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Countering the Rise of Syphilis: A Role for Doxycycline Post-Exposure Prophylaxis?

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Abstract

Doxycycline post-exposure prophylaxis (PEP) holds the potential to mitigate increasing rates of syphilis among sexual minority men (SMM) in the US yet has received limited attention. Since evaluation of this intervention in actual populations is not currently feasible, we used agent-based models (ABM) to assess the population-level impact of this strategy. We adapted ABM of HIV and HPV transmission, representing a population of 10,230 SMM in Philadelphia, Pennsylvania, US. Parameter inputs were derived from the literature, and ABM outputs during the pre-intervention period were calibrated to local surveillance data. Intervention scenarios varied doxycycline uptake by 20, 40, 60, 80, and 100%, while assuming continued condom use and syphilis screening and treatment. Under each intervention scenario, we incorporated treatment adherence at the following levels: 0, 20, 40, 60, 80, and 100%. Long-term population impact of prophylactic doxycycline was measured using the cumulative incidence over the 10-year period and the percentage of infections prevented attributable to doxycycline at year 10. An uptake scenario of 20% with an adherence level of 80% would reduce the cumulative incidence of infections by 10% over the next decade, translating to 57 fewer cases per 1,000 SMM. At year 10, under the same uptake and adherence level, 22% of infections would be prevented due to doxycycline PEP in the instances where condoms were not used or failed. Findings suggest that doxycycline PEP will have a modest impact on syphilis incidence when assuming a reasonable level of uptake and adherence. Doxycycline PEP may be most appropriate as a secondary prevention measure to condoms and enhanced syphilis screening for reducing infections among SMM.

Keywords

Agent-based models; Doxycycline prophylaxis; Bacterial STI; Syphilis; Sexual minority men

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CONFLICT OF INTERESTS

The authors do not have any competing interests to declare.

SUPPLEMENTARY MATERIALS

All research materials related to our paper, including the literature source for our inputs, the code for creating the models, and simulation data, are provided in the Supplemental Material file and following link: https://doi.org/10.5281/zenodo.4701677.

INTRODUCTION

Bacterial sexually transmitted infections (STI) have been steadily rising in gay, bisexual, and other sexual minority men (SMM) in the US over the past 2 decades.[1] Syphilis is but one class of bacterial STI and is a major public health concern. From 2001 to 2017, the Centres for Disease and Control Prevention (CDC) reported a 4.5-fold increase in the estimated syphilis diagnosis among SMM.[1] In Philadelphia alone, the increase was more than 2.8-fold among men, with SMM consistently representing more than 69% of primary and secondary infections and 54% of early latent infections annually within the last decade.[2] If left untreated, syphilis can cause short-term sequelae such as skin rashes and mucous membrane lesions as well as long-term complications such as cardiovascular syphilis and neurosyphilis.[3]

Reasons for increasing rates of syphilis include the potential changes in sexual behaviours (e.g., decreased condom use) related to the adoption biomedical strategies (e.g., treatment as prevention, HIV pre-exposure prophylaxis [PrEP]),[4,5] and increased but suboptimal sustainment of syphilis screening that may result in a higher rate of new infections in the population.[6] However, the causal nature of these explanations remains unclear while the sharp increase in syphilis incidence necessitates the evaluation of prevention strategies that can mitigate these growing trends.

The current repertoire of syphilis prevention strategies include condom use and STI screening, with prior work suggesting that consistent condom use and enhanced STI screening can substantially reduce incident cases.[7,8] However, less research has considered the potential population-level impact of chemoprophylaxis for syphilis control despite promising evidence. Clinical studies indicate that doxycycline post-exposure prophylaxis (PEP) may be efficacious, reducing the risk of syphilis infection to about 70% among SMM receiving the treatment compared to the control.[9] In addition, some modelling work has demonstrated that chemoprophylaxis has the potential to reduce 85% of infections over 10 years assuming an uptake level of 50% and efficacy of 70% among Australian SMM.[10]

Although these data provide encouraging evidence that doxycycline PEP has the potential to lower the population burden of syphilis among SMM, suboptimal adherence holds the potential to thwart the efficacy of any prophylactic regimen.[11] Yet, there has been limited research on evaluating the population impact of adherence on doxycycline PEP effectiveness. Such information can support implementation decisions and program evaluation in health departments by projecting different scale-up strategies that could theoretically optimize the reduction of syphilis incidence in a given population. In this proof-of-concept study, we sought to develop agent-based models (ABM) to determine whether and to what extent doxycycline PEP would reduce syphilis incidence and how adherence would modify this relationship over time.

METHODS

Model Overview

We adapted previously described discrete-time ABM of HIV[12] and HPV[13] prevention that progressed in daily time steps to estimate the impact of doxycycline PEP on syphilis incidence. For our analysis, we built upon the existing model structure, parameterization, and analysis to reflect the estimated demography and infection rate of syphilis among SMM in Philadelphia, Pennsylvania, US. Model parameters were non-systematically derived from the literature. Details and references of assumptions, parameters, and model specifications are presented in Table 1.

Sexual Network Dynamics and Assumptions

Our models simulated a dynamic cohort of 10,230 SMM engaging in zero or more sexual encounters annually over 10 years. Our sample size was calculated using estimates of SMM living in Philadelphia County (i.e., the City of Philadelphia),[14] CDC's indications for PrEP eligibility among HIV-negative SMM,[15] and the National HIV Behavioural Surveillance estimates of HIV prevalence among SMM in Philadelphia (Supplemental Appendix 1).[16] Sexual partnerships were modelled to be serial relationships. Casual and main partnerships did not occur concurrently but differed by the frequency of sexual contact and partnership duration. For instance, to model casual partnerships, sexual dyads did not extend for more than one day, but agents were able to repeatedly match with previous partners, while main partnerships could potentially continue for the entire duration of the simulation. Assortative partnership formation varied by partnership availability, race mixing,[17] and HIV serosorting.[18] Age mixing was not considered given research to suggest that it may not explain sexual transmission of HIV/STI among SMM.[19] Relationship length varied stochastically, with a mean partnership duration of 100 days. For agents having a sexual encounter on a given day, they were able to engage in anal sex, oral sex, both, or abstain (if serosorting). Upon matching with a partner, partners negotiated sexual positioning (i.e. insertive, receptive, or both) for anal or oral intercourse,[20–22] based on preferences assigned when the baseline population was initialized. However, in the case where both partners have the same preference, we relied on a coin flip to determine the partners' roles.[12] Sexual preference of each agent persisted for the duration of the simulation. The total number of expected sexual partners that may form during the simulated year was gamma distributed (shape=0.5, scale=10),[23,24] while the total number of sex acts per partnership followed a Poisson distribution (lambda=81).[25]

STI Transmission and Progression

Individuals started as either susceptible or infected with primary and secondary or early latent syphilis. This estimate was calculated from multiplying a pooled syphilis incidence rate with the average duration of disease from published literature among SMM.[26] Estimates specific to demographic characteristics, HIV status (discussed later), stage of syphilis infection, and anatomic site (i.e., oropharyngeal and anogenital) were then calculated by multiplying the proportion of each parameter together.[27,28] The starting prevalence aggregated across demographic, HIV status, and stage of syphilis infection (i.e., primary, secondary, and early latent) was 6.9% for anal syphilis and 5.9% for oral syphilis

(Supplemental Appendix 1).[26–28] We also considered the following simplifying assumptions for our models: 1) there was concordance between penile and anal infection for anogenital syphilis for an individual agent and 2) only one category for primary and secondary syphilis was included as it is less clear whether transmission probability differs between these stages of infection. However, SMM could be infected at both anatomical sites with either primary and secondary or early latent syphilis. Those infected with primary and secondary syphilis, if left untreated, remained symptomatic and infectious for up to one year at which point they transitioned to early latent syphilis.[3] For our models, this transition point was akin to a resolution of syphilis infection in which individuals were less infectious but remained infected until one of the following endpoints occurred: 1) antibiotic treatment or 2) end of the simulation follow-up. Agents were considered vulnerable to reinfection of primary and secondary syphilis based on lack of evidence surrounding acquired immunity.[3]

We considered HIV infection and progression in our models as this would impact seroadaptive practices (i.e., seroadaption may impact sexual behaviours to prevent HIV and indirectly influence syphilis infection) and biological susceptibility of syphilis co-infection.[29] Specifically, we assumed that there was a multiplicative increase in the per contact probability of syphilis infection for SMM living with HIV by two-fold.[29] Additional assumptions about the natural history of HIV and its modifications by antiretroviral therapy (ART) for those HIV positive and aware of their status are more thoroughly discussed in LeVasseur et al.[12]

STI Prevention Strategies

In the base scenario serving as a comparison group, we assumed 0% of the modelled population to be on doxycycline PEP during the 10-year period. The probability distribution of condoms use for anal sex was: 25% used condoms all of the time, 21% used condoms 75% of the time, 16% used condoms 50% of the time, 14% used condoms 25% of time, and 24% never used a condom.[30] This distribution was modified by race such that white SMM were less likely to use a condom consistently than non-white SMM.[30] Condom use during oral sex was infrequent and limited data suggested a 4% probability.[31] The failure rate of condoms for syphilis prevention was unclear for syphilis; thus, approximated using estimates from other STI at 30%.[32] Assumptions of syphilis testing was based on the CDC guidelines and extent literature.[33–35] During baseline data generation, agents were randomly assigned to a specific day throughout the year in which they received syphilis testing; the frequency in which agents were tested differed by HIV status. SMM living with HIV were assumed to test more frequently than those who did not have HIV, with 22% of SMM living with HIV testing quarterly, 21% testing semi-annually, 28% testing annually, and 29% who never receive testing.[33] Among SMM who were HIV negative or unaware of their status, we assumed 31% receive testing annually.[34,35] Treatment after testing was assumed to be 95% efficacious.[36]

We compared the base scenario to the following intervention scenarios that varied doxycycline PEP uptake and adherence over 10 years, while assuming condom use and syphilis testing continued at the previously described rates for the entire population. Implementation of doxycycline PEP was informed by current research,[9] such that agents

were simulated to take the treatment after any anal or oral sex event during the intervention period. To simulate uptake of doxycycline PEP and its theorized benefits, we conducted counterfactual analyses by replicating the models at several population-levels of uptake: 20%, 40%, 60%, 80%, and 100%. Furthermore, at each uptake scenario, we incorporated treatment adherence at the following levels: 0% (reference level), 20%, 40%, 60%, 80%, and 100% to reflect the likelihood in which an individual might discontinue the use of doxycycline at any point in time. Within each combination of treatment uptake and adherence scenario, we assumed a 73% treatment efficacy which was sampled from a Beta distribution (alpha = 6.6, beta = 2.4).[9]

Model Calibration

To externally validate our ABM, our models were tuned to represent HIV and syphilis incidence among SMM living in Philadelphia from 2010 to 2018. To do this, we used a best-fit, *ex ante* input validation approach[37] and compared nine years of HIV and syphilis surveillance data from the Philadelphia Department of Health[2,16] to our model predicted estimates. A one-year burn-in period was discarded and we calibrated sexual network parameters including number of partners, number of sexual contacts, and type of sex until targets were achieved.

Simulation and Analysis

Sexual networks were estimated using *EpiModel v1.5.0*[38] and disease transmission models were implemented using the *R Platform for Statistical Computing v3.6.3*. For each scenario, we simulated the model 25 times over 10 years of follow-up and used means and simulation intervals (2.5% and 97.5% quantiles) to summarize the results. Primary outcomes of interests included the cumulative incidence per 1,000 SMM over follow-up and percentage of infections prevented attributable to doxycycline PEP when condom use fail at year 10. Annotated source code and simulated datasets can be downloaded from https://doi.org/10.5281/zenodo.5116284.

To determine whether our results were robust to the assumptions of our sexual behaviour parameters, we conducted two sensitivity analyses. First, we evaluated the percentage of infections prevented attributed to doxycycline PEP when condoms failed at year 10 by quartiles of annual sexual partners. Second, we assessed the cumulative incidence and percentage of infections prevented after increasing the frequency of sex acts in our models by 25% and 50%.

RESULTS

All simulations started with 10,230 agents to be reflective of the number of HIV-negative and positive SMM that were considered high risk for syphilis in Philadelphia. After discarding the burn-in period, the aggregated baseline prevalence of anal syphilis was 7.1% and 5.8% for oral syphilis. The mean number of agents at the end of the 10-year simulation was 15,000 (standard deviation = 75.3) after allowing for population migration. Agents had a median number of 17 sex partners (interquartile range: 7 – 31) and engaged in a median of

861 sex acts (oral, anal, or both; interquartile range: 330 – 1584). Approximately 67.5% had ≥10 sexual partners over the 10-year period.

Figure 1 compares annual surveillance data from Philadelphia to model predictions over a nine-year period. For both HIV and syphilis, the surveillance data from 2010 to 2018 were consistent with of the simulated number of new cases, and largely were captured within the simulation intervals. The consistency over time between simulated outcome and surveillance data indicated that our models produced estimates that paralleled surveillance data and could be used to predict future syphilis incidence.

Over the 10-year intervention period, increasing levels of adherence modified the association between doxycycline PEP uptake and cumulative syphilis incidence, with adherence having the greatest impact on syphilis incidence under scenarios of higher uptake levels (Figure 2). Results were similar when we stratified by anatomic site of infection (Supplemental Figure 1 and 2). Without any doxycycline PEP, the cumulative incidence at year 1, 5, and 10 were 51.7, 279.2, and 567.7 per 1,000 SMM. Assuming a population level uptake of 20% among SMM, an adherence level of 100% was projected to reduce the cumulative incidence of syphilis by 11.6% (66 fewer cases per 1,000 SMM) relative to base scenario (i.e., no adherence) over the intervention period, compared to 2.2, 5.6, 6.2, and 10.0% reduction with 20, 40, 60, and 80% adherence, respectively. Even with an uptake level of 100%, our models projected that with 100% adherence, there would only be a reduction of syphilis incidence by 55.3%, translating to 314 fewer cases per 1,000 SMM.

At year 10, the proportion of syphilis infections prevented by doxycycline PEP also varied by levels of uptake and treatment adherence (Figure 3). Assuming an uptake level of 20% and adherence level of 80%, doxycycline PEP prevented 22% of infections in the instances where condom use failed. Although increasing levels of doxycycline PEP uptake and adherence lead to a greater proportion of syphilis infections that were prevented, the maximum proportion of infections prevented peaked at 63%. Similar patterns were demonstrated after stratifying by anatomic site of infection (Supplement Figure 3 and 4).

Results of our sensitivity analyses were robust to our sexual behaviour parameter assumptions. For instance, even among SMM in the highest quartile of annual sexual partners (32 – 156 partners), with an uptake and adherence level of 20% and 80%, respectively, doxycycline PEP prevented 26% of infections when condom use failed (Supplemental Figure 5). Likewise, when we assumed a 50% increase in the frequency of sex acts, there were few changes to the cumulative incidence and percentage of infections prevented (Supplemental Figure 6 – 9). At an uptake and adherence of 100%, we could expect a 54.4% reduction in syphilis incidence relative to the base scenario (665 cases per 1,000 SMM), or 362 fewer cases per 1,000 SMM.

DISCUSSION

Our model indicated that implementation of doxycycline PEP would result in modest declines in the cumulative incidence of syphilis among SMM over a 10-year period. Assuming an uptake scenario of 20% (a plausible level of uptake) and an adherence level

of 80% (similar to prior clinical trials with 84% adherence),[9] syphilis incidence decreased only by 10% over follow-up (57 fewer cases per 1,000 SMM). At year 10, we also found evidence that under realistic level of uptake (20%) and adherence (80%) among SMM, doxycycline PEP would prevent roughly one-quarter of syphilis infection in the instances where condom use failed. These data suggest that doxycycline PEP might be most beneficial as a targeted prevention strategy for syphilis infections that are often underdiagnosed such as oral secondary syphilis.[39]

Prior modelling work has evaluated the impact of chemoprophylaxis on syphilis in the absence of other interventions or behavioural change among Australian SMM, suggesting a substantial reduction in syphilis after 10 years.[10] Our work differs from the Australian study, in that we specifically considered how doxycycline PEP could be implemented within the context of existing prevention strategies and whether different assumptions of adherence would modify the population level effectiveness of doxycycline PEP uptake on syphilis incidence. Furthermore, the Australian model was developed before the HIV PrEP era, with levels of greater condom use and fewer syphilis transmission than the current period.[40] Despite some limitations with our modelling assumptions (i.e., infections prevented attributable to doxycycline PEP only occurred during sex events where condom use failed), our results underscore the importance of incorporating existing prevention strategies and treatment adherence to estimate the population level effect of a chemoprophylactic regimen within the current STI prevention context.

We choose to estimate the impact of doxycycline PEP on syphilis incidence, rather than doxycycline PrEP, to replicate a more realistic scenario that could be optimized to mitigate the growing syphilis incidence. The primary concerns with uptake of doxycycline PrEP is the increased likelihood of selecting antibiotic-resistant microorganisms[41] and potential side effects (e.g., gastrointestinal symptoms, pruritic skin reactions, and photosensitivity) due to daily long-term use.[42,43] Although there are similar concerns with doxycycline PEP, tolerability of doxycycline PrEP is unclear and the potential for antibiotic-resistant bacteria due to prolong use possesses a threat to public health (i.e., diseases which are currently treatable with antibiotics may become life-threatening if current treatments stopped working). Our data suggest that implementing doxycycline PEP, which can be used as a temporary prophylactic intervention among SMM, may contribute to population-level syphilis control over time when used in conjunction with condoms and STI screening.

Our findings should be interpreted considering the following limitations. First, to make the complex natural history of syphilis infection into a tractable problem, we combined primary and secondary syphilis infection as well as assumed that agents in the early latent stage of infections remained latent until treatment or the end of the simulation. This is in concordance with literature to suggest that the latent stage of infection can last for >10 years.[3] We also did not model spontaneous re-emergence of symptoms for agents in the latent stage as there is limited data to indicate how this might differ by demographic characteristics and impact transmission probability. However, re-emergence of symptoms among those with latent infection is uncommon and would likely have little effect in the per-contact probability of syphilis infection. Second, we assumed concordance between penile and anal infections for anogenital syphilis; however, this may not be the case. Given prior

evidence on the anatomic site of chancres among men diagnosed with primary syphilis,[44] it is possible that our models have underestimated the incidence of anal infections. Third, transmission rates of syphilis may have also been underestimated given that we did not allow for concurrent partnerships, but evidence suggest that concurrent partnerships may not necessarily be frequent[45] or result in a higher risk of STI compared to sexual dyads due to increased condom use.[46] Fourth, we did not explicitly include changes of sexual behaviours due to HIV PrEP uptake in our model, which may have led to underestimating the population-level effectiveness of doxycycline PEP on syphilis incidence. Future work may need to consider how different projections of HIV PrEP uptake may affect syphilis transmission. Finally, inputs for sexual behaviours and HIV infection dynamics were taken from other populations, which may not be transportable to SMM in Philadelphia,[47] where we did not have such measures. However, the ability of our models to successfully calibrate to Philadelphia surveillance data suggested validity of the model inputs.

Our results have important implications for the role of doxycycline prophylaxis as an intervention for syphilis prevention. Although uptake led to decreased syphilis infection, potential impacts were moderate. Doxycycline PEP could not compete with the current effectiveness of condom use (when used consistently and correctly) in combination with routine STI testing and treatment unless we assume extreme, and likely unrealistic, levels of doxycycline uptake and adherence. From a public health perspective, persuading a large percentage of the SMM population to take doxycycline regularly may prove to be difficult, especially with the concerns regarding antibiotic resistance and possible side effects.[41,48] These results underscore the need to emphasize routine STI screening and treatment as well as condom use as the primary strategy to prevent syphilis transmission. The use of doxycycline PEP in targeted interventions as a secondary measure in combination with other prevention strategies is possibly the more feasible public health approach given the available evidence around bacterial STI chemoprophylaxis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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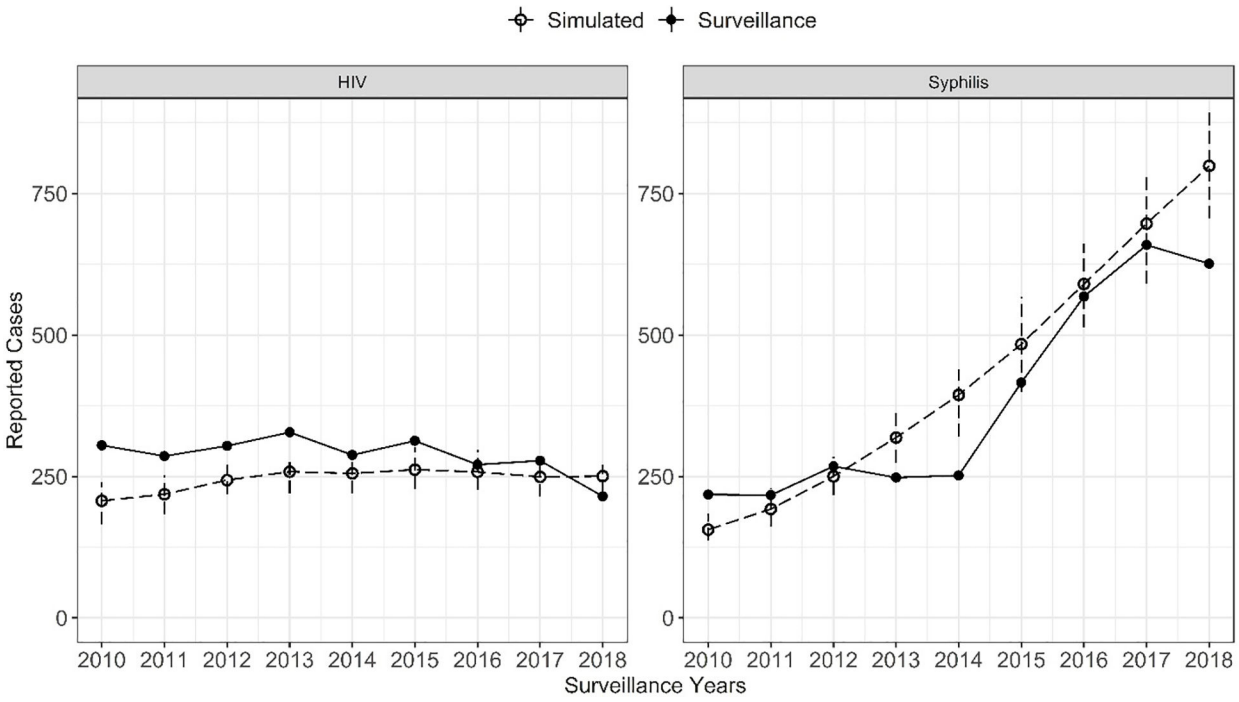

Figure 1.

Calibration results predicting nine-year HIV and syphilis incidence among sexual minority men compared to Philadelphia surveillance. Error bars indicate simulation intervals (2.5% and 97.5% quantiles) across 25 iterations. A one-year burn-in period was discarded.

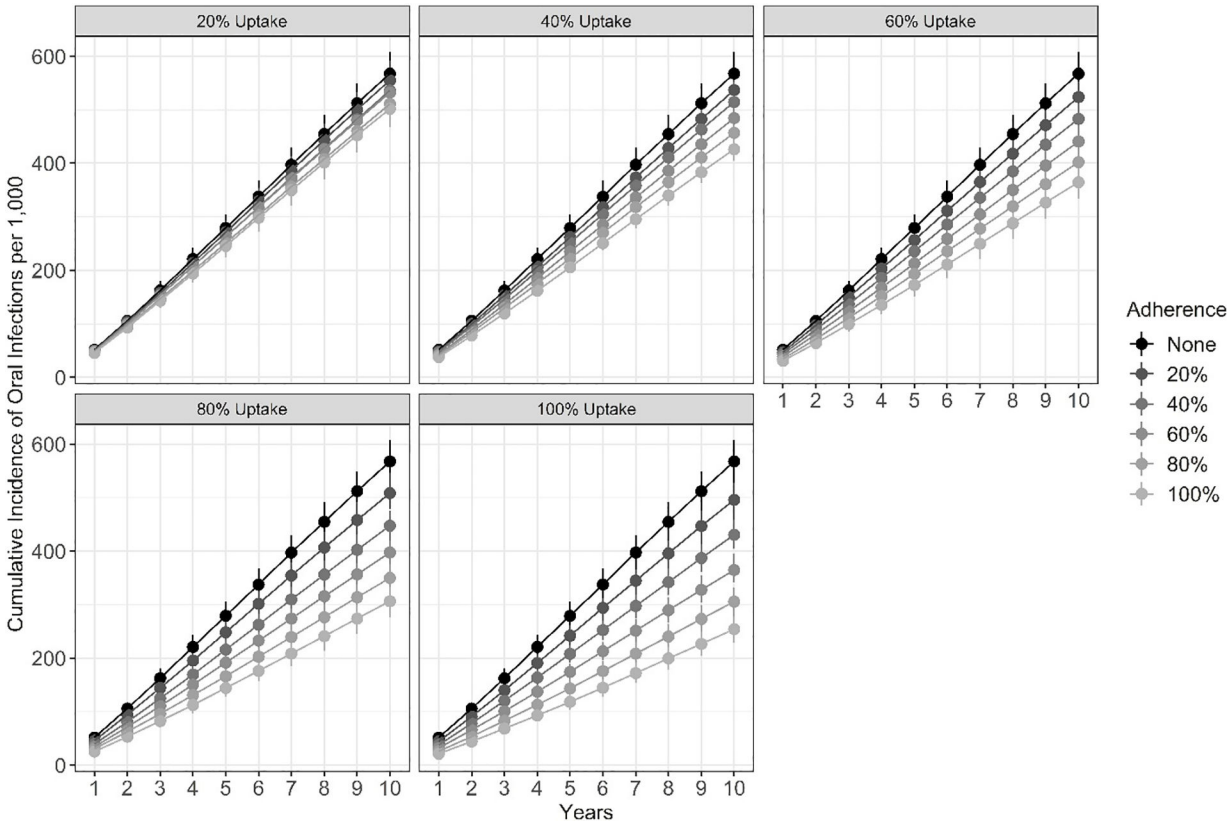

Figure 2.

Cumulative incidence of syphilis infections under varying doxycycline prophylaxis uptake and adherence levels among sexual minority men over 10 years. Error bars indicate simulation intervals (2.5% and 97.5% quantiles) across 25 iterations.

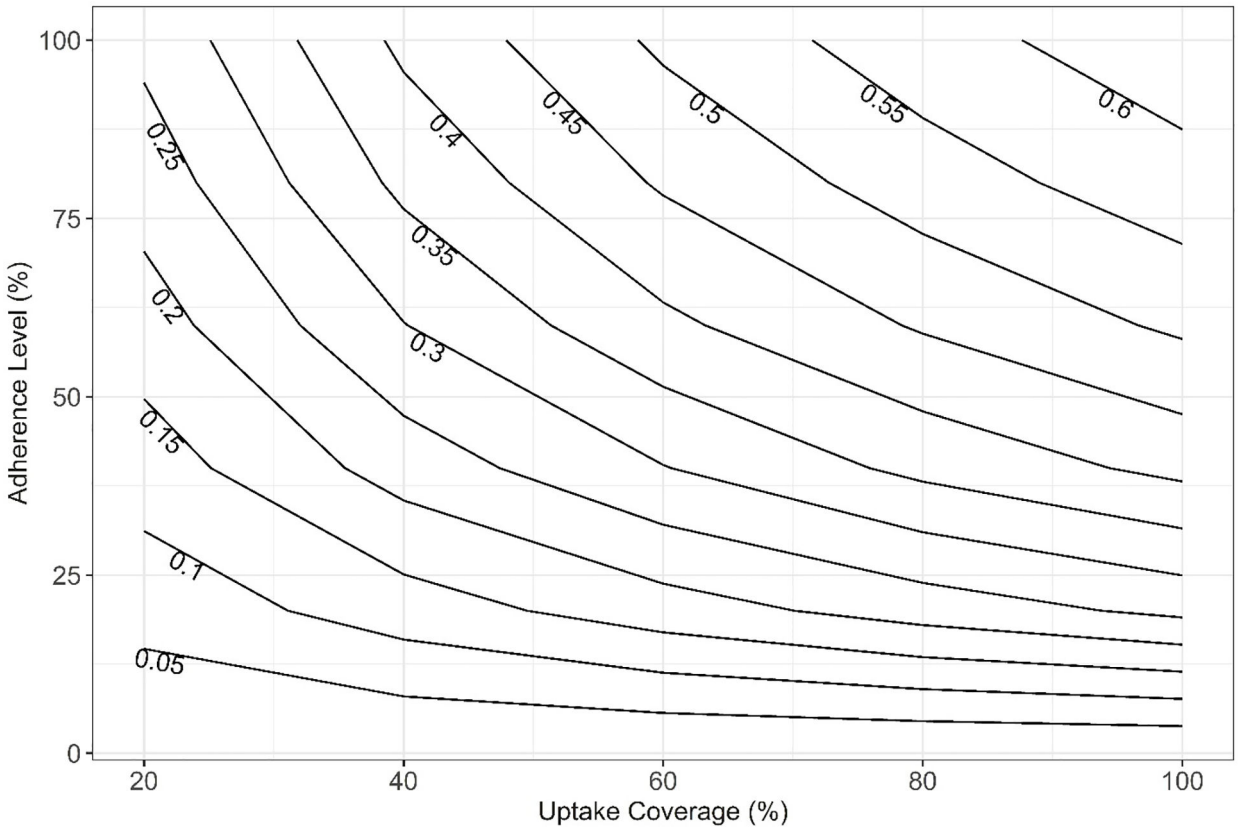

Figure 3.
Proportion of infections prevented for syphilis under varying doxycycline prophylaxis uptake and adherence levels among sexual minority men at year 10 of 25 simulations.

Table 1.

Assumptions and input parameters for men who have sex with men syphilis simulation model.

Parameter	Values	Population	Year	Source
Demographic				
Hypothetical location of simulation	Philadelphia, PA	NA	NA	Assumption
Age of SMM population	≤24 years: 23% >24 years: 77%	Philadelphia	NA	ACS & literature[14]
Size of SMM population (number of agents in model)[a]	10,230	Philadelphia & SMM from 21 cities in the US (NHBS) (Supplemental Appendix 1 for more details)	2008 & 2015	Literature[14,49,50]
Racial breakdown of SMM population	White: 37% Non-white: 63%	Philadelphia	NA	ACS & literature[14]
Entry and exit rate from the study population per year	12.8%	Philadelphia	NA	ACS
Sexual behavior				
Expected number of sexual partners per year[b,c]	Gamma (0.5,10)	National sample of SMM in Australia	1997	Literature[23,24]
Expected number of sexual acts per year	Poisson (80.6)	Online sample of SMM in US	2009	Literature[25]
Probability of same-race partner selection	White: 50% Non-white: 7%	TLS sample of SMM in San Francisco, California, US	2007–2008	Literature[17]
Sexual act(s) performed for a given encounter	Anal only: 22% Oral only: 44% Both: 34%	SOPV sample of SMM in Melbourne, Australia & online sample of SMM in US	2007 & 2011	Literature[20,21]
Mean duration of sexual partnerships	100 days	NA	NA	Assumption
Anal sexual positioning for a given encounter[d]	Insertive only: 24% Receptive only: 32% Both: 44%	TLS sample of SMM in Atlanta, Georgia, US	2011–2013	Literature[22]
Oral sexual positioning for a given encounter[d]	Insertive only: 16% Receptive only: 14% Both: 70%	SOPV sample of SMM in Melbourne, Australia & online sample of SMM in US	2007 & 2011	Literature[20,21]
Distribution of condom use for anal intercourse, white	100% of time: 23% 75% of time: 20% 50% of time: 15% 25% of time: 14% Never: 28%	SMM in US	NA	Literature[30]
Distribution of condom use for anal intercourse, non-white	100% of time: 27% 75% of time: 22% 50% of time: 17% 25% of time: 14% Never: 20%	SMM in US	NA	Literature[30]
Condom use for oral intercourse	4%	SMM attending sexual health clinic in Melbourne, Australia	2015	Literature[31]

Parameter	Values	Population	Year	Source
Condom effectiveness, per sex-act	Anal: 70.5% Oral: 70.5%	Estimate from 2 HIV prevention trials in the United States (VAX 004 and Project Explore)	1998–2001	Literature (anal)[32] & assumption (oral)
Syphilis				
Stage of infection	Primary/secondary: 56% Early latent: 44%	SMM in US	NA	Literature[27]
Prevalence of anal syphilis, white, ≤ 24 years[e]	Anal, HIV−: 0.5% Oral, HIV−: 0.4% Anal, HIV+: 0.3% Oral, HIV+: 0.3%	Estimate from meta-analysis of trials and demonstration studies (Supplemental Appendix 1 for more details)	NA	ACS & Literature[26–28]
Prevalence of oral syphilis, non-white, ≤ 24 years[e]	Anal, HIV−: 0.8% Oral, HIV−: 0.7% Anal, HIV+: 0.6% Oral, HIV+: 0.5%	Estimate from meta-analysis of trials and demonstration studies (Supplemental Appendix 1 for more details)	NA	ACS & Literature[26–28]
Prevalence of anal syphilis, white, > 24 years[e]	Anal, HIV−: 1.6% Oral, HIV−: 1.4% Anal, HIV+: 1.1% Oral, HIV+: 0.9%	Estimate from meta-analysis of trials and demonstration studies (Supplemental Appendix 1 for more details)	NA	ACS & Literature[26–28]
Prevalence of oral syphilis, non-white, > 24 years[e]	Anal, HIV−: 2.7% Oral, HIV−: 2.3% Anal, HIV+: 1.8% Oral, HIV+: 1.6%	Estimate from meta-analysis of trials and demonstration studies (Supplemental Appendix 1 for more details)	NA	ACS & Literature[26–28]
Frequency of syphilis testing among HIV+	3mos: 25% 6mos: 21% 12mos: 28% Never: 29%	HIV+ SMM in the US from the Medical Monitoring Project	2013–2014	Literature[35,51]
Frequency of syphilis testing among HIV−	12mos: 31% Never: 69%	HIV− SMM in Baltimore, Maryland, US	2004–2011	Literature[34,35]
Efficacy of penicillin treatment after testing	95%	A review including multiple different populations	2014	Literature[36]
HIV				
Baseline prevalence of being HIV seropositive	≤24 years, white: 2.3% >24 years, non-white: 13.6% ≤24 years, white: 19.3% >24 years, non-white: 32.4%	SMM in Philadelphia, Pennsylvania, US (NHBS)	2014	NHBS
Knowledge of HIV status	HIV−: 36.9% HIV+: 44.0%	SMM from 21 cities in the US (NHBS)	2008	Literature[52]
Last tested for HIV	<6mos: 19% 6–12mos: 11% >12mos: 36% Never: 30%	SMM in US	NA	Literature[30]
Treatment as prevention	42%	SMM in US	2010	Literature[53]
Seroadaption, HIV−	Insertive: 9.5% Serosort: 30.7% Neither: 59.8%	SMM in San Francisco, California, US (NHBS)	2011	Literature[18]
Seroadaption, HIV+	Receptive: 13.3% Serosort: 21.4% Neither: 65.3%	SMM in San Francisco, California, US (NHBS)	2011	Literature[18]

Parameter	Values	Population	Year	Source
Seroadaption, HIV?	Insertive: 5.3% Serosort: 32.1% Neither: 62.6%	SMM in San Francisco, California, US (NHBS)	2011	Literature[18]
HIV− and on pre-exposure prophylaxis[f]	18.4%	SMM in Philadelphia, Pennsylvania, US (NHBS)	2014, 2017	Literature[54]
Transmission				
Duration syphilis infection by stages of infection	Primary/secondary: 1 year Early latent: 10 years	NA	NA	Literature[3]
Per sex-act probability of anal syphilis transmission[g]	Primary/secondary: 1.0% Early latent: 0.5%	Online sample of SMM in Sydney, Australia	2009	Literature[10,55,56] and Assumption
Per sex-act probability of oral syphilis transmission[g]	Primary/secondary: 0.4% Early latent: 0.2%	Online sample of SMM in Sydney, Australia	2009	Literature[10,55,56] and Assumption
Per sex-act probability of anal transmission for primary HIV	Receptive: 12.8% Insertive: 5.7%	SMM in the United Kingdom	NA	Literature[57]
Per sex-act probability of anal transmission for chronic HIV	Receptive: 1.3% Insertive: 0.6%	SMM in the United Kingdom	NA	Literature[57]
Per sex-act multiplicative increase in transmission probability for HIV−infected men	2.0	NA	NA	Literature[29]
Doxycycline				
Clinical efficacy	73%	SMM participating in a clinical trial in Lyon, France	2016	Literature[9]
Population uptake of treatment regimen	20%, 40%, 60%, 80%, 100%	NA	NA	Assumption
Adherence to treatment regimen	0%, 20%, 40%, 60%, 80%, 100%	SMM participating in a clinical trial in Lyon, France	2016	Literature[9] and Assumption

ACS, American Community Survey 2016 5-year estimates; *HIV*, human immunodeficiency virus; *NHBS*, National HIV Behavioural Surveillance Philadelphia 2014 and 2017; *SMM*, sexual minority men; *PrEP*, pre-exposure prophylaxis; *TLS*, time-location sampling; *SOPV*, sex-on-premises venues.

[a]Population of high risk SMM was calculated by applying estimate of potentially PrEP eligible HIV negative and HIV positive SMM to estimated SMM population in Philadelphia county.

[b]Gamma distribution represents a right-skewed distribution of number of partnerships.

[c]We adapted a similar method of modelling the expected number of partners based on a study of non-cohabiting sex partners in sub-Sharan Africa. However, estimates used to inform the distribution was based on the study of Australian SMM.

[d]Sexual positioning was regarded as a preference. When two agents had the same preference (i.e. insertive /insertive or receptive/receptive) we applied a “scale of dominance” approach whereby the agent regarded as more dominant had their preference honoured.

[e]Baseline syphilis prevalence was calculated from multiplying a pooled incidence rate with the average duration of disease. Estimates specific to demographic characteristics, HIV status, and stage of syphilis infection were calculated by multiplying the proportion of each parameter together.

[f]Average prevalence of HIV PrEP uptake for 2014 and 2017.

[g]The relative infectiousness of primary versus secondary syphilis and insertive versus receptive is unknown. In the absence of reliable data, we assume uniform infectiousness over the duration of infectious syphilis stages and sexual positioning. The probability of transmission during the

early latent stage is assumed to be half the probability in the primary and secondary stages. We assume that penile-oral sex has a lower transmission probability per act than penile-anal sex.