, FitzGerald M. 2018 UK national guideline for the management of infection with Neisseria gonorrhoeae. *Int J STD AIDS*. 2020;31(1):4-15. doi:10.1177/0956462419886775

82. Unemo M, Ross JDC, Serwin AB, Gomberg M, Cusini M, Jensen JS. 2020 European guideline for the diagnosis and treatment of gonorrhoea in adults. *Int J STD AIDS*. Published online 2020. doi:10.1177/0956462420949126

83. Gonorrhoea - STI Guidelines Australia. Accessed April 27, 2022. https://sti.guidelines.org.au/sexually-transmissible-infections/gonorrhoea/

84. Wind CM, de Vries E, Schim Van Der Loeff MF, et al. Decreased Azithromycin Susceptibility of Neisseria gonorrhoeae Isolates in Patients Recently Treated with Azithromycin. *Clinical Infectious Diseases*. Published online 2017. doi:10.1093/cid/cix249

85. Kirkcaldy R, Soge OO, Papp JR, et al. Analysis of Neisseria gonorrhoeae azithromycin susceptibility in the United States by the Gonococcal Isolate Surveillance Project, 2005 to 2013. *Antimicrob Agents Chemother*. 2015;59(2):998-1003. doi:10.1128/AAC.04337-14

86. Centers for Disease Control and Prevention. Neisseria Gonorrhoeae Reference Strains for Antimicrobial Susceptibility Testing (Revised February 2005). Accessed May 8, 2022. https://www.cdc.gov/std/gonorrhea/arg/b88-feb-2005.pdf

87. Raphael BH, Pham CD, Sharpe S, et al. Implementation and Evaluation of Gradient Strip Antimicrobial Susceptibility Testing in US Public Health Laboratories to Respond to Resistant Gonorrhea. *Sex Transm Dis*. 2021;48(12S Suppl 2):S157-S160. doi:10.1097/OLQ.0000000000001535

88. Liu Q, Shepherd B, Li C. PResiduals: An R Package for Residual Analysis Using Probability-Scale Residuals. *Journal of Statistical Software*. 2020;94(12):1-27. doi:10.18637/JSS.V094.I12

89. Olesen SW, Torrone EA, Papp JR, Kirkcaldy RD, Lipsitch M, Grad YH. Azithromycin Susceptibility among Neisseria gonorrhoeae Isolates and Seasonal Macrolide Use. *Journal of Infectious Diseases*. Published online 2019. doi:10.1093/infdis/jiy551

90. Gieseker KE, Learner ER, Mauk K, et al. Demographic and Epidemiological Characteristics Associated With Reduced Antimicrobial Susceptibility to Neisseria gonorrhoeae in the United States, Strengthening the US Response to Resistant Gonorrhea, 2018 to 2019. *Sexually Transmitted Diseases*. 2021;48(12S):S118-S123. doi:10.1097/OLQ.0000000000001541

91. Olesen SW, Grad YH. Deciphering the Impact of Bystander Selection for Antibiotic Resistance in Neisseria gonorrhoeae. *The Journal of Infectious Diseases*. 2020;221(7):1033. doi:10.1093/INFDIS/JIZ156

92. Malhotra-Kumar S, Lammens C, Coenen S, van Herck K, Goossens H. Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy

volunteers: a randomised, double-blind, placebo-controlled study. *Lancet*. Published online 2007. doi:10.1016/S0140-6736(07)60235-9

93. Roberts MC, Chung WO, Roe D, et al. Erythromycin-resistant Neisseria gonorrhoeae and oral commensal Neisseria spp. carry known rRNA methylase genes. *Antimicrobial Agents and Chemotherapy*. 1999;43(6):1367-1372. doi:10.1128/aac.43.6.1367

94. Barbee LA, Soge OO, Khosropour CM, et al. The Duration of Pharyngeal Gonorrhea: A Natural History Study. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. 2021;73(4):575. doi:10.1093/CID/CIAB071

95. Unemo M. Current and future antimicrobial treatment of gonorrhoea – the rapidly evolving Neisseria gonorrhoeae continues to challenge. *BMC Infectious Diseases*. 2015;15(1):364. doi:10.1186/S12879-015-1029-2

96. Barbee LA, Nayak SU, Blumer JL, et al. A Phase 1 Pharmacokinetic and Safety Study of Extended-Duration, High-dose Cefixime for Cephalosporin-resistant Neisseria gonorrhoeae in the Pharynx. *Sexually Transmitted Diseases*. 2018;45(10):677-683. doi:10.1097/OLQ.0000000000000844

97. Sánchez-Busó L, Golparian D, Corander J, et al. The impact of antimicrobials on gonococcal evolution. *Nature Microbiology*. 2019;4(11):1941-1950. doi:10.1038/s41564-019-0501-y

98. Palmer HM, Young H, Winter A, Dave J. Emergence and spread of azithromycin-resistant Neisseria gonorrhoeae in Scotland. *Journal of Antimicrobial Chemotherapy*. 2008;62(3):490-494. doi:10.1093/jac/dkn235

99. Chisholm SA, Wilson J, Alexander S, et al. An outbreak of high-level azithromycin resistant Neisseria gonorrhoeae in England. *Sexually Transmitted Infections*. 2016;92(5):365-367. doi:10.1136/sextrans-2015-052312

100. Fifer H, Cole M, Hughes G, et al. Sustained transmission of high-level azithromycin-resistant Neisseria gonorrhoeae in England: an observational study. *The Lancet Infectious Diseases*. 2018;18(5):573-581. doi:10.1016/S1473-3099(18)30122-1

101. Kwong JC, Chow EPF, Stevens K, et al. Whole-genome sequencing reveals transmission of gonococcal antibiotic resistance among men who have sex with men: an observational study. *Sex Transm Infect*. 2018;94(2):151-157. doi:10.1136/SEXTRANS-2017-053287

102. Demczuk W, Martin I, Peterson S, et al. Genomic Epidemiology and Molecular Resistance Mechanisms of Azithromycin-Resistant Neisseria gonorrhoeae in Canada from 1997 to 2014. *Journal of Clinical Microbiology*. Published online 2016. doi:10.1128/jcm.03195-15

103. Grad YH, Harris SR, Kirkcaldy RD, et al. Genomic epidemiology of gonococcal resistance to extended-spectrum cephalosporins, macrolides, and fluoroquinolones in the United States, 2000-2013. *Journal of Infectious Diseases*. 2016;214(10):1579-1587. doi:10.1093/infdis/jiw420

104. Kenyon CR, Schwartz IS. Effects of sexual network connectivity and antimicrobial drug use on antimicrobial resistance in neisseria gonorrhoeae. *Emerging Infectious Diseases*. 2018;24(7):1195-1203. doi:10.3201/eid2407.172104

105. George CRR, Enriquez RP, Gatus BJ, et al. Systematic review and survey of Neisseria gonorrhoeae ceftriaxone and azithromycin susceptibility data in the Asia Pacific, 2011 to 2016. *PLoS ONE*. 2019;14(4). doi:10.1371/journal.pone.0213312

106. Kenyon C, Buyze J, Wi T. Antimicrobial consumption and susceptibility of Neisseria gonorrhoeae: A global ecological analysis. *Frontiers in Medicine*. 2018;5(NOV):329. doi:10.3389/fmed.2018.00329

107. Rowlinson E, Golden MR, Berzkalns A, Thibault C, Barbee LA. Epidemiologic Treatment for Contacts to Neisseria gonorrhoeae and Chlamydia trachomatis Infection in Sexually Transmitted Disease Clinic Patients in Seattle, WA; 1994 to 2018. *Sexually Transmitted Diseases*. 2020;47(10):665-671. doi:10.1097/OLQ.0000000000001234

108. Anker B, Jaffar S, Patani H, Bristow CC, Sukhija-Cohen AC. Clinical Factors Associated With Accurate Presumptive Treatment of Neisseria gonorrhoeae Infections in Men Who Have Sex with Men and Transgender Women. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. 2021;73(9):e3156. doi:10.1093/CID/CIAA1828

109. Shover CL, Beymer MR, Unger EM, Javanbakht M, Bolan RK. Accuracy of Presumptive Gonorrhea Treatment for Gay, Bisexual, and Other Men Who Have Sex with Men: Results from a Large Sexual Health Clinic in Los Angeles, California. *LGBT Health*. 2018;5(2):139-144. doi:10.1089/LGBT.2017.0115

110. Pugsley RA, Peterman TA. Presumptive and Follow-up Treatment for Gonorrhea and Chlamydia Among Patients Attending Public Health Department Clinics in Virginia, 2016. *Sex Transm Dis*. 2019;46(3):199-205. doi:10.1097/OLQ.0000000000000922

111. Andric B, Drowos J, Trepka MJ, Suciu G, Alonso A, Hennekens CH. High frequencies of negative pretreatment results following presumptive antibiotic treatment for chlamydia and gonorrhea. *Southern Medical Journal*. 2013;106(5):321-326. doi:10.1097/SMJ.0b013e318291b3c2

112. Richardson D, Samarasekara K, Ringshall M, et al. The characteristics of men who have sex with men who present as sexual contacts of gonorrhoea from a clinic-based population. *Journal of the European Academy of Dermatology and Venereology*. 2021;35(12):e926-e928. doi:10.1111/JDV.17589

113. Dutt K, Chow EPF, Huffam S, et al. High prevalence of rectal gonorrhoea among men reporting contact with men with gonorrhoea: Implications for epidemiological treatment. *BMC Public Health*. 2015;15(1):1-6. doi:10.1186/S12889-015-1971-3/TABLES/2

114. Rasul R, Mciver R, Patel P, Foster R, Mcnulty A, Sexual S. Non-empirical management of asymptomatic chlamydia and gonorrhoea reduces unnecessary antibiotic use fivefold: a before and after study. *Sexually Transmitted Infections*. 2022;0:sextrans-2021-055382. doi:10.1136/SEXTRANS-2021-055382

1. Sexually Transmitted Disease Surveillance, 2020. Accessed April 24, 2022. https://www.cdc.gov/std/statistics/2020/default.htm

2. Holmes KK. *Sexually Transmitted Diseases*. McGraw-Hill Medical; 2008.

3. Heumann CL, Quilter LAS, Eastment MC, Heffron R, Hawes SE. Adverse Birth Outcomes and Maternal Neisseria gonorrhoeae Infection: a Population-Based Cohort Study in Washington State. *Sex Transm Dis*. 2017;44(5):266. doi:10.1097/OLQ.0000000000000592

4. Gao R, Liu B, Yang W, et al. Association of Maternal Sexually Transmitted Infections With Risk of Preterm Birth in the United States. *JAMA Netw Open*. 2021;4(11):e2133413. doi:10.1001/JAMANETWORKOPEN.2021.33413

5. Unemo M, Shafer WM. Antimicrobial resistance in Neisseria gonorrhoeae in the 21st Century: Past, evolution, and future. *Clinical Microbiology Reviews*. 2014;27(3):587-613. doi:10.1128/CMR.00010-14

6. Fingerhuth SM, Bonhoeffer S, Low N, Althaus CL. Antibiotic-Resistant Neisseria gonorrhoeae Spread Faster with More Treatment, Not More Sexual Partners. Levin BR, ed. *PLOS Pathogens*. 2016;12(5):e1005611. doi:10.1371/journal.ppat.1005611

7. Rowlinson, Emily; Berzkalns, Anna; Thibault, Christina; Golden, Matthew R; Barbee LA. High incidence of antimicrobial use and overuse in cisgender MSM at high risk of bacterial STIs. In: *STI & HIV World Congress*. ; 2021.

8. Rowlinson, Emily; Golden, Matthew R; Berzkalns, Anna; Thibault, Christina; Barbee LA. Epidemiologic treatment of contacts to Neisseria gonorrhea and Chlamydia trachomatis infection in STD clinic patients in Seattle, WA 1994-2018. *Sexually Transmitted Diseases*. 2020;Publish Ah.

9. Horner P, Saunders J. Should azithromycin 1 g be abandoned as a treatment for bacterial STIs? The case for and against. *Sexually Transmitted Infections*. 2017;93(2):85-87. doi:10.1136/SEXTRANS-2015-052414

10. Wadsworth CB, Arnold BJ, Sater MRA, Grad YH. Azithromycin resistance through interspecific acquisition of an epistasis-dependent efflux pump component and transcriptional regulator in Neisseria gonorrhoeae. *mBio*. 2018;9(4). doi:10.1128/mBio.01419-18

11. Manoharan-Basil SS, Laumen JGE, Dijck C van, Block T de, Baetselier I de, Kenyon C. Evidence of Horizontal Gene Transfer of 50S Ribosomal Genes rplB, rplD, and rplY in Neisseria gonorrhoeae. *Frontiers in Microbiology*. 2021;12. doi:10.3389/FMICB.2021.683901

12. Chisholm SA, Dave J, Ison CA. High-level azithromycin resistance occurs in Neisseria gonorrhoeae as a result of a single point mutation in the 23S rRNA genes. *Antimicrob Agents Chemother*. 2010;54(9):3812-3816. doi:10.1128/AAC.00309-10

13. Soge OO, Harger D, Schafer S, et al. Emergence of Increased Azithromycin Resistance During Unsuccessful Treatment of Neisseria gonorrhoeae Infection With Azithromycin (Portland, OR, 2011). *Sex Transm Dis*. 2012;39(11):877. doi:10.1097/OLQ.0B013E3182685D2B

14. Young H, Moyes A, McMillan A. Azithromycin and erythromycin resistant Neisseria gonorrhoeae following treatment with azithromycin. *Int J STD AIDS*. 1997;8(5):299-302. doi:10.1258/0956462971920127

15. Clifton S, Town K, Furegato M, et al. Is previous azithromycin treatment associated with azithromycin resistance in Neisseria gonorrhoeae ? A cross-sectional study using national surveillance data in England. *Sexually Transmitted Infections*. Published online 2018. doi:10.1136/sextrans-2017-053461

16. Allen H, Merrick R, Ivanov Z, et al. Is there an association between previous infection with *Neisseria gonorrhoeae* and gonococcal AMR? A cross-sectional analysis of national and sentinel surveillance data in England, 2015–2019. *Sexually Transmitted Infections*. Published online March 4, 2022:sextrans-2021-055298. doi:10.1136/SEXTRANS-2021-055298

17. Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2018*.; 2019. doi:10.15620/cdc.79370

18. Speckmann A, Verbeek K. Necklace maps. *IEEE Transactions on Visualization and Computer Graphics*. 2010;16(6):881-889. doi:10.1109/TVCG.2010.180

19. Slocum TA, McMaster RB, Kessler FC, Howard HH. Thematic Cartography and Geovisualization. *Prentice Hall series in geographic information science*. Published online 2008:576. Accessed February 9, 2022. http://www.amazon.com/Thematic-Cartography-Geovisualization-3rd-Edition/dp/0132298341

20. Hogben M, Leichliter JS. Social determinants and sexually transmitted disease disparities. *Sex Transm Dis*. 2008;35(12 Suppl). doi:10.1097/olq.0b013e31818d3cad

21. Biello KB. Residential racial segregation and disparities in sexually transmitted disease risk in the United States: The growing evidence. *Sexually Transmitted Diseases*. 2013;40(6):444-446. doi:10.1097/01.olq.0000430673.76944.b8

22. Ibragimov U, Beane S, Friedman SR, et al. States with higher minimum wages have lower STI rates among women: Results of an ecological study of 66 US metropolitan areas, 2003-2015. *PLoS ONE*. 2019;14(10). doi:10.1371/journal.pone.0223579

23. Ibragimov U, Beane S, Friedman SR, et al. Police killings of Black people and rates of sexually transmitted infections: A cross-sectional analysis of 75 large US metropolitan areas, 2016. *Sexually Transmitted Infections*. 2019;96(6). doi:10.1136/sextrans-2019-054026

24. US Department of Health and Human Services, Centers for Disease Control and Prevention. CDC WONDER Online Database. Sexually Transmitted Disease Morbidity 1984-2014. Accessed January 27, 2022. http://wonder.cdc.gov/std-sex.html

25. Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2019*.; 2021.

26. Hogben M, Leichliter JS. Social determinants and sexually transmitted disease disparities. *Sex Transm Dis*. 2008;35(12 Suppl). doi:10.1097/olq.0b013e31818d3cad

27. Adimora AA, Schoenbach VJ. Social context, sexual networks, and racial disparities in rates of sexually transmitted infections. *Journal of Infectious Diseases*. 2005;191(SUPPL. 1):S115-S122. doi:10.1086/425280

28. US Department of Health and Human Services. *Sexually Transmitted Infections National Strategic Plan for the United States: 2021-2025*.; 2020.

29. Chesson HW, Kent CK, Owusu-Edusei K, Leichliter JS, Aral SO. Disparities in sexually transmitted disease rates across the "eight Americas." *Sexually Transmitted Diseases*. 2012;39(6):458-464. doi:10.1097/OLQ.0B013E318248E3EB

30. Farley TA. Sexually transmitted diseases in the Southeastern United States: Location, race, and social context. *Sexually Transmitted Diseases*. 2006;33(7 SUPPL.). doi:10.1097/01.olq.0000175378.20009.5a

31. Martin EG, Ansari B, Rosenberg ES, et al. Variation in Patterns of Racial and Ethnic Disparities in Primary and Secondary Syphilis Diagnosis Rates Among Heterosexually Active Women by Region and Age Group in the United States. *Sexually Transmitted Diseases*. 2022;49(5):330. doi:10.1097/OLQ.0000000000001607

32. McCree DH, Chesson H, Bradley ELP, Lima A, Fugerson AG. US Regional Changes in Racial/Ethnic Disparities in HIV Diagnoses Among Women in the United States, 2012 and 2017. *AIDS and Behavior*. 2020;24(4):1118-1123. doi:10.1007/S10461-019-02736-W/TABLES/1

33. AtlasPlus - Maps. Accessed February 29, 2020. https://gis.cdc.gov/grasp/nchhstpatlas/maps.html

34. Stenger M, Bauer H, Klingler E, et al. How Good Is Your Rule of Thumb? Validating Male-to-Female Case Ratio as a Proxy for Men Who Have Sex With Men Involvement in N. gonorrhoeae Incidence at the County Level. *Sexually Transmitted Diseases*. 2018;45(3):212-215. doi:10.1097/OLQ.0000000000000720

35. Grey JA, Bernstein KT, Sullivan PS, et al. Estimating the Population Sizes of Men Who Have Sex With Men in US States and Counties Using Data From the American Community Survey. *JMIR Public Health and Surveillance*. 2016;2(1):e14. doi:10.2196/publichealth.5365

36. Emerson B, Braxton J, Llata L, TorroneE, KlinglerE, TourdotL, Schumacher C, Wilson C, Hsu K, ToevsK, Madera R, Kohn R S, MR S. *How Missing and Misclassified Race and Hispanic Ethnicity Affect Reported Case Rates in the STD Surveillance Network (SSuN)*.; 2020.

37. National Center for Health Statistics. Vintage 2019 postcensal estimates of the resident population of the United States (April 1, 2010, July 1, 2010-July 1, 2019), by year, county, single-year of age (0, 1, 2, .., 85 years and over), bridged race, Hispanic origin, and sex.

38. Schober P, Schwarte LA. Correlation coefficients: Appropriate use and interpretation. *Anesthesia and Analgesia*. 2018;126(5):1763-1768. doi:10.1213/ANE.0000000000002864

39. Asada Y. On the Choice of Absolute or Relative Inequality Measures. *The Milbank Quarterly*. 2010;88(4):616. doi:10.1111/J.1468-0009.2010.00614.X

40. Moonesinghe R, Beckles GLA. Measuring health disparities: a comparison of absolute and relative disparities. *PeerJ*. 2015;3(11). doi:10.7717/PEERJ.1438

41. Chesson HW, Patel CG, Gift TL, Bernstein KT, Aral SO. Using Reported Rates of Sexually Transmitted Diseases to Illustrate Potential Methodological Issues in the Measurement of Racial and Ethnic Disparities. *Sex Transm Dis*. 2017;44(9):513. doi:10.1097/OLQ.0000000000000646

42. William, Sarah RBS, Kyle U, Aaron W, Murphy. urbnmapr R package. https://urbaninstitute.github.io/urbnmapr/

43. Learner ER, Kreisel K, Kirkcaldy RD, Schlanger K, Torrone EA. Gonorrhea Prevalence Among Young Women and Men Entering the National Job Training Program, 2000-2017. *Am J Public Health*. 2020;110(5):710-717. doi:10.2105/AJPH.2019.305559

44. Penman-Aguilar A, Talih M, Huang D, Moonesinghe R, Bouye K, Beckles G. Measurement of Health Disparities, Health Inequities, and Social Determinants of Health to Support the Advancement of Health Equity. *J Public Health Manag Pract*. 2016;22(Suppl 1):S33. doi:10.1097/PHH.0000000000000373

45. Jones CP. Levels of racism: a theoretic framework and a gardener's tale. *American Journal of Public Health*. 2000;90(8):1212. doi:10.2105/AJPH.90.8.1212

46. Logan JR, Stults Florida BJ. Metropolitan Segregation: No Breakthrough in Sight. Published online 2021.

47. US Preventive Services Task Force. Screening for Chlamydia and Gonorrhea: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2021;326(10):949-956. doi:10.1001/JAMA.2021.14081

48. Whelan J, Eeuwijk J, Bunge E, Beck E. Systematic Literature Review and Quantitative Analysis of Health Problems Associated with Sexually Transmitted Neisseria gonorrhoeae Infection. *Infect Dis Ther*. 2021;10(4):1887-1905. doi:10.1007/S40121-021-00481-Z

49. Prevention C for DC and. *Sexually Transmitted Disease Surveillance 2019*.; 2021.

50. Andreatos N, Grigoras C, Shehadeh F, et al. The impact of HIV infection and socioeconomic factors on the incidence of gonorrhea: A county-level, US-wide analysis. *PLoS ONE*. 2017;12(9). doi:10.1371/journal.pone.0183938

51. Du P, McNutt LA, O'Campo P, Coles FB. Changes in community socioeconomic status and racial distribution associated with gonorrhea rates: An analysis at the community level. *Sexually Transmitted Diseases*. 2009;36(7):430-438. doi:10.1097/OLQ.0B013E31819B8C2F

52. Thomas JC, Gaffield ME. Social structure, race, and gonorrhea rates in the southeastern United States. *Ethnicity & Disease*. 2003;13(3):362-368. Accessed February 22, 2022. https://europepmc.org/article/med/12894961

53. Chesson HW, Patel CG, Gift TL, Aral SO. Trends in Selected Measures of Racial and Ethnic Disparities in Gonorrhea and Syphilis in the United States, 1981–2013. *Sexually Transmitted Diseases*. 2016;43(11):661-667. doi:10.1097/OLQ.0000000000000518

54. Kaufman HW, Gift TL, Kreisel K, Niles JK, Alagia DP. Chlamydia and Gonorrhea: Shifting Age-Based Positivity Among Young Females, 2010-2017. *Am J Prev Med*. 2020;59(5):697-703. doi:10.1016/J.AMEPRE.2020.05.023

55. Newman LM, Dowell D, Bernstein K, et al. A tale of two gonorrhea epidemics: Results from the STD surveillance network. *Public Health Reports*. Published online 2012. doi:10.1177/003335491212700308

56. Weston EJ, Kirkcaldy RD, Stenger M, Llata E, Hoots B, Torrone EA. Narrative review: Assessment of neisseria gonorrhoeae infections among men who have sex with men in national and sentinel surveillance systems in the United States. *Sexually Transmitted Diseases*. 2018;45(4):243-249. doi:10.1097/OLQ.0000000000000740

57. Nagin DS. *Group-Based Modeling of Development*. (1, ed.). Harvard University Press; 2005.

58. Baltrus P, Malhotra K, Rust G, Levine R, Li C, Gaglioti AH. *Identifying County-Level All-Cause Mortality Rate Trajectories and Their Spatial Distribution Across the United States*. Vol 16. Centers for Disease Control and Prevention (CDC); 2019:180486. doi:10.5888/pcd16.180486

59. DuPre NC, Karimi S, Zhang CH, et al. County-level demographic, social, economic, and lifestyle correlates of COVID-19 infection and death trajectories during the first wave of the pandemic in the United States. *Sci Total Environ*. 2021;786. doi:10.1016/J.SCITOTENV.2021.147495

60. JONES BL, NAGIN DS, ROEDER K. A SAS Procedure Based on Mixture Models for Estimating Developmental Trajectories. *Sociological Methods & Research*. 2001;29(3):374-393. doi:10.1177/0049124101029003005

61. Jones BL, Nagin DS. Advances in group-based trajectory modeling and an SAS procedure for estimating them. *Sociological Methods and Research*. 2007;35(4):542-571. doi:10.1177/0049124106292364

62. Andruff H, Carraro N, Thompson A, Gaudreau P. Latent Class Growth Modelling: A Tutorial. *Tutorials in Quantitative Methods for Psychology*. 2009;5(1):11-24.

63. Center for Health Statistics N. *2013 NCHS Urban-Rural Classification Scheme for Counties Series 2, Number 166*.; 2013.

64. Nagin DS. *No Title*. Vol 65. S. Karger AG; 2014:205-210. doi:10.1159/000360229

65. Rothenberg R, Potterat JJ. Gonorrhea surveillance: The missing links. *Sexually Transmitted Diseases*. 2002;29(12):806-810. doi:10.1097/00007435-200212000-00012

66. Gesink DC, Sullivan AB, Norwood TA, Serre ML, Miller WC. Does core area theory apply to sexually transmitted diseases in rural environments? *Sex Transm Dis*. 2013;40(1):32-40. doi:10.1097/OLQ.0b013e3182762524

67. Oster AM, Wertheim JO, Hernandez AL, Ocfemia MCB, Saduvala N, Hall HI. Using molecular HIV surveillance data to understand transmission between subpopulations in the United States. In: *Journal of Acquired Immune Deficiency Syndromes*. Vol 70. Lippincott Williams and Wilkins; 2015:444-451. doi:10.1097/QAI.0000000000000809

68. Adimora AA, Schoenbach VJ, Bonas DM, Martinson FEA, Donaldson KH, Stancil TR. Concurrent sexual partnerships among women in the United States. *Epidemiology*. 2002;13(3):320-327. doi:10.1097/00001648-200205000-00013

69. Buot MLG, Docena JP, Ratemo BK, et al. Beyond race and place: Distal sociological determinants of HIV disparities. *PLoS ONE*. 2014;9(4):91711. doi:10.1371/journal.pone.0091711

70. Sales JM, Smearman EL, Swartzendruber A, Brown JL, Brody G, Diclemente RJ. Socioeconomic-related Risk and STI Infection among African-American Adolescent Females. *J Adolesc Health*. 2014;55(5):698. doi:10.1016/J.JADOHEALTH.2014.05.005

71. Hill A v., de Genna NM, Perez-Patron MJ, Gilreath TD, Tekwe C, Taylor BDP. Identifying Syndemics for Sexually Transmitted Infections Among Young Adults in the United States: A Latent Class Analysis. *J Adolesc Health*. 2019;64(3):319-326. doi:10.1016/J.JADOHEALTH.2018.09.006

72. Lee AJ, Montgomery MC, Patel RR, Raifman J, Dean LT, Chan PA. Improving insurance and healthcare systems to ensure better access to sexually transmitted disease testing and prevention. *Sex Transm Dis*. 2018;45(4):283. doi:10.1097/OLQ.0000000000000727

73. Adimora AA, Schoenbach VJ, Taylor EM, Khan MR, Schwartz RJ, Miller WC. Sex ratio, poverty, and concurrent partnerships among men and women in the United States: A multilevel analysis. *Annals of Epidemiology*. 2013;23(11):716-719. doi:10.1016/j.annepidem.2013.08.002

74. Pouget ER. Social determinants of adult sex ratios and racial/ethnic disparities in transmission of HIV and other sexually transmitted infections in the USA. *Philosophical Transactions of the Royal Society B: Biological Sciences*. 2017;372(1729). doi:10.1098/rstb.2016.0323

75. Harling G, Subramanian S v., Bärnighausen T, Kawachi I. Income inequality and sexually transmitted in the United States: who bears the burden? *Soc Sci Med*. 2014;102:174-182. doi:10.1016/J.SOCSCIMED.2013.11.025

76. Noah AJ, Yang TC, Wang WL. The Black-White Disparity in Sexually Transmitted Diseases During Pregnancy: How Do Racial Segregation and Income Inequality Matter? *Sex Transm Dis*. 2018;45(5):301-306. doi:10.1097/OLQ.0000000000000820

77. Holtgrave DR, Crosby RA. Social capital, poverty, and income inequality as predictors of gonorrhoea, syphilis, chlamydia and AIDS case rates in the United States. *Sexually Transmitted Infections*. 2003;79(1):62-64. doi:10.1136/sti.79.1.62

78. Pugsley RA, Chapman DA, Kennedy MG, Liu H, Lapane KL. Residential segregation and gonorrhea rates in US metropolitan statistical areas, 2005-2009. *Sex Transm Dis*. 2013;40(6):439-443. doi:10.1097/OLQ.0B013E31828C6416

79. CDC. *Antibiotic Resistance Threats in the United States, 2019.*; 2019.

80. st. Cyr S, Barbee L, Workowski KA, et al. Update to CDC’s Treatment Guidelines for Gonococcal Infection, 2020. *MMWR Morbidity and Mortality Weekly Report*. 2020;69(50):1911-1916. doi:10.15585/mmwr.mm6950a6

81. Fifer H, Saunders J, Soni S, Sadiq ST, FitzGerald M. 2018 UK national guideline for the management of infection with Neisseria gonorrhoeae. *Int J STD AIDS*. 2020;31(1):4-15. doi:10.1177/0956462419886775

82. Unemo M, Ross JDC, Serwin AB, Gomberg M, Cusini M, Jensen JS. 2020 European guideline for the diagnosis and treatment of gonorrhoea in adults. *Int J STD AIDS*. Published online 2020. doi:10.1177/0956462420949126

83. Gonorrhoea - STI Guidelines Australia. Accessed April 27, 2022. https://sti.guidelines.org.au/sexually-transmissible-infections/gonorrhoea/

84. Wind CM, de Vries E, Schim Van Der Loeff MF, et al. Decreased Azithromycin Susceptibility of Neisseria gonorrhoeae Isolates in Patients Recently Treated with Azithromycin. *Clinical Infectious Diseases*. Published online 2017. doi:10.1093/cid/cix249

85. Kirkcaldy R, Soge OO, Papp JR, et al. Analysis of Neisseria gonorrhoeae azithromycin susceptibility in the United States by the Gonococcal Isolate Surveillance Project, 2005 to 2013. *Antimicrob Agents Chemother*. 2015;59(2):998-1003. doi:10.1128/AAC.04337-14

86. Centers for Disease Control and Prevention. Neisseria Gonorrhoeae Reference Strains for Antimicrobial Susceptibility Testing (Revised February 2005). Accessed May 8, 2022. https://www.cdc.gov/std/gonorrhea/arg/b88-feb-2005.pdf

87. Raphael BH, Pham CD, Sharpe S, et al. Implementation and Evaluation of Gradient Strip Antimicrobial Susceptibility Testing in US Public Health Laboratories to Respond to Resistant Gonorrhea. *Sex Transm Dis*. 2021;48(12S Suppl 2):S157-S160. doi:10.1097/OLQ.0000000000001535

88. Liu Q, Shepherd B, Li C. PResiduals: An R Package for Residual Analysis Using Probability-Scale Residuals. *Journal of Statistical Software*. 2020;94(12):1-27. doi:10.18637/JSS.V094.I12

89. Olesen SW, Torrone EA, Papp JR, Kirkcaldy RD, Lipsitch M, Grad YH. Azithromycin Susceptibility among Neisseria gonorrhoeae Isolates and Seasonal Macrolide Use. *Journal of Infectious Diseases*. Published online 2019. doi:10.1093/infdis/jiy551

90. Gieseker KE, Learner ER, Mauk K, et al. Demographic and Epidemiological Characteristics Associated With Reduced Antimicrobial Susceptibility to Neisseria gonorrhoeae in the United States, Strengthening the US Response to Resistant Gonorrhea, 2018 to 2019. *Sexually Transmitted Diseases*. 2021;48(12S):S118-S123. doi:10.1097/OLQ.0000000000001541

91. Olesen SW, Grad YH. Deciphering the Impact of Bystander Selection for Antibiotic Resistance in Neisseria gonorrhoeae. *The Journal of Infectious Diseases*. 2020;221(7):1033. doi:10.1093/INFDIS/JIZ156

92. Malhotra-Kumar S, Lammens C, Coenen S, van Herck K, Goossens H. Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study. *Lancet*. Published online 2007. doi:10.1016/S0140-6736(07)60235-9

93. Roberts MC, Chung WO, Roe D, et al. Erythromycin-resistant Neisseria gonorrhoeae and oral commensal Neisseria spp. carry known rRNA methylase genes. *Antimicrobial Agents and Chemotherapy*. 1999;43(6):1367-1372. doi:10.1128/aac.43.6.1367

94. Barbee LA, Soge OO, Khosropour CM, et al. The Duration of Pharyngeal Gonorrhea: A Natural History Study. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. 2021;73(4):575. doi:10.1093/CID/CIAB071

95. Unemo M. Current and future antimicrobial treatment of gonorrhoea – the rapidly evolving Neisseria gonorrhoeae continues to challenge. *BMC Infectious Diseases*. 2015;15(1):364. doi:10.1186/S12879-015-1029-2

96. Barbee LA, Nayak SU, Blumer JL, et al. A Phase 1 Pharmacokinetic and Safety Study of Extended-Duration, High-dose Cefixime for Cephalosporin-resistant Neisseria gonorrhoeae in the Pharynx. *Sexually Transmitted Diseases*. 2018;45(10):677-683. doi:10.1097/OLQ.0000000000000844

97. Sánchez-Busó L, Golparian D, Corander J, et al. The impact of antimicrobials on gonococcal evolution. *Nature Microbiology*. 2019;4(11):1941-1950. doi:10.1038/s41564-019-0501-y

98. Palmer HM, Young H, Winter A, Dave J. Emergence and spread of azithromycin-resistant Neisseria gonorrhoeae in Scotland. *Journal of Antimicrobial Chemotherapy*. 2008;62(3):490-494. doi:10.1093/jac/dkn235

99. Chisholm SA, Wilson J, Alexander S, et al. An outbreak of high-level azithromycin resistant Neisseria gonorrhoeae in England. *Sexually Transmitted Infections*. 2016;92(5):365-367. doi:10.1136/sextrans-2015-052312

100. Fifer H, Cole M, Hughes G, et al. Sustained transmission of high-level azithromycin-resistant Neisseria gonorrhoeae in England: an observational study. *The Lancet Infectious Diseases*. 2018;18(5):573-581. doi:10.1016/S1473-3099(18)30122-1

101. Kwong JC, Chow EPF, Stevens K, et al. Whole-genome sequencing reveals transmission of gonococcal antibiotic resistance among men who have sex with men: an observational study. *Sex Transm Infect*. 2018;94(2):151-157. doi:10.1136/SEXTRANS-2017-053287

102. Demczuk W, Martin I, Peterson S, et al. Genomic Epidemiology and Molecular Resistance Mechanisms of Azithromycin-Resistant Neisseria gonorrhoeae in Canada from 1997 to 2014. *Journal of Clinical Microbiology*. Published online 2016. doi:10.1128/jcm.03195-15

103. Grad YH, Harris SR, Kirkcaldy RD, et al. Genomic epidemiology of gonococcal resistance to extended-spectrum cephalosporins, macrolides, and fluoroquinolones in the United States, 2000-2013. *Journal of Infectious Diseases*. 2016;214(10):1579-1587. doi:10.1093/infdis/jiw420

104. Kenyon CR, Schwartz IS. Effects of sexual network connectivity and antimicrobial drug use on antimicrobial resistance in neisseria gonorrhoeae. *Emerging Infectious Diseases*. 2018;24(7):1195-1203. doi:10.3201/eid2407.172104

105. George CRR, Enriquez RP, Gatus BJ, et al. Systematic review and survey of Neisseria gonorrhoeae ceftriaxone and azithromycin susceptibility data in the Asia Pacific, 2011 to 2016. *PLoS ONE*. 2019;14(4). doi:10.1371/journal.pone.0213312

106. Kenyon C, Buyze J, Wi T. Antimicrobial consumption and susceptibility of Neisseria gonorrhoeae: A global ecological analysis. *Frontiers in Medicine*. 2018;5(NOV):329. doi:10.3389/fmed.2018.00329

107. Rowlinson E, Golden MR, Berzkalns A, Thibault C, Barbee LA. Epidemiologic Treatment for Contacts to Neisseria gonorrhoeae and Chlamydia trachomatis Infection in Sexually Transmitted Disease Clinic Patients in Seattle, WA; 1994 to 2018. *Sexually Transmitted Diseases*. 2020;47(10):665-671. doi:10.1097/OLQ.0000000000001234

108. Anker B, Jaffar S, Patani H, Bristow CC, Sukhija-Cohen AC. Clinical Factors Associated With Accurate Presumptive Treatment of Neisseria gonorrhoeae Infections in Men Who Have Sex with Men and Transgender Women. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. 2021;73(9):e3156. doi:10.1093/CID/CIAA1828

109. Shover CL, Beymer MR, Unger EM, Javanbakht M, Bolan RK. Accuracy of Presumptive Gonorrhea Treatment for Gay, Bisexual, and Other Men Who Have Sex with Men: Results from a Large Sexual Health Clinic in Los Angeles, California. *LGBT Health*. 2018;5(2):139-144. doi:10.1089/LGBT.2017.0115

110. Pugsley RA, Peterman TA. Presumptive and Follow-up Treatment for Gonorrhea and Chlamydia Among Patients Attending Public Health Department Clinics in Virginia, 2016. *Sex Transm Dis*. 2019;46(3):199-205. doi:10.1097/OLQ.0000000000000922

111. Andric B, Drowos J, Trepka MJ, Suciu G, Alonso A, Hennekens CH. High frequencies of negative pretreatment results following presumptive antibiotic treatment for chlamydia and gonorrhea. *Southern Medical Journal*. 2013;106(5):321-326. doi:10.1097/SMJ.0b013e318291b3c2

112. Richardson D, Samarasekara K, Ringshall M, et al. The characteristics of men who have sex with men who present as sexual contacts of gonorrhoea from a clinic-based population. *Journal of the European Academy of Dermatology and Venereology*. 2021;35(12):e926-e928. doi:10.1111/JDV.17589

113. Dutt K, Chow EPF, Huffam S, et al. High prevalence of rectal gonorrhoea among men reporting contact with men with gonorrhoea: Implications for epidemiological treatment. *BMC Public Health*. 2015;15(1):1-6. doi:10.1186/S12889-015-1971-3/TABLES/2

114. Rasul R, Mciver R, Patel P, Foster R, Mcnulty A, Sexual S. Non-empirical management of asymptomatic chlamydia and gonorrhoea reduces unnecessary antibiotic use fivefold: a before and after study. *Sexually Transmitted Infections*. 2022;0:sextrans-2021-055382. doi:10.1136/SEXTRANS-2021-055382