**INTRODUCTION**

Syphilis is resurgent in the United States. The most striking epidemiological feature of the current epidemic is the disproportionate representation of men who have sex with men (MSM) among cases, with incidence also varying by geography and race/ethnicity [1]. Cases of congenital syphilis have been increasing in recent years, as have rates in women, indicative of a changing epidemic [1]. In particular, these trends suggest that the previously primarily MSM-focused epidemic has expanded into heterosexual populations in some regions of the United States. Another unique feature of the ongoing syphilis epidemic is its longevity; many jurisdictions have observed elevated syphilis rates since the late 1990s/early 2000s and these rates show no sign of decline.

Current public health efforts are not having the desired effect on syphilis control. Mathematical modeling studies have suggested that frequent screening may be an effective and cost-effective approach to syphilis control among populations with high rates of syphilis incidence [2-5]. Based on past experience with syphilis resurgence following apparent control [6], it is also important to consider how to target screening to those most at risk, in order to maximize impact in a sustained manner.

Predicting the future trajectory of the syphilis epidemic is a difficult task. As historical epidemiological data show, social change, the shifting focus of public health investment, and the evolving HIV epidemic may trigger or contribute to upsurges or declines in infection rates [7-9]. The complexity of syphilis natural history in humans further complicates our ability to project the impact of interventions [10]. Despite these challenges, mathematical models are useful understanding the potential effects of public health interventions on epidemic dynamics.

Most mathematical models of syphilis have focused on MSM, who experience a disproportionate burden of infection in many high-income countries [refs]. We sought to evaluate the potential impact of different approaches to syphilis screening using a transmission describing syphilis transmission in both MSM and heterosexual populations. We hypothesized that epidemic characteristics would impact the potential impact of interventions. To address this, we developed a mathematical model that described syphilis transmission at the state level, and fit it to data from the US states of Massachusetts and Louisiana, two states experiencing a significant burden of infection, but with different epidemic characteristics in terms of the role of heterosexual transmission and the race/ethnic composition of cases.

**METHODS**

*Model overview*

We developed a dynamic compartmental metapopulation mathematical model that described syphilis transmission in MSM and heterosexual populations of different racial/ethnic groups (Figure 1). We modeled non-Hispanic black, Hispanic, and non-Hispanic non-black heterosexual subpopulations. Although we did not model HIV co-transmission, the model stratified the MSM population by HIV status, given the high rates of syphilis infection among HIV-infected individuals and the potential for targeted inventions in this group [11-14]. The population was further stratified by age group: 20-44 years and 45-64 years and sexual activity level: low and high.

The natural history of syphilis was modeled using a previously described approach [10] and included the following health states: ‘susceptible’ (S), ‘incubating’ (E), ‘primary syphilis’ (I1), ‘secondary syphilis’ (I2), ‘early latent syphilis’ (L1), and ‘late latent syphilis’ (L2). The primary and secondary stages were assumed to be infectious. In the absence of treatment, infected individuals progressed through the different stages of syphilis and remained in the late latent state for the duration of their time in the model. With treatment, individuals entered a ‘treated’ (T1-T3) state before returning to the ‘susceptible, prior infection’ (SR) state. Consistent with data suggesting that there may be a period transient protection from re-infection after treatment that increases with duration of infection [10, 15], time spent in the treated state varied with infection stage at treatment. Individuals with prior treated infections were modeled separately from those with no prior infections, to allow for the investigation of interventions focused in individuals with a history of syphilis infection. The natural history of infection was not assumed to differ in those experiencing multiple infections. We began tracking individuals with a prior infection 5 years before the start of the calibration period. We included a ‘never sexually active’ (NSA) compartment to capture the proportion of the population reporting no sexual activity and to allow for transitions into the sexually active class as individuals aged. Additional details about the modeling approach, including mixing within and across subpopulations, are provided in the Technical Appendix.

*Testing and treatment*

Syphilis infections could be identified and treated either by: (i) individuals seeking medical care for symptoms or (ii) opportunistic screening. There was an associated probability that an identified and treated case was reported and would be reported and included in syphilis surveillance data. Reporting probabilities were allowed to differ by mechanism of case detection (actively seeking care vs. screening). We also included a background antibiotic treatment rate, allowing for treatment of syphilis without diagnosis. This rate was assumed to be relatively high (10% per year) in the pre-calibration period, representing the introduction of penicillin treatment to the population and was reduced to a low level (1% per year) after the initial introductory period.

*Model fitting*

We developed separate models for Louisiana and Massachusetts. These models differed in the underlying population characteristics. Population sizes and population distributions by race/ethnicity were based on estimates from the 2015 census [ref]. The proportion of males allocated to the MSM compartment was based on a recent study [16]. Estimates of HIV prevalence in MSM were provided by the Louisiana and Massachusetts Departments of Public Health.

For model fitting, we used data on reported syphilis cases aged 20-64 years in Louisiana and Massachusetts for the time period 2012-2016. Available information included rates of primary, secondary, and early latent syphilis by race/ethnicity and age group. We also used data on the proportion of male cases reported in MSM and proportion of syphilis cases in MSM with an identified HIV co-infection (available for the years 2014-2016 only for Louisiana). Finally, we used state-level estimates of the proportion of all reported cases (including late latent) that were early infections [17].

We used an adaptive Metropolis-Hastings Markov Chain Monte Carlo algorithm [18] for model calibration of parameters describing syphilis natural history, sexual mixing, and testing and treatment processes. Prior distributions were based on estimates from the biomedical literature, where available, or expert opinion and assumption otherwise (**Tables 1** and **2**).

*Model outputs and analyses*

We used the calibrated models to project the impact of different approaches to screening in the two epidemic contexts. We considered a 10-year time horizon beginning after the calibration period.

The scenarios included:

1. Screening continues at 2016 levels
2. Screen entire sexually active population annually
3. Screen MSM at levels recommended in US syphilis screening guidelines, maintain screening in remaining population at 2016 levels (annual screening for all MSM, 3-monthly for high sexual activity MSM, regardless of HIV status)
4. Screen MSM at levels recommended in guidelines, screen rest of the population annually
5. Screen individuals with prior syphilis infection every 3 months, maintain screening in remaining population at 2016 levels
6. Screen individuals with prior syphilis infection every 3 months, screen rest of population annually

**RESULTS**

*Syphilis in Louisiana and Massachusetts 2012-2016*

For the time period 2012-2016, both Louisiana and Massachusetts experienced an increase in rates of early (primary, secondary, and early latent) syphilis in the population aged 20-64 years. In Louisiana, the proportion of male cases identified as MSM increased in both age groups over this time period: from 0.49 to 0.77 in males 20-44y and 0.16 to 0.30 in males aged 45-65 y (p<0.001 for both age groups). There was a trend of increasing proportion of MSM cases with HIV co-infection for the younger age group only (p=0.16, only have data for 3 years here). In the older age group, HIV-co-infection was common in MSM cases (~75%) and did not change significantly between 2014 and 2016 (p=0.75). The proportion of cases occurring in MSM was high in Massachusetts in 2012 (0.85) and declined over time (chi-squared test for trend in proportions, p<0.001 for both age groups). In Massachusetts, the proportion of MSM cases with HIV co-infection declined over time (younger age group: 0.54 in 2012 to 0.35 in 2016, p<0.001, for older age group: 0.78 in 2012 to 0.73 in 2016, p=0.024).

Racial/ethnic disparities…

**DISCUSSION**

To our knowledge, this is the first model to simultaneously model syphilis spread in MSM and heterosexual populations and the linkages between them.

Estimates of HIV prevalence in MSM by state, are similar to our age-stratified estimates [19].

**References**

1. Centers for Disease Control and Prevention. Sexually transmitted disease surveillance 2014. Accessed 23 Dec 2015: <http://www.cdc.gov/std/stats>, **2014**.

2. Tuite A, Fisman D. Go big or go home: impact of screening coverage on syphilis infection dynamics. Sex Transm Infect **2015**.

3. Tuite AR, Burchell AN, Fisman DN. Cost-effectiveness of enhanced syphilis screening among HIV-positive men who have sex with men: a microsimulation model. PLoS One **2014**; 9:e101240.

4. Tuite AR, Fisman DN, Mishra S. Screen more or screen more often? Using mathematical models to inform syphilis control strategies. BMC Public Health **2013**; 13:606.

5. Gray RT, Hoare A, Prestage GP, Donovan B, Kaldor JM, Wilson DP. Frequent testing of highly sexually active gay men is required to control syphilis. Sex Transm Dis **2010**; 37:298-305.

6. Rekart ML, Patrick DM, Chakraborty B, et al. Targeted mass treatment for syphilis with oral azithromycin. Lancet **2003**; 361:313-4.

7. Breban R, Supervie V, Okano JT, Vardavas R, Blower S. Is there any evidence that syphilis epidemics cycle? Lancet Infect Dis **2008**; 8:577-81.

8. Gilbertson A, Gelpi A, Tucker JD. The impact of penicillin on sexual healthcare delivery systems in mid-20th century Britain. Sex Transm Infect **2015**; 91:70-1.

9. Peterman TA, Su J, Bernstein KT, Weinstock H. Syphilis in the United States: on the rise? Expert Rev Anti Infect Ther **2014**:1-8.

10. Garnett GP, Aral SO, Hoyle DV, Cates W, Anderson RM. The natural history of syphilis. Implications for the transmission dynamics and control of infection. Sex Transm Dis **1997**; 24:185-200.

11. Guy R, El-Hayek C, Fairley CK, et al. Opt-out and opt-in testing increases syphilis screening of HIV-positive men who have sex with men in Australia. PLoS One **2013**; 8:e71436.

12. Callander D, Baker D, Chen M, Guy R. Including syphilis testing as part of standard HIV management checks and improved syphilis screening in primary care. Sex Transm Dis **2013**; 40:338-40.

13. Bissessor M, Fairley CK, Leslie D, Howley K, Chen MY. Frequent screening for syphilis as part of HIV monitoring increases the detection of early asymptomatic syphilis among HIV-positive homosexual men. J Acquir Immune Defic Syndr **2010**; 55:211-6.

14. Cohen CE, Winston A, Asboe D, et al. Increasing detection of asymptomatic syphilis in HIV patients. Sex Transm Infect **2005**; 81:217-9.

15. Magnuson H, Evan T, Sidney O, Kaplan B, De Mello L, Cutler J. Inoculation syphilis in human volunteers. Medicine **1956**; 32:33-82.

16. Grey AJ, Bernstein TK, Sullivan SP, 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 Surveill **2016**; 2:e14.

17. Centers for Disease Control and Prevention. Sexually transmitted disease surveillance 2016. Accessed 28 Sep 2017: <https://www.cdc.gov/std/stats16/default.htm>, **2017**.

18. Camacho A, Funk S. fitR: Tool box for fitting dynamic infectious disease models to time series. R package version 0.1. <http://sbfnk.github.io/mfiidd/fitR.tar.gz>, **2016**.

19. Rosenberg ES, Grey JA, Sanchez TH, Sullivan PS. Rates of Prevalent HIV Infection, Prevalent Diagnoses, and New Diagnoses Among Men Who Have Sex With Men in US States, Metropolitan Statistical Areas, and Counties, 2012-2013. JMIR Public Health Surveill **2016**; 2:e22.