Variation in Syphilis Among Men who Have Sex with Men and Women in the United States and Association with Syphilis in Women

Chase A. Cannon

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

Master of Public Health

University of Washington

2020

Committee:

Matthew Golden

Julia Dombrowski

Christine Khosropour

James Hughes

Program Authorized to Offer Degree:

Epidemiology

University of Washington

Abstract

Variation in Syphilis Among Men who Have Sex with Men and Women in the United States and Association with Syphilis in Women

Chase A. Cannon

Chair of the Supervisory Committee:

Matthew Golden

Department of Medicine

We aimed to evaluate the percentage of early syphilis (ES) cases in men who have sex with men (MSM) occurring in behaviorally-bisexual men (MSMW) in the US; determine how that percentage varies by race/ethnicity, region and over time; and to assess the relationship of measures of MSMW syphilis with syphilis rates in women. We used linear mixed-effects regression models to analyze aggregate 2013-2017 surveillance data from 16 US jurisdictions with high syphilis morbidity.

Of all MSM ES cases, the mean percentage occurring in MSMW was stable over time at 11.5% but was higher in the South, and in Black men ($P<0.01$). The association between this percentage and race/ethnicity differed by region. Rates of all-stage syphilis in women were positively associated with the log number of MSMW cases per 100,000 men ($P<0.01$). Higher levels of syphilis morbidity among MSMW were associated with higher rates in women, and "bridging" may partially explain observed disparities. The interaction of race, region, and sex behavior and its implications within the current syphilis epidemic merit renewed focus.

INTRODUCTION

Syphilis rates in the United States (US) and many other nations have been consistently rising for almost 20 years and are now at their highest levels since 2000.[1–3] The contemporary syphilis epidemic has primarily affected gay and bisexual men who have sex with men (MSM), but occurs in the context of a longstanding, persistent epidemic that disproportionately affects Blacks/African-Americans, including women in the South.[1] In recent years, syphilis rates have increased dramatically in women, a change accompanied by a concurrent increase in congenital syphilis cases,[1] leading to heightened emphasis on identifying and screening women and their partners during pregnancy.[4]

Syphilis is highly associated with human immunodeficiency virus (HIV) acquisition,[5,6] and both infections disproportionately affect similar subpopulations, particularly MSM and minority women.[1,7] Men who have sex with men and women (MSMW) have long been identified as a potential "bridge" for HIV transmission to heterosexual women and other men.[8,9] However, defining the size of this potential bridge population and its role, if any, in linking MSM and heterosexual epidemics of HIV and other sexually transmitted infections has proven difficult. Studies conducted in the US, South America, Sub-Saharan Africa, Asia, and the United Kingdom have reported that from 12 to 79% of MSM have had at least one female sex partner in their lifetime.[8,10–15] Using data from 28 HIV prevalence studies published between 1993 and 2012, Friedman et al. found the weighted mean of US MSM who were bisexually active in the past year to be 33.8%.[16] Additionally, bisexual behavior is often higher among Black and Hispanic MSM compared to MSM of other race/ethnicity groups.[17–19] Disclosure of bisexual behavior is variable in men who may not identify as gay or bisexual,[17,20,21] with some studies finding Black men may be less likely to disclose than other groups.[18]

Studies investigating the potential epidemiologic link between MSMW and other groups are limited. A 2006 review of HIV surveillance records for college men in North Carolina found that newly HIV-infected MSMW were more likely to be Black and were central nodes within dense sexual networks that accounted for over 65% of HIV transmissions within student communities.[22] Phylogenetic analyses of US HIV surveillance data suggest that the epidemics in MSM and among heterosexual women and women who inject drugs are linked, with a higher percentage of cases among heterosexual Black women linked to MSM than among Whites.[23] While few studies have suggested similar transmission dynamics may be occurring for syphilis internationally,[24,25] variance of bisexual behavior among MSM with syphilis and the association of this variance with syphilis burden in women in the US has not been addressed.

We used population-level, US public health surveillance data to evaluate what percentage of MSM early syphilis cases occurred among MSMW; how that percentage varied over time, and between different racial/ethnic groups and different regions of the US; and the relationship between measures of MSMW syphilis and syphilis rates in women. We hypothesized that MSMW would comprise a larger percentage of syphilis cases in the South compared to other regions, and among Black men compared to other race/ethnicity groups. We further hypothesized that racial disparities in the percentage of MSMW with early syphilis would be greatest in the South and areas with larger syphilis epidemics in MSMW would also have larger epidemics in women.

METHODS

Sampling Frame

We used the 2017 Centers for Disease Control and Prevention (CDC) Sexually Transmitted Disease (STD) Surveillance Report to create a diverse sample of US sites with high

syphilis morbidity. This report provides syphilis statistics for states and metropolitan statistical areas (MSA) in groupings by stage: primary and secondary (P&S), early latent, late and late latent, and congenital. To avoid combining counts with differing denominators, we opted to use P&S syphilis measures (counts and rates of symptomatic syphilis) alone to compile the list of eligible areas with high morbidity. First, we identified the 20 states with the highest P&S syphilis rates both overall and in women in 2017 and narrowed this group to sites with at least 50 cases of P&S syphilis in women in 2017. Second, we selected the 30 MSA with the highest rates of P&S syphilis. To prevent inclusion of overlapping states and MSA, we included counties or cities rather than states in our sample if the county or city contributed >50% of all syphilis cases to their state in 2017, and the county or city health department was directly funded by the CDC to receive STD prevention money (i.e. funding goes directly from the CDC to the county or city health department without first going to the state department of health). We chose to selectively include cities and counties rather than states since directly funded areas often manage STD partner services somewhat independently from their state departments of health; consequently, we believed that they would be more likely to have data on sex of sex partners. Finally, to meet our objective of comparing estimates from Southern vs non-Southern areas, we added South Carolina to achieve an equal number of sites from the South and outside the South.

Our sample included exceptions to the schema described above. First, because the state department of health rules in Washington State required suppressing race/ethnicity-specific data related to syphilis, we utilized case information from King County rather than Washington State. Though King County is not directly funded by the CDC and had fewer than 50 P&S cases in women for 2017, 65% of all P&S cases in the state of Washington occurred in King County residents in 2017. Second, although we initially categorized Baltimore as meeting all of our

inclusion criteria, the area had fewer than 50 cases of P&S syphilis in women in 2017. We elected to retain Baltimore in the sample despite this fact since we had already collected data and inclusion of the city's data allowed us to maintain a regional balance between participating areas.

We categorized each site into one of four regions – Northeast, Midwest, West, and South – according to CDC criteria.[1] The final sample included: 11 jurisdictions in the South (Louisiana, Georgia, Florida, North Carolina, Mississippi, Arkansas, Oklahoma, Alabama, Texas, South Carolina, Baltimore) and 11 jurisdictions in the non-South (Nevada; Arizona; New York City; Missouri; Oregon; King County, WA; Ohio; Los Angeles County, CA; San Francisco, CA; Philadelphia, PA; Chicago, IL).

Power

Based on preliminary data collected from Florida, Seattle and North Carolina (data not shown), we estimated that the percentage of the MSM population with early syphilis categorized as MSMW in the South would be 12% vs 5% in the non-South. Assuming a coefficient of variance of 50% between sites, and data from 22 sites contributing approximately 18,952 male P&S syphilis cases in 2017 (harmonic mean of 395 and 517 in the South and non-South, respectively), we estimated that our linear regression models would have 90.5% power (alpha = 0.05) to detect an absolute difference of 7% in the percentage of MSMW with early syphilis by race/ethnicity and region.

Data Collection & Analysis

We collected site-specific, aggregate syphilis case counts by stage, gender, race/ethnicity, and sex of sex partners (cisgender men only; using standard, CDC stage-specific syphilis contact periods) for cases occurring from January 2013 through December 2017. When available, we also collected data on whether cisgender men reported transgender partners and

whether surveillance data classified index syphilis cases as transgender; however, these data were excluded from primary analyses due to low numbers per stratum overall. Thus, we categorized cisgender case counts into groupings of early syphilis (primary, secondary or early latent stages when syphilis is most likely to be transmitted to sex partners) and late syphilis (late latent or unknown duration) for analyses. Two participating areas suppressed data for categories with counts <6-10; data from these areas contributed to total case counts but were excluded from race/ethnicity-specific analyses when data were unavailable. For descriptive analyses, we calculated the percentages of men who have sex with women (MSW), men who have sex with men exclusively (MSME), and MSMW with early syphilis (ES) using both the denominators of total cases in men with known sex of sex partner and total cases in men overall with ES. For all inferential analyses, we utilized linear mixed-effects models, with random effects for site, to account for correlated data within sites. We calculated two measures of syphilis morbidity to use as model variables. The first was the percentage of all MSMW ES cases occurring in MSM (a measure of the relative frequency of MSMW syphilis compared to MSM syphilis) – calculated as the number of cases of ES in MSMW divided by total ES cases in all MSM. For analyses using this percentage as an outcome variable, we weighted linear models by total cases in MSM to account for between-site variations in the denominator used to calculate these percentages. The second morbidity measure was the number of ES cases in MSMW per 100,000 men in each area per year (a measure of the absolute burden of MSMW syphilis in the population).

The first linear model evaluated the association between the independent variable of ES case counts in MSMW and the dependent variable of syphilis rates in women using calculated values for years 2013-2017 for each site. MSMW syphilis counts in this model were log transformed to improve linearity of the relationship with the outcome. For these analyses, we

elected to use the rate of all-stage syphilis in women – not ES rates – as an outcome since a large percentage of syphilis cases in women of reproductive age may be categorized as late latent or unknown duration.[26,27] The rate in women was calculated as the total number of syphilis cases in women per 100,000 women in the general population within each area per year using estimates from the US Census Bureau.[28]

Using race-specific [non-Hispanic (NH) Black, NH White, Hispanic] male population estimates for the year 2017 obtained from US Census data[28] as denominators, we also calculated race-stratified measures of ES cases in MSMW per 100,000 men in each area (e.g. number of ES cases in NH Black MSMW per 100,000 NH Black men in a given site) for comparative evaluation. Complete race-specific population estimates to calculate these measures were not readily attainable for each year, thus statistical analyses using race-specific measures of ES cases per 100,000 men were only performed for the year 2017.

We used a second linear mixed-effects model, with random effects for site, to evaluate the association of the percentage of ES cases among MSMW with race/ethnicity and/or region in both bivariate and multivariate analysis, i.e. race/ethnicity as predictor variable adjusted for region and vice-versa. We then evaluated whether the association between the percentage of MSM ES cases among MSMW and region varied by race/ethnicity using interaction terms in the regression models. All analyses were conducted using R version 3.5.1 (R Foundation for Statistical Computing, 2018) and used an alpha level of 0.05 for statistical significance. The project, which did not collect or analyze individual-level data, was determined not to be human subject research and thus was exempt from review by the University of Washington's institutional review board.

RESULTS

Of the initial 22 sites offered participation, 16 (73%) provided data for 2013-2017. Overall, 184,784 syphilis cases were reported for cisgender men across this period, of which 122,071 (66.1%) were ES and 62,713 (33.9%) were late latent or unknown duration. Sex of sex partners for men was reported on average in 81.0% of all ES cases versus 58.4% of all late cases. Of all cases for which sex of sex partner was known, the mean percentage of ES cases occurring in MSME, MSW and MSMW across participating sites was 74.7% [standard deviation (SD): 10.7], 15.1% (SD: 7.12), and 9.4% (SD: 5.6), respectively. Table 1 presents the 2017 ES case counts and percentages in men by site and sex partner classification. The mean percentage of MSMW cases occurring in MSM was 11.5% for ES (Table 1) and 13.7% for late latent/unknown duration syphilis in 2017 (Suppl. Table 3).

The overall mean percentage of MSMW ES cases occurring in MSM was highest in 2014 at 12.5% and stable in the remaining years at a mean of 11.1%. Though the percentage of MSMW cases occurring in MSM did vary by region, with the highest percentage occurring in the South (12.5%) and the lowest in the Northeast (3.2%), comparative estimates to the referent South did not reach statistical significance (Table 2). This percentage was higher among NH Black MSM (14.5%, referent), compared to Hispanic MSM (9.0%, $P<0.01$) and NH White MSM (7.6%, $P<0.01$) when adjusted for region (Table 2). The observation that Black MSM compared to MSM of other racial/ethnic groups more frequently reported female sex partners was consistent across regions, but racial/ethnic variations for other regions were otherwise inconsistent by region. Figure 1 depicts this relationship based on available data in 2017. In addition to race/ethnicity and region each being independently associated with the percentage of MSMW ES cases occurring in MSM for 2013-2017, the magnitude of association for this percentage and race/ethnicity varied by region ($P<0.01$ for interaction) (Suppl. Figure 3).

Like the percentage of MSMW cases occurring in MSM, the aggregated mean number of ES cases in MSMW per 100,000 men for 2013-2017 varied by region, with 3.6 cases in the West (P=0.29), 2.3 in the Midwest (P=0.24), 3.9 in the Northeast (P=0.52), and 5.6 in the South (referent). In 2017, NH Black MSMW experienced a mean of 10.6 cases of ES per 100,000 NH Black men (referent) in their respective sites, compared to 3.6 cases in Hispanic MSMW per 100,000 Hispanic men (P<0.01), and 1.6 cases in NH White MSMW per 100,000 NH White men (P<0.01).

The majority of syphilis cases in women (57.6%) were diagnosed as late latent or unknown duration infections, with early latent and P&S cases representing 25.6% and 16.8%, respectively. The region-adjusted mean rate of all-stage syphilis per 100,000 women in 2013 was 10.1 and increased on average by 1.76 (P<0.01) annually through 2017. The greatest increases in all-stage syphilis rates in women over this time occurred in the South and West (Suppl. Figure 4). We found that a 10% increase in the number of MSMW ES cases per 100,000 men in the population was associated with an estimated mean increase in syphilis among women of 0.53 per 100,000 (P<0.01), whereas a doubling of the number of MSMW ES cases per 100,000 men was associated with an estimated 3.84 per 100,000 higher mean rate of syphilis in women (Figure 2).

Thirteen of 16 (81.3%) sites provided transgender-specific data. Surveillance data classified the stage as ES in 1762 (65.3%) cases among transgender persons and late latent/unknown duration in 935 (34.7%) cases. Cisgender men with ES reported having transgender sex partners in 1129 cases, while 235 men with late stage syphilis reported transgender partners. The plurality of syphilis cases among transgender persons occurred in Blacks (44.1%), followed by Hispanics (32.3%), Whites (6.9%), and persons classified as Multiracial/other race (5.4%).

DISCUSSION

We used aggregate US surveillance data to describe variation in the percentage of MSMW syphilis cases occurring in MSM by race and region, and the association of syphilis in MSMW with rates of infection in women. The overall mean percentage of MSMW ES cases occurring in MSM was 11.5% and was highest for Black men and in the Southern US region. We observed an association between a greater absolute burden of ES in MSMW and rates of overall syphilis in women, a finding that is consistent with the hypothesis that syphilis epidemics in these populations are epidemiologically linked.

Our finding that the percentage of MSM who are MSMW is higher in Black and Hispanic MSM than in White MSM is consistent with some, but not all, prior reports.[18] National 2017 HIV Behavioral Surveillance data indicate that 17.1% of Black MSM, 11.4% Hispanic MSM and 8.1% White MSM reported vaginal sex with female partners in the past year.[29] Using older nationally-representative population survey data, Binson found that Black men reported bisexual behavior more often than White, but not Hispanic men in the prior five years,[10] while Jeffries reported that Latino men were more likely than Black men to have both male and female partners, even after adjusting for various confounders.[30] Divergence in these reports may be a result of variation in the makeup of the populations sampled and perhaps reflects how respondents were questioned about their sexual behavior. This study included a population designed to be representative of the contemporary US population with syphilis in high morbidity areas and adds to evidence suggesting that bisexual behavior is more common among MSM of color with syphilis.

We also observed that the percentage of MSMW ES cases occurring among MSM was higher in the South compared to other regions of the US, suggesting that the specific

environmental and sociocultural factors that influence sexual behavior in that region may affect men from all race/ethnicity groups included in our data. The factors that shape bisexual behavior are ill-defined; however, it is notable that national trends toward greater acceptance of LGBTQ persons have not affected all regions or groups equally.[31] Disparities by region and race/ethnicity remain prevalent, with lower levels of acceptance observed in the Southern US[31,32] and among Blacks[33,34] – the region and population in which we found a larger percentage of MSM with syphilis were MSMW.

We found that the number of MSMW ES cases per 100,000 men – a population-level measure of the syphilis burden in MSMW – was associated with incidence rates of syphilis in women. This finding is consistent with the conclusion that epidemics in these populations are linked, and the disparate impact of syphilis in Black women may be a consequence of both the greater racial homophily observed in sex partners[23] and the relatively high percentage of Black MSM who also have sex with women. Notwithstanding, our ecologic analysis is not definitive in establishing a transmission link between these groups.

Data on linkages of STI epidemics in MSM and women are limited, and most studies investigating sexual epidemiologic links between MSM and heterosexual populations have focused on HIV. Behavioral studies have described MSMW, and their sexual behavior, drug use patterns and partnerships,[16,17,20,30,35] but have not provided direct evidence on the role of MSMW in HIV/STD transmission. However, an analysis of public health partner services data from North Carolina showed a linkage of MSMW and HIV transmission networks that included women,[22] and phylogenetic analyses suggest that HIV epidemics in MSM and women are linked – specifically, when compared to other groups a higher percentage of Black MSM and MSM in the South can be linked to heterosexual women.[23]

These data support the idea that bridging between the population occurs. How often this occurs is less clear. We believe that the high rates of syphilis observed among MSM likely contribute to the syphilis epidemic in women under some circumstances, but that epidemiologic links between the populations are not completely or even consistently a primary explanation for the persistence of syphilis among women in the US. The syphilis epidemic among primarily heterosexual persons in the late 1980s was associated with the use of crack cocaine and occurred in the absence of a concurrent epidemic in MSM.[36] Moreover, the current heterosexual epidemic in the US has been concentrated in California and the regional Southwest[1] – areas in which a relatively low percentage of MSM ES syphilis cases occur in MSMW – suggesting that increased rates in this region may be unrelated to the epidemic in MSM. Other factors, such as increasing drug use among women and MSW, reported sex with persons who use drugs,[37] exchange sex and homelessness[38] may be greater contributors to the epidemic in some parts of the West.

This study has several limitations. First and most important, this was an ecologic study and we are unable to draw definitive causal conclusions from the analyses. Second, we used public health data, and information on cases' sex of sex partner was based on field services interviews and direct inquiries by public health staff. Insofar as these investigations, or factors influencing self-reported sexual behavior, vary by region or between populations, these biases could have affected our data and findings. In particular, the percentage of ES cases in men for which data on sex of sex partner were missing varied, resulting in the exclusion of these cases from analysis. Overall, several sites with fewer prevalent cases had more complete sex partner data. While we attempted to statistically account for these inconsistencies by weighing percentages on the total number of reported cases in MSM, it is possible that our results would differ if these missing case counts were included in analyses. Third, classifications of

race/ethnicity depend on both self-report and a combination of provider and laboratory reporting, thus misclassification of race/ethnicity status in these data is possible. Fourth, not all sites included in the initial sampling frame provided data, resulting in fewer total cases in the Midwest and Northeast compared to other areas. Small, missing or censored values in the Northeast or Midwest may have decreased our ability to detect stratum-level differences between regions. However, we feel power remained adequate for our chosen analyses utilizing the number of cases with available data. Fifth, though P&S syphilis rates are increasing rapidly among women in California in recent years, we only included data from San Francisco and Los Angeles County. Without including data from the state as a whole, it is plausible that the strength of association was attenuated between syphilis rates in women and measures in MSMW in this area.

Epidemiologists have long considered the association between MSMW and heterosexual populations for STD transmission.[9,21,22] We found that among MSM with syphilis, Black MSM and MSM in the Southern US were more likely to report also having sex with women, and that a higher number of MSMW ES cases per 100,000 men is associated with higher rates of syphilis in women. These findings lend support to the hypothesis that sexual bridging between MSM and women is a contributor to observed longstanding racial and regional disparities in the epidemiology of syphilis. Efforts to control syphilis and eliminate racial and regional disparities require a better understanding of the factors underlying differences in observed patterns of sexual behavior and concerted efforts to address the burden of STD on diverse vulnerable populations.

REFERENCES

1. Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2018*. U.S. Department of Health and Human Services; 2019. doi:10.15620/cdc.79370

2. Spiteri G, Unemo M, Mårdh O, Amato-Gauci AJ. The resurgence of syphilis in high-income countries in the 2000s: a focus on Europe. *Epidemiol Infect*. 2019;147. doi:10.1017/S0950268819000281

3. Fenton KA, Breban R, Vardavas R, et al. Infectious syphilis in high-income settings in the 21st century. *The Lancet Infectious Diseases*. 2008;8(4):244-253. doi:10.1016/S1473-3099(08)70065-3

4. Bowen V, Su J, Torrone E, Kidd S, Weinstock H. Increase in incidence of congenital syphilis - United States, 2012-2014. *MMWR Morb Mortal Wkly Rep*. 2015;64(44):1241-1245. doi:10.15585/mmwr.mm6444a3

5. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect*. 1999;75(1):3-17. doi:10.1136/sti.75.1.3

6. Solomon MM, Mayer KH, Glidden DV, et al. Syphilis predicts HIV incidence among men and transgender women who have sex with men in a preexposure prophylaxis trial. *Clin Infect Dis*. 2014;59(7):1020-1026. doi:10.1093/cid/ciu450

7. Sullivan PS, Purcell DW, Grey JA, et al. Patterns of Racial/Ethnic Disparities and Prevalence in HIV and Syphilis Diagnoses Among Men Who Have Sex With Men, 2016: A Novel Data Visualization. *Am J Public Health*. 2018;108(S4):S266-S273. doi:10.2105/AJPH.2018.304762

8. Reinisch JM, Sanders SA, Ziemba-Davis M. The study of sexual behavior in relation to the transmission of human immunodeficiency virus: Caveats and recommendations. *American Psychologist*. 1988;43(11):921-927. doi:10.1037/0003-066X.43.11.921

9. Doll LS, Beeker C. Male bisexual behavior and HIV risk in the United States: synthesis of research with implications for behavioral interventions. *AIDS Educ Prev*. 1996;8(3):205-225.

10. Binson D, Michaels S, Stall R, Coates TJ, Gagnon JH, Catania JA. Prevalence and Social Distribution of Men Who Have Sex with Men: United States and Its Urban Centers. *The Journal of Sex Research*. 1995;32(3):245-254.

11. Kerr-Pontes LRS, Gondim R, Mota RS, Martins TA, Wypij D. Self-reported sexual behaviour and HIV risk taking among men who have sex with men in Fortaleza, Brazil: *AIDS*. 1999;13(6):709-717. doi:10.1097/00002030-199904160-00012

12. Tabet S, Sanchez J, Lama J, et al. HIV, syphilis and heterosexual bridging among Peruvian men who have sex with men: *AIDS*. 2002;16(9):1271-1277. doi:10.1097/00002030-200206140-00010

13. Mercer CH, Fenton KA, Copas AJ, et al. Increasing prevalence of male homosexual partnerships and practices in Britain 1990–2000: evidence from national probability surveys. *AIDS*. 2004;18(10):1453-1458. doi:10.1097/01.aids.0000131331.36386.de

14. Baral S, Trapence G, Motimedi F, et al. HIV Prevalence, Risks for HIV Infection, and Human Rights among Men Who Have Sex with Men (MSM) in Malawi, Namibia, and Botswana. Ng LFP, ed. *PLoS ONE*. 2009;4(3):e4997. doi:10.1371/journal.pone.0004997

15. Bowring AL, Veronese V, Doyle JS, Stoove M, Hellard M. HIV and Sexual Risk Among Men Who Have Sex With Men and Women in Asia: A Systematic Review and Meta-Analysis. *AIDS Behav*. 2016;20(10):2243-2265. doi:10.1007/s10461-015-1281-x

16. Friedman MR, Wei C, Klem ML, Silvestre AJ, Markovic N, Stall R. HIV Infection and Sexual Risk among Men Who Have Sex with Men and Women (MSMW): A Systematic Review and Meta-Analysis. Remis RS, ed. *PLoS ONE*. 2014;9(1):e87139. doi:10.1371/journal.pone.0087139

17. Montgomery JP, Mokotoff ED, Gentry AC, Blair JM. The extent of bisexual behaviour in HIV-infected men and implications for transmission to their female sex partners. *AIDS Care*. 2003;15(6):829-837. doi:10.1080/09540120310001618676

18. Millett G, Malebranche D, Mason B, Spikes P. Focusing "Down Low": Bisexual Black Men, HIV Risk and Heterosexual Transmission. *J Natl Med Assoc*. 2005;97(7):8.

19. Centers for Disease Control and Prevention. HIV Risk, Prevention, and Testing Behaviors Among Men Who Have Sex With Men --- National HIV Behavioral Surveillance System, 21 U.S. Cities, United States, 2008. *MMWR Morb Mortal Wkly Rep*. 2011;60(14). Accessed November 13, 2019. https://www.cdc.gov/mmwr/preview/mmwrhtml/ss6014a1.htm

20. McKirnan DJ, Stokes JP, Doll L, Burzette RG. Bisexually active men: Social characteristics and sexual behavior. *Journal of Sex Research*. 1995;32(1):65-76. doi:10.1080/00224499509551775

21. Operario D, Smith CD, Arnold E, Kegeles S. Sexual Risk and Substance Use Behaviors Among African American Men Who Have Sex with Men and Women. *AIDS Behav*. 2011;15(3):576-583. doi:10.1007/s10461-009-9588-0

22. Hightow LB, Leone PA, MacDonald PDM, McCoy SI, Sampson LA, Kaplan AH. Men Who Have Sex With Men and Women: A Unique Risk Group for HIV Transmission on North Carolina College Campuses: *Sexually Transmitted Diseases*. 2006;33(10):585-593. doi:10.1097/01.olq.0000216031.93089.68

23. 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: *JAIDS Journal of Acquired Immune Deficiency Syndromes*. 2015;70(4):444-451. doi:10.1097/QAI.0000000000000809

24. Yun K, Xu JJ, Reilly KH, et al. Prevalence of bisexual behaviour among bridge population of men who have sex with men in China: a meta-analysis of observational studies. *Sexually Transmitted Infections*. 2011;87(7):563-570. doi:10.1136/sextrans-2011-050079

25. Liao M, Kang D, Jiang B, et al. Bisexual behavior and infection with HIV and syphilis among men who have sex with men along the east coast of China. *AIDS Patient Care STDS*. 2011;25(11):683-691. doi:10.1089/apc.2010.0371

26. Slutsker JS, Hennessy RR, Schillinger JA. Factors Contributing to Congenital Syphilis Cases — New York City, 2010–2016. *MMWR Morb Mortal Wkly Rep*. 2018;67(39):1088-1093. doi:10.15585/mmwr.mm6739a3

27. Stafford IA, Berra A, Minard CG, et al. Challenges in the Contemporary Management of Syphilis among Pregnant Women in New Orleans, LA. *Infectious Diseases in Obstetrics and Gynecology*. 2019;2019:1-7. doi:10.1155/2019/2613962

28. *American FactFinder*. United States Census Bureau Accessed August 28, 2019. https://factfinder.census.gov

29. Centers for Disease Control and Prevention. HIV Infection Risk, Prevention, and Testing Behaviors Among Men Who Have Sex With Men—National HIV Behavioral Surveillance, 23 U.S. Cities, 2017. 2019;(22):30.

30. Jeffries IV WL, Dodge B. Male Bisexuality and Condom Use at Last Sexual Encounter: Results From a National Survey. *The Journal of Sex Research*. 2007;44(3):278-289. doi:10.1080/00224490701443973

31. Movement Advancement Project. Equality Maps Snapshot: LGBTQ Equality By State. Accessed April 3, 2020. https://www.lgbtmap.org/equality-maps

32. Lax JR, Phillips JH. Gay Rights in the States: Public Opinion and Policy Responsiveness. *Am Polit Sci Rev*. 2009;103(3):367-386. doi:10.1017/S0003055409990050

33. Glick SN, Golden MR. Persistence of racial differences in attitudes toward homosexuality in the United States. *J Acquir Immune Defic Syndr*. 2010;55(4):516-523. doi:10.1097/QAI.0b013e3181f275e0

34. Smith TW, Marsden PV, Hout M, Kim J. General Social Surveys, 1972-2018. Published online March 19, 2019. Accessed April 3, 2020. https://gssdataexplorer.norc.org/trends/

35. Zule WA, Bobashev GV, Wechsberg WM, Costenbader EC, Coomes CM. Behaviorally Bisexual Men and their Risk Behaviors with Men and Women. *J Urban Health*. 2009;86(S1):48-62. doi:10.1007/s11524-009-9366-3

36. Centers for Disease Control (CDC). Primary and secondary syphilis--United States, 1981-1990. *MMWR Morb Mortal Wkly Rep*. 1991;40(19):314-315, 321-323.

37. Kidd SE, Grey JA, Torrone EA, Weinstock HS. Increased Methamphetamine, Injection Drug, and Heroin Use Among Women and Heterosexual Men with Primary and Secondary Syphilis - United States, 2013-2017. *MMWR Morb Mortal Wkly Rep*. 2019;68(6):144-148. doi:10.15585/mmwr.mm6806a4

38. Gorbach PM, Murphy R, Weiss RE, Hucks-Ortiz C, Shoptaw S. Bridging Sexual Boundaries: Men Who Have Sex with Men and Women in a Street-Based Sample in Los Angeles. *J Urban Health*. 2009;86(S1):63-76. doi:10.1007/s11524-009-9370-7

TABLE 1: Counts and Percentages of Early Syphilis Cases in Men by United States Jurisdiction and Sex of Sex Partners, 2017

	Total cases	Percent cases with reported sex of sex partner	MSW, *N* (%)[a]	MSM, *N* (%)[a]	MSMW, *N* (%)[a]	Percent of MSMW cases in MSM[b]
Arizona	1243	96.9	251 (20.8)	767 (63.7)	162 (13.4)	17.4
Baltimore	342	95.6	62 (19.0)	212 (64.8)	53 (16.2)	20.0
Chicago	1475	64.2	63 (6.7)	811 (85.6)	73 (7.7)	8.3
Florida	4726	95.9	703 (15.5)	3005 (66.3)	823 (18.2)	21.5
Georgia	2488	52.1	186 (14.3)	1010 (77.9)	101 (7.8)	9.1
King County	646	96.4	20 (3.2)	575 (92.3)	28 (4.5)	4.6
Los Angeles County	4077	88.3	350 (9.7)	3103 (86.1)	142 (3.9)	4.4
Mississippi	613	97.2	177 (29.7)	296 (49.7)	123 (20.6)	29.4
Missouri	773	85.6	178 (26.9)	437 (66.0)	47 (7.1)	9.7
Nevada	419	69.2	33 (11.4)	208 (71.7)	18 (6.2)	8.0
New York City	4944	45.2	206 (9.2)	1900 (85.0)	89 (4.0)	4.5
North Carolina	1652	90.0	320 (21.5)	1060 (71.3)	106 (7.1)	9.1
Oregon	511	81.6	81 (19.4)	268 (64.3)	68 (16.3)	20.2
Philadelphia	884	91.1	146 (18.1)	617 (76.6)	42 (5.2)	6.4
San Francisco	1416	39.8	13 (2.3)	521 (92.4)	16 (2.8)	3.0
Texas	4746	84.0	734 (18.4)	2856 (71.6)	397 (10.0)	12.2
Overall	30 996	79.5	3535 (15.4)	17 685 (74.2)	2284 (9.4)	11.5

Note. Counts and percentages are based upon index cases in cisgender men only. MSW (men who have sex with women); MSM (men who have sex with men); MSMW (men who have sex with men and women)

[a]Percent represents number of cases in men divided by total cases with available data on sex of sex partner(s)

[b]Percent represents number of MSMW cases divided by total MSM cases (MSM only + MSMW)

TABLE 2: Percentages of Early Syphilis Cases Among Men who Have Sex with Men and Women by United States Region and Race/Ethnicity, 2013-2017

	Unadjusted[a]		Adjusted[b]	
	Mean Percent of MSMW cases among MSM[c]	p-value	Mean Percent of MSMW cases among MSM[c]	p-value
Region[d]				
West	9.0	0.07	7.6	0.22
Midwest	7.9	0.13	5.0	0.18
Northeast	7.5	0.11	3.2	0.10
South	16.7	Ref.	12.5	Ref.
Race/Ethnicity				
White NH	8.6	<0.01	7.6	<0.01
Hispanic	9.9	<0.01	9.0	<0.01
Multiracial/Other	10.2	<0.01	9.2	<0.01
Missing	10.2	<0.01	9.2	<0.01
Black NH	15.5	Ref.	14.5	Ref.

Note. MSM (men who have sex with men); MSMW (men who have sex with men and women); Ref. (referent group); NH (Non-Hispanic)

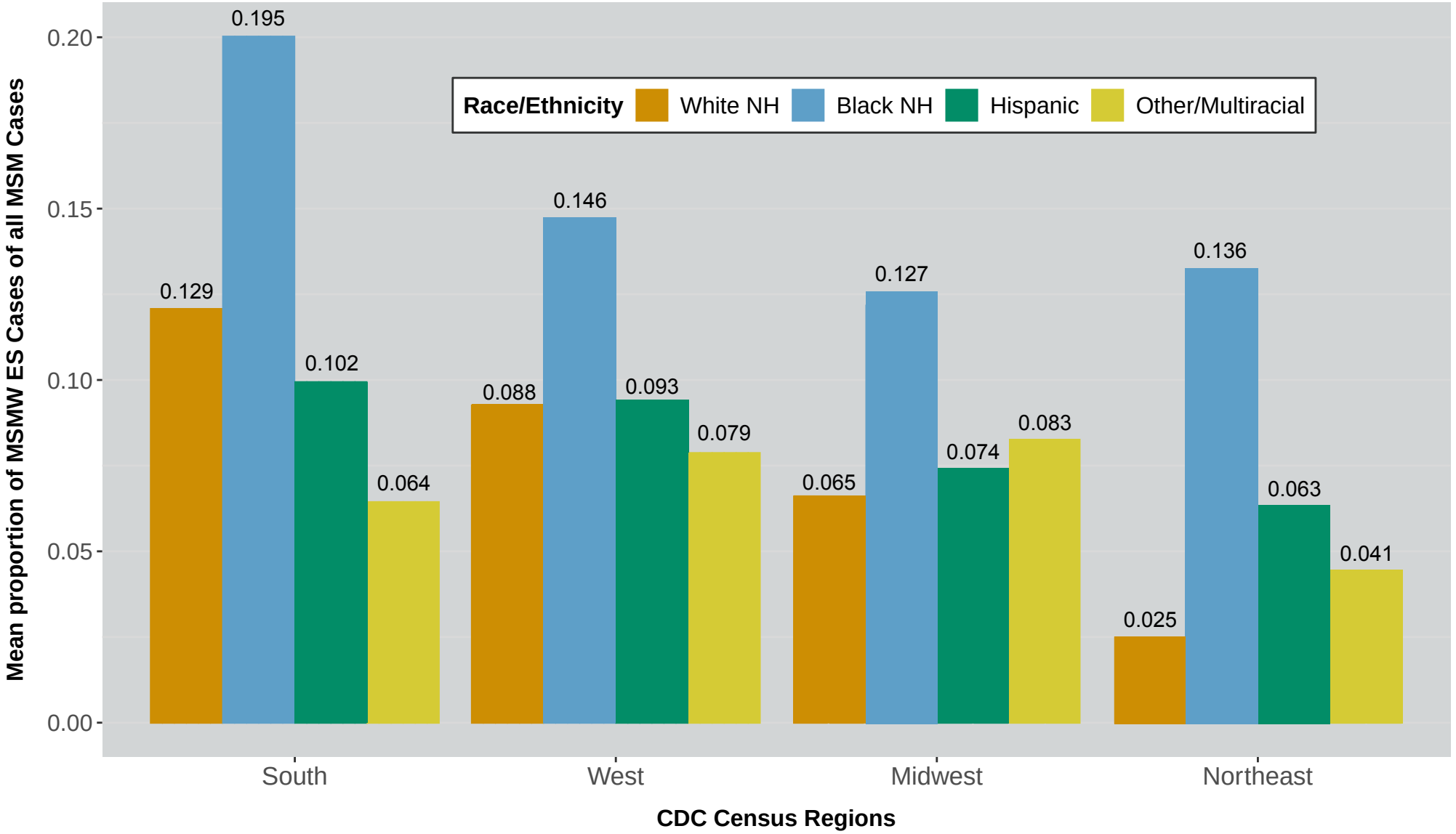
[a]Unadjusted (base) models: univariate linear mixed model accounting for jurisdiction-level clustering and weighted by total MSM counts

[b]Adjusted model: base model with addition of region and race/ethnicity as covariates

[c]Percent represents number of MSMW cases divided by total MSM cases (MSM only + MSMW) in each category

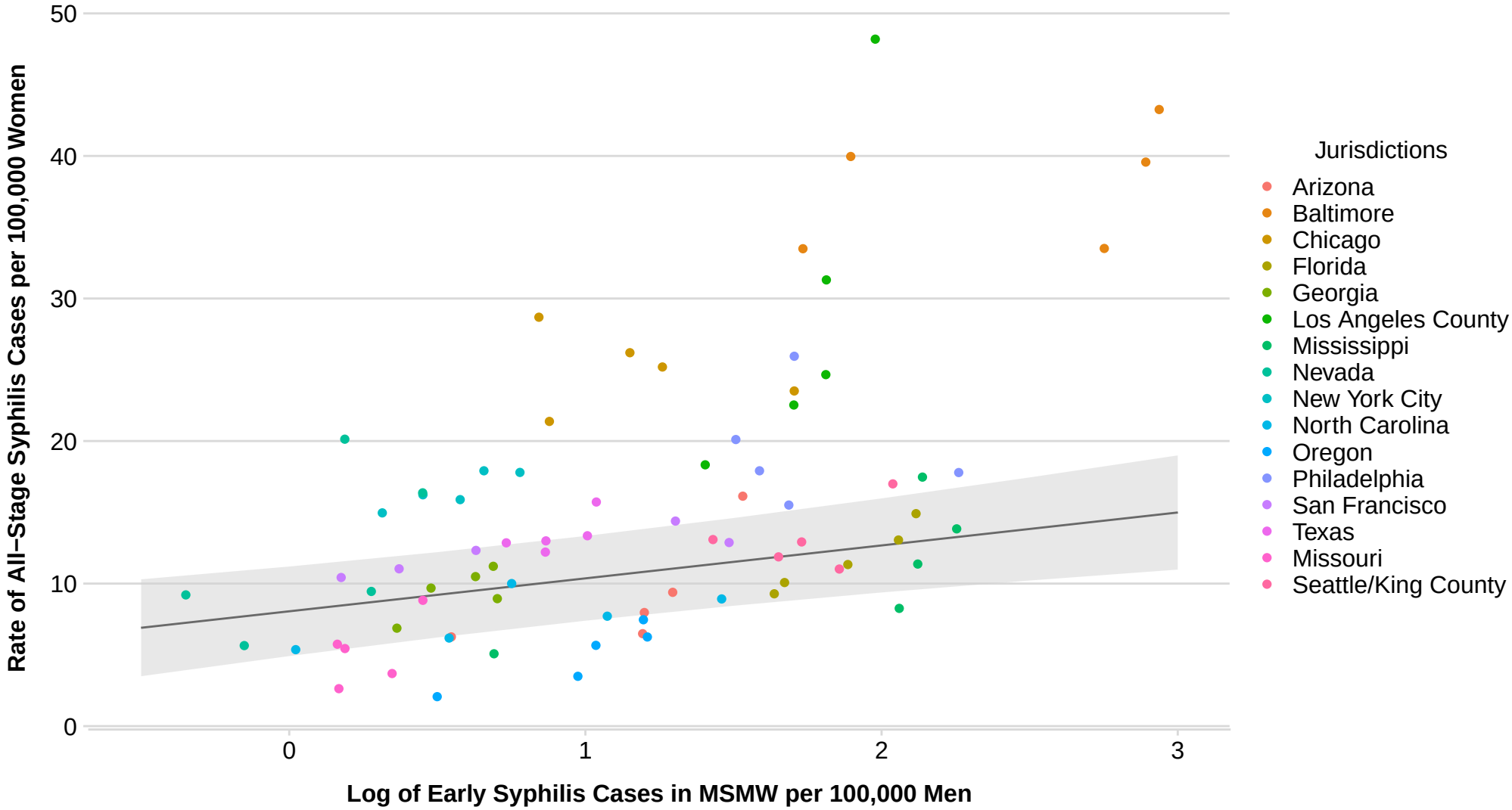
[d]Jurisdictions in each region include: **West** (Arizona; Los Angeles County, CA; Nevada; Oregon; San Francisco, CA; Seattle/King County, WA), **Midwest** (Chicago, IL; Missouri), **Northeast** (New York City, NY; Philadelphia, PA), **South** (Baltimore, MD; Florida; Georgia; Mississippi; North Carolina; Texas)

Figure 1: Relative Mean Proportions of Early Syphilis Cases in Men who Have Sex with Men and Women by Race/Ethnicity & United States Region, 2017



Note: ES: early syphilis; MSMW: men who have sex with men and women; MSM: men who have sex with men; CDC: Centers for Disease Control & Prevention; NH: Non−Hispanic

Figure 2: Mixed Effects Regression of Syphilis Rates in Women on Log−Transformed Early Syphilis Case Counts in Men who Have Sex with Men and Women within High−Morbidity United States Jurisdictions, 2013−2017



Note: MSMW: men who have sex with men and women, CDC: Centers for Disease Control and Prevention.

Random effects model accounts for jurisdiction level clustering.

Supplemental TABLE 3: Counts and Percentages of Late Latent/Unknown Duration Syphilis Cases in Men by United States Jurisdiction & Sex of Sex Partners, 2017

	Total cases	Percent cases with reported gender of sex partner	MSW, *N* (%)[a]	MSM, *N* (%)[a]	MSMW, *N* (%)[a]	Percent of MSMW cases in MSM[b]
Arizona	578	68.5	120 (30.3)	225 (56.8)	44 (11.1)	16.4
Baltimore	129	94.6	49 (40.2)	58 (47.5)	15 (12.3)	20.5
Chicago	624	36.2	26 (11.5)	190 (84.1)	10 (4.4)	5.0
Florida	2602	89.7	633 (27.1)	1331 (57.1)	369 (15.8)	21.7
Georgia	1270	19.9	69 (27.3)	164 (64.8)	20 (7.9)	10.9
King County	154	84.4	28 (21.5)	98 (75.4)	4 (3.1)	3.9
Los Angeles County	1833	49.5	280 (30.8)	569 (62.7)	55 (6.1)	8.8
Mississippi	54	70.4	11 (28.9)	16 (42.1)	11 (28.9)	40.7
Missouri	279	66.7	52 (28.0)	119 (64.0)	15 (8.1)	11.2
Nevada	395	64.8	64 (25.0)	121 (47.3)	14 (5.5)	10.4
New York City	2420	20.2	137 (28.1)	326 (66.8)	20 (4.1)	5.8
North Carolina	735	68.0	180 (36.0)	268 (53.6)	52 (10.4)	16.2
Oregon	212	75.9	65 (40.4)	71 (44.1)	25 (15.5)	26.0
Philadelphia	154	41.6	22 (34.4)	40 (62.5)	[c]	[c]
San Francisco	206	1.5	[c]	[c]	0 (N/A)	N/A
Texas	4346	73.2	918 (28.8)	1963 (61.7)	302 (9.5)	13.3
Overall	15 991	57.8	2656 (31.6)	5560 (57.7)	956 (9.5)	14.0

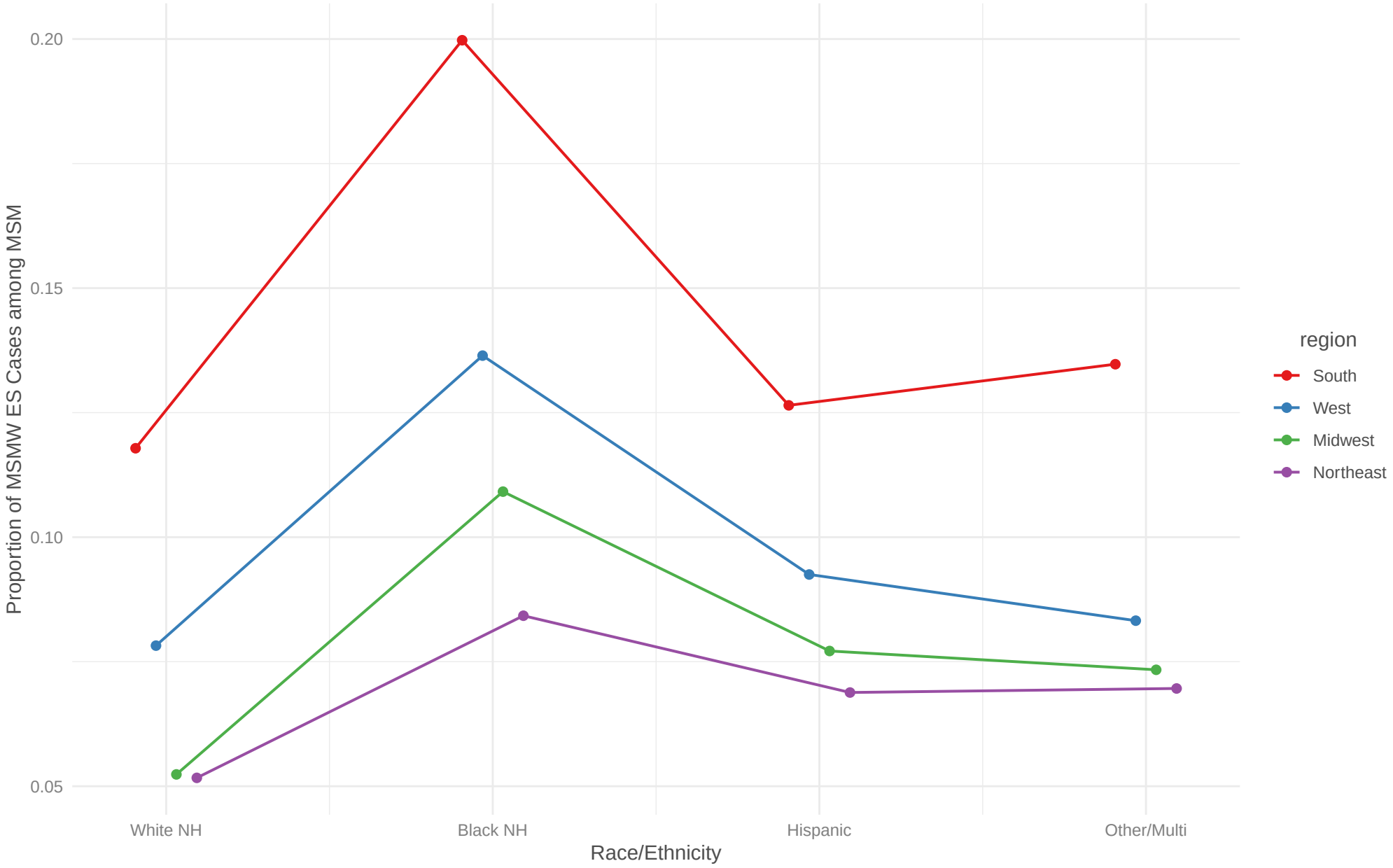
Note. Counts and percentages are based upon index cases in cisgender men only. MSW (men who have sex with women); MSM (men who have sex with men); MSMW (men who have sex with men and women); N/A: unable to calculate

[a]Percent represents number of cases in men divided by total cases with available data on sex of sex partner(s)

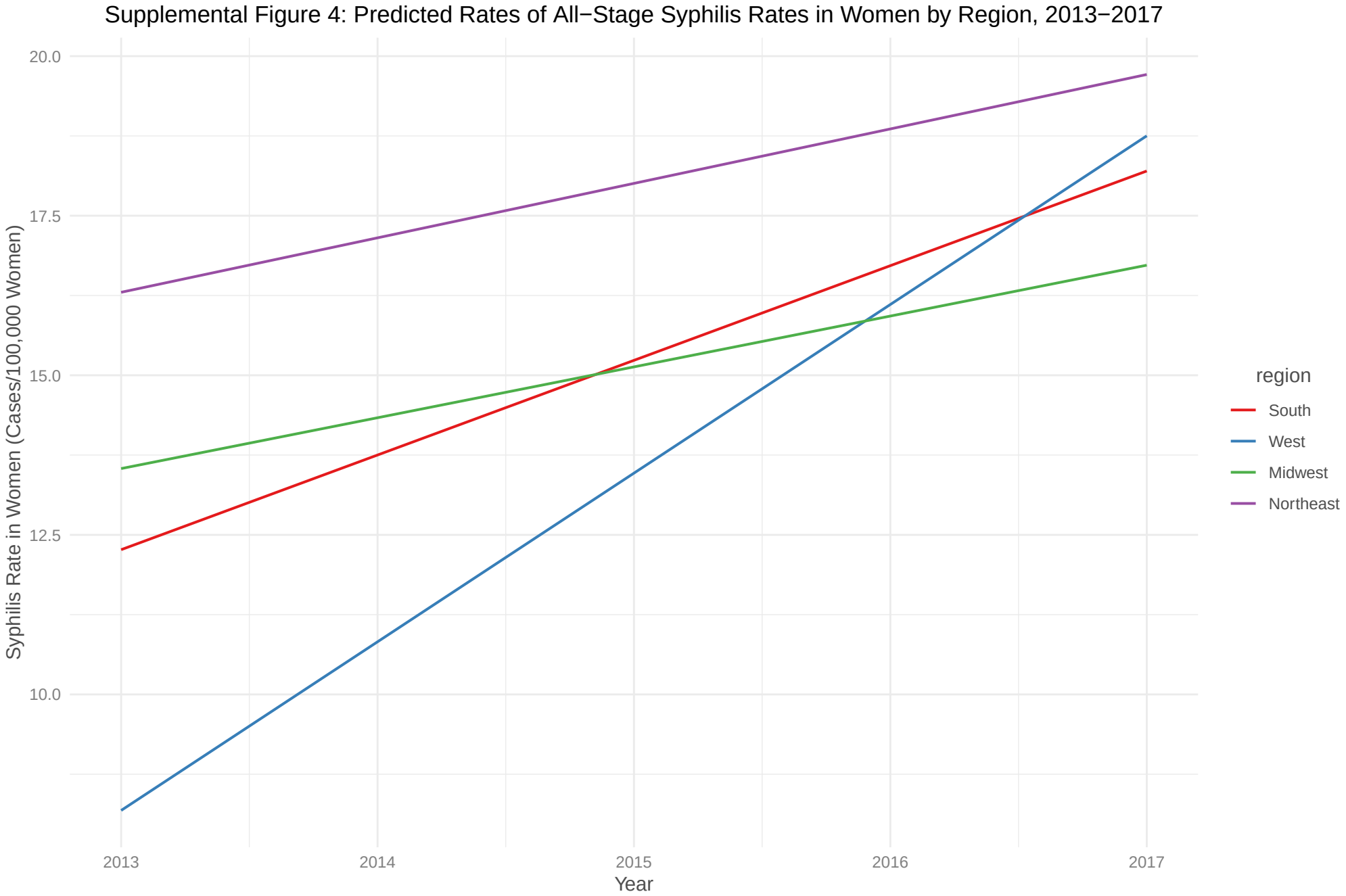
[b]Percent represents number of MSMW cases divided by total MSM cases (MSM only + MSMW)

[c]Data suppressed due to small cell or subpopulation size

Supplemental Figure 3: Predicted Proportions of Early Syphilis Cases in MSMW Occurring in MSM by Race/Ethnicity and Region, 2013−2017



Note: MSMW (men who have sex with men and women); MSM (men who have sex with men); ES (early syphilis); NH (non-Hispanic)


Supplemental Figure 4: Predicted Rates of All−Stage Syphilis Rates in Women by Region, 2013−2017
Syphilis Rate in Women (Cases/100,000 Women)
20.0
17.5
15.0
12.5
10.0
2013
2014
2015
2016
2017
Year
region
South
West
Midwest
Northeast