Impact of screening and doxycycline prevention on the syphilis epidemic among men who have sex with men in British Columbia: a mathematical modelling study

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The Lancet Regional Health - Americas 2024;33: 100725

Published Online xxx
https://doi.org/10.1016/j.lana.2024.100725

Summary

Background Men who have sex with men (MSM) in British Columbia (BC) are disproportionately affected by infectious syphilis and HIV. In this study, we developed a co-interaction model and evaluated the impact and effectiveness of possible interventions among different MSM subgroups on the syphilis epidemic.

Methods We designed a deterministic compartmental model, which stratified MSM by HIV status and HIV pre-exposure prophylaxis (HIV-PrEP) usage into (1) HIV-negative/unaware MSM (HIV-PrEP not recommended, not on HIV-PrEP), (2) HIV-negative/unaware MSM with HIV-PrEP recommended (not on HIV-PrEP), (3) HIV-negative/unaware MSM actively on HIV-PrEP, and (4) MSM diagnosed with HIV. We estimated the effect of scaling up syphilis testing frequency from Status Quo to six-, four-, and three-months, increasing the percentage of MSM using doxycycline prevention (Doxy-P) to 25%, 50%, and 100% of the target level, and a combination of both among subgroups (2)–(4). We also assessed the impact of these interventions on the syphilis incidence rates from 2020 to 2034 in comparison to the Status Quo scenario where no intervention was introduced.

Findings Under the Status Quo scenario, with the expansion of the HIV-PrEP program to improve syphilis testing, the syphilis incidence rate was estimated to peak at 16.1 [Credible Interval (CI):14.2–17.9] per 1,000 person-years (PYs) in 2023 and decrease to 6.7 (CI:3.8–10.9) per 1,000 PYs by 2034. The syphilis incidence rate in 2034 was estimated at 0.7 (0.3–1.3) per 1,000 PYs if MSM diagnosed with HIV could be tested every four months, and at 1.5 (0.7–3.0) per 1,000 PYs if HIV-negative/unaware MSM actively on HIV-PrEP could be tested every three months. By achieving 100% of the target coverage of Doxy-P, the syphilis incidence rate was estimated at 1.4 (0.5–3.4) if focusing on MSM diagnosed with HIV, and 2.6 (1.2–5.1) per 1,000 PYs if focusing on HIV-negative/unaware MSM actively on HIV-PrEP. Under the combined interventions, the syphilis incidence rate could be as low as 0.0 (0.0-0.1) and 0.8 (0.3–1.8) per 1,000 PYs, respectively.

Interpretation The HIV-PrEP program in BC plays a crucial role in increasing syphilis testing frequency among high-risk MSM and reducing syphilis transmission among this group. In addition, introducing Doxy-P can be an effective complementary strategy to minimize syphilis incidence, especially among MSM diagnosed with HIV.

Funding This work was funded by the Canadian Institutes of Health Research.

Keywords: Men who have sex with men; MSM; Syphilis; HIV; Pre-exposure prophylaxis; Interventions; Testing frequency; Doxycycline prophylaxis; Incidence rate

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Research in context

Evidence before this study

Since the early 2000s, the rates of infectious syphilis have been increasing steadily in Canada, disproportionately affecting men who have sex with men (MSM). In British Columbia, Canada, the number of MSM diagnosed with infectious syphilis increased from 154 in 2011 to 737 in 2022. We searched for articles from PubMed and abstracts from the Conference on Retroviruses and Opportunistic Infections (CROI) and AIDS conferences. We included a combination of the search terms "syphilis", "gay, bisexual and other men who have sex with men", "gbMSM", "men who have sex with men", "MSM", "HIV", "HIV-PrEP", "doxycycline", "doxycycline prophylaxis", "mathematical model", and "syphilis testing". These studies show that the uptake of syphilis testing is low, and increasing syphilis testing and treatment remains vital to prevent onward transmission among MSM. Additionally, they showed that doxycycline prevention is a promising complementary strategy.

Added value of this study

To the best of our knowledge, this is the first study to use mathematical models to explore the potential impact of doxycycline implementation among MSM and improving syphilis testing frequency in reducing the syphilis incidence rates among these individuals. This study was conducted in a setting where HIV pre-exposure prophylaxis (HIV-PrEP) is publicly funded and widely available. By improving syphilis testing frequency and introducing doxycycline prevention (Doxy-P), the incidence of syphilis can be significantly reduced from the current levels. We also highlighted that increasing syphilis testing frequency among MSM who use Doxy-P is the best-suited intervention, especially among MSM diagnosed with HIV.

Implications of all the available evidence

The results of this study reflect the impact of an HIV-PrEP program and identify the MSM subgroup at the highest risk of infection that needs to be targeted to reduce the burden of syphilis. Our findings suggest that in addition to focusing on MSM diagnosed with HIV who are already linked to care, other strategies to increase enrollment of HIV-negative MSM into the HIV-PrEP program and improve access to self-testing and point-of-care testing can lead to early syphilis diagnosis and treatment, and prevent onward transmission. As Doxy-P continues to gain traction and concerns about antimicrobial resistance are addressed, this prevention strategy could benefit all at-risk populations.

Introduction

Infectious syphilis diagnoses have been increasing in Canada for the past 20 years, disproportionately affecting men who have sex with men (MSM).[1] In British Columbia (BC), Canada, 1,973 individuals were diagnosed with infectious syphilis in 2022, and 37% of those affected were MSM, while MSM accounts for less than 5% of BC's population.[2,3] Similarly, the MSM population is disproportionately affected by the HIV epidemic, an important consideration in understanding the transmission dynamics of infectious syphilis in this population.[4] People living with HIV (PLWH) frequently experience syphilis infections and reinfections.[5] In BC, based on the most recent information available in 2017, MSM living with HIV accounted for approximately 43% of MSM syphilis diagnoses.[6] The syndemic of HIV and syphilis is concerning and calls for further investigation as syphilis infections among HIV-negative MSM are strongly associated with increased risk of HIV transmission.[7] While serious complications are rare, MSM may experience unusual and more serious sequelae from syphilis infections, including ocular syphilis.[8]

In BC, the Treatment as Prevention (TasP) strategy has led to a significant decline in HIV-related morbidity, mortality, and new HIV diagnoses.[9] To further prevent HIV transmission among at-risk groups, HIV pre-exposure prophylaxis (HIV-PrEP) has been publicly funded and widely available since January 2018 in BC.[10] Since the implementation of the HIV-PrEP program, the number of new HIV cases among MSM has declined substantially and was below 100 in 2019 for the first time since the 1980s.[11] According to a recent mathematical modelling study, HIV elimination in BC was possible with TasP optimization and further expansion of HIV-PrEP to high-risk MSM, which achieved less than one new HIV case per 1,000 susceptible MSM as early as 2024.[12]

One possible reason for the persistent high syphilis diagnoses is specific sexual behaviours among sexual networks of MSM.[13–16] For example, choosing sexual partners with the same HIV status (i.e., serosorting) and using recreational drugs before or during sex (i.e., chemsex) may likely increase condomless anal sex.[13,14] In addition, HIV-PrEP uptake has been associated with increased syphilis ascertainment through an increase in syphilis testing frequency as recommended by HIV-PrEP protocols.[15] HIV-PrEP is also associated with syphilis diagnosis via sexual risk behaviours, such as more anal sex partners.[16] Educational campaigns promoting syphilis awareness and testing are one strategy to support syphilis prevention but have had limited impact on syphilis rates.[17] Novel approaches (e.g., antibiotic pre-exposure or post-exposure prophylaxis) have recently been shown to be potentially effective in preventing the spread of syphilis among MSM. Specifically, studies have shown promising potential for the use of doxycycline as pre-exposure or post-exposure prophylaxis (Doxy-PrEP or Doxy-PEP, hereafter referred to as

Doxy-P) used as a sexually transmitted infection (STI) prevention strategy. Doxy-PEP after condomless sex has been shown to reduce the incidence of bacterial STIs, including syphilis, by over 70% among MSM and transgender women on HIV-PrEP, as well as PLWH who had an STI episode in the previous year.[18] Doxy-PrEP has also shown encouraging results in pilot studies involving MSM, albeit with a smaller sample size.[19] The recent success of the DoxyPEP study (ClinicalTrials.gov number: NCT03980223), which was conducted in San Francisco and Seattle with 637 participants (the largest trial so far), is only starting to be incorporated into STI management guidelines.[20]

Given these therapeutic advances and the significant effect that increasing syphilis testing frequency can have in controlling the syphilis epidemic, we modified our previously published mathematical model of HIV and syphilis co-interaction in an environment of widely expanding HIV-PrEP.[21] We used the model to evaluate the impact and effectiveness of optimizing syphilis testing frequency and introducing Doxy-P among different MSM population subgroups on the syphilis epidemic in BC.

Methods

HIV and syphilis transmission model

Our previous theoretical deterministic compartmental model for the co-interaction of HIV and syphilis transmission among MSM was modified and calibrated to BC's setting, considering the HIV-PrEP program's implementation in 2018.[21] Our new model consisted of 18 compartments, representing different health states of the MSM population, specified by HIV and syphilis disease progression and the status of HIV-PrEP use.

The model schematic is shown in Fig. 1. New MSM entered the model as individuals susceptible to both HIV and syphilis (S) at a rate $\vec{\pi}$, which was determined by the growth rate of the male population in BC. Susceptible MSM acquired HIV and became undiagnosed HIV-positive (U_H) at a rate $\vec{\lambda}_H$, determined by the HIV transmission probability (per year) among partners who engage in unprotected (not protected by condoms or HIV-PrEP) anal sex (UAS), number of anal sex partners, condom use, and status of HIV-PrEP use. The undiagnosed HIV-positive MSM were tested and moved to the aware compartment (A_H) at a rate $\vec{\alpha}$. The MSM diagnosed with HIV initiated antiretroviral treatment (ART) and entered the on-ART compartment (T_H) at a rate ρ. Those in the on-ART compartment who experienced treatment interruption moved to the off-ART compartment (O_H) at a rate ν_{off}, and then re-engaged with HIV care and were back on ART at a rate ν_{on}, shown as the cyclical process between T_H and O_H.

For syphilis transmission, susceptible MSM were infected with syphilis and became syphilis-positive (I_S) at a rate $\vec{\lambda}_S$, which was determined by the syphilis transmission probability per UAS (not protected by condoms or Doxy-P) partner per year, number of anal sex partners, condom use, and possible use of Doxy-P. Then those with infectious syphilis were diagnosed, treated, and became susceptible to syphilis again at a rate $\vec{\sigma}_S$. Similarly, syphilis acquisition, diagnosis, and treatment among HIV-positive MSM were shown as the cyclical process between HIV-positive compartments (U_H, A_H, T_H, O_H) and co-positive compartments (U_{HS}, A_{HS}, T_{HS}, O_{HS}). The transmission rates ($\vec{\lambda}_{S_U}$, λ_{S_A}, λ_{S_T}, λ_{S_O} for compartments U_H, A_H, T_H, O_H respectively) and testing and treatment rates ($\vec{\sigma}_U$, σ_A, σ_T, σ_O) for syphilis were greater than the ones for susceptible MSM if among MSM diagnosed with HIV, and were assumed to be the same as the ones for susceptible MSM if among undiagnosed HIV-positive MSM. The HIV acquisition rates among syphilis-positive MSM, $\gamma\vec{\lambda}_H$, were higher than among syphilis-negative MSM, where the parameter γ (γ>1) represented the higher relative risk of HIV acquisition among syphilis-positive MSM. The HIV progression process among syphilis-positive MSM was similar to syphilis-negative MSM. The mortality rate for each compartment was determined by the HIV disease stage, and we assumed that no excess deaths were caused by infectious syphilis, even though early syphilis can cause death in rare cases.[22] For HIV-negative/unaware MSM (S, I_S, U_H, U_{HS}), states of actively on HIV-PrEP were introduced in 2016 when Health Canada approved HIV-PrEP.[23] Those not on HIV-PrEP were further stratified into two subgroups: HIV-PrEP not recommended (lower HIV/syphilis acquisition risk) and HIV-PrEP recommended (higher HIV/syphilis acquisition risk). The number of newly enrolled active HIV-PrEP users was modelled by sigmoid functions, increasing from 2016 to 2020, and it was assumed to be half of the 2021 level of new enrollments by 2025.[24]

The transition rates in Fig. 1 were estimated through either literature or calibration (Supporting Information in Supplementary Tables S1 and S2). The model was calibrated to fit the HIV and syphilis epidemic indicators in BC from multiple data sources: (1) the estimates of HIV prevalence and incidence of the MSM population from the Public Health Agency of Canada[25]; (2) the estimated percentages of MSM diagnosed with HIV, MSM with ART initiation, and MSM currently on ART from our previous modelling study, based on historical data obtained from the BC Centre for Excellence in HIV/AIDS (BC-CfE)[12]; (3) the annual number of HIV diagnosis among MSM obtained from the BC-CfE[11]; and (4) the annual number of infectious syphilis diagnosis among all MSM in BC, and the percentage of those diagnosed with HIV obtained from annual reports from the BC Centre for Disease Control.[26] In addition, to account for the impact of the HIV-PrEP program in BC, the model was calibrated to fit the number of infectious syphilis and HIV diagnoses among active HIV-PrEP users in 2018 and 2019.[12,24] The MSM population was

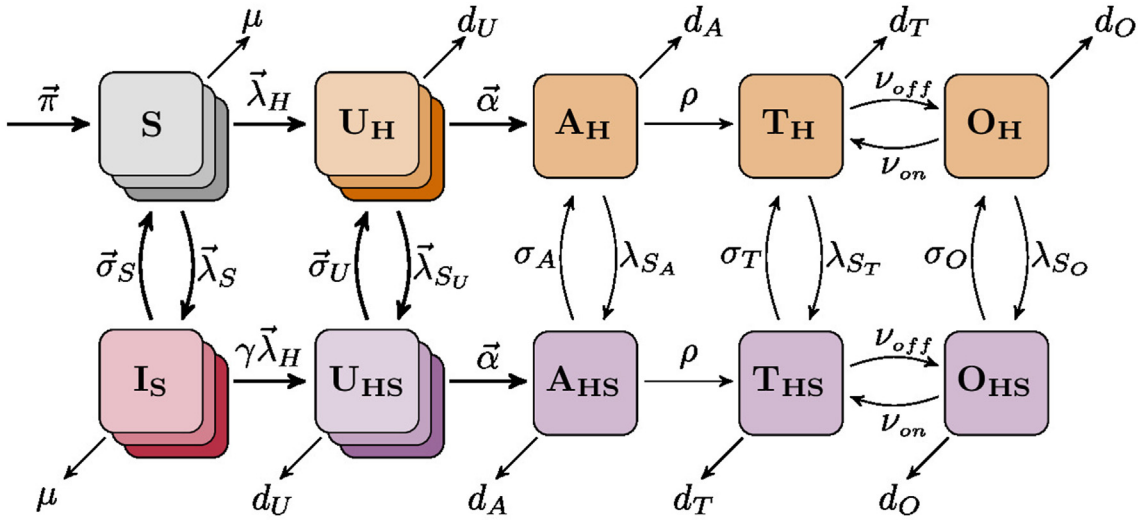

Fig. 1: Model schematic for HIV and syphilis transmission and disease progression.

assumed to grow over time and the size of the population was assumed to be 50,900 in 2015.[27]

For the calibration process, we first calibrated the model to fit the HIV and syphilis epidemics separately, and then, we re-calibrated the model to fit both epidemics simultaneously. The initial conditions were chosen from 1,000 sets based on the Latin Hypercube sampling method that gave the smallest squared residual between model simulation and historical data.[28,29] Finally, we re-calibrated the co-interaction model to best fit the data from 2011 to 2019, based on 1,000 sets of different parameter values, sampled by the Latin Hypercube method, to account for the parameter uncertainty from the literature.

The model calibration and simulations were implemented using the NUMPY and SCIPY libraries in Python™.[30,31] A detailed description of the model structure, parameters, and calibration process can be found in the Supporting Information in the Supplementary Material.

Modelling scenarios

Once calibrated, model simulations were projected from 2020 to 2034 with different interventions introduced in 2020. Under the Status Quo scenario, different testing frequencies for infectious syphilis among different subgroups were kept the same as those in 2019 (Table 1), and no Doxy-P was provided. We evaluated the impact of the implementation of the HIV-PrEP program in BC by a series of counterfactual scenarios: (1) HIV-PrEP was never introduced; (2) the combined testing and treatment rate for infectious syphilis among those actively on HIV-PrEP was assumed to be the same as those not on HIV-PrEP; (3) the percentage of MSM actively on HIV-PrEP who consistently used condom was assumed to be zero, to explore the impact of the HIV-PrEP program in BC in curbing the syphilis epidemic with lower condom use than the Status Quo scenario (i.e., no consistent condom use as the lowest estimate); and (4) expansion of the HIV-PrEP program with an additional 400 active HIV-PrEP users enrolled each year. These counterfactual scenarios were examined to show what could happen under assumptions different from the Status Quo.

To explore the intervention strategies that may curb the syphilis epidemic, we focused on three subgroups with a relatively higher risk of syphilis acquisition: (1) HIV-negative/unaware MSM with HIV-PrEP recommended (not on HIV-PrEP); (2) HIV-negative/unaware MSM actively on HIV-PrEP; and (3) MSM diagnosed with HIV. This classification was based on the heterogeneity of the MSM population, as shown in Table 1. For each subgroup, we examined the effect of the following interventions (Table 2): (1) improving syphilis testing frequency from the Status Quo to every six months (Low), every four months (Medium), and every three months (High) in the model (Note: current guidelines recommend testing every three months for MSM actively on HIV-PrEP and three to six months for those living with HIV, but this is not the case based on recent data)[24,32–34]; (2) implementing Doxy-P by increasing the percentage of MSM using Doxy-P from 0% in 2019 to 25% (Low), 50% (Medium), and 100% (High) of the target level in one year and keeping the percentage fixed until 2034, where the target level was determined by the proportion in each subgroup that was eligible for DoxyPEP study (i.e., the proportion of MSM in each subgroup with bacterial STI diagnosis in the past 12 months), using data from the Momentum Health Study Phase II[18,35]; and (3) improving syphilis

Subgroups	HIV-negative/unaware MSM (HIV-PrEP not recommended, not on HIV-PrEP)	HIV-negative/unaware MSM with HIV-PrEP recommended (not on HIV-PrEP)	HIV-negative/unaware MSM actively on HIV-PrEP	MSM diagnosed with HIV
Population size in 2019[a]	18,978 (15,349–22,516)	24,465 (20,926–28,091)	5,219[c]	4,899 (4,858–4,939)
Population size in 2034[a]	23,780 (19,236–28,172)	20,627 (16,272–25,129)	16,194 (16,187–16,202)	4,679 (4,530–4,836)
Average testing frequency for infectious syphilis[b]	Every 274 days	Every 274 days	Every 143 days	Every 185 days
Condom coverage in 2019 (%)[b]	68.3 (57.5–79.0)	33.4 (24.4–42.4)	19.0 (13.9–24.2)	32.5 (17.5–47.4)
Average number of anal sex partners[b]	2.0 (1.5–2.5)	5.0 (4.0–6.1)	5.9 (4.6–7.1)	6.7 (4.4–9.1)
HIV incidence rate in 2019[a] (per 1,000 PYs)	1.0 (0.7–1.5)	3.7 (3.3–4.2)	0.8 (0.8–0.9)	–
Syphilis incidence rate in 2019[a] (per 1,000 PYs)	3.3 (2.2–4.8)	12.4 (11.2–13.9)	15.7 (13.8–18.0)	80.8 (78.3–82.9)

Note: MSM: men who have sex with men; BC: British Columbia; HIV-PrEP: pre-exposure prophylaxis for HIV; PYs: person-years. Numbers in brackets represent the range between 2.5th and 97.5th percentiles of the estimated population size, sampled condom coverage, average number of anal sex partners, HIV, and syphilis incidence rates in 2019. [a]Based on model simulations under the Status Quo scenario after calibrations. [b]The average testing frequency was estimated as the difference between the reciprocal of the testing and treatment rate and the time from diagnosis to recovery, and details of the other parameters can be found in Supplementary Table S1 in the Supporting Information. [c]Same value for 1,000 simulations after calibrations.

Table 1: **Description of the subgroups among the MSM population in BC considered in the mathematical model under the Status Quo scenario after model calibrations.**

testing frequency similar to (1) among MSM using Doxy-P in (2). In addition, we assessed the effect of the combined interventions (1) and (2) (e.g., under the Medium scenario, improving syphilis testing frequency for all MSM in the specific subgroup to every four months and implementing Doxy-P to 50% of the target level). The effectiveness of Doxy-P was estimated based on the relative risk of any syphilis infection from the Luetkemeyer et al. DoxyPEP study.[18] Of note, no further improvements were made for HIV testing, ART initiation, and adherence in all scenarios since the study interventions targeted the syphilis epidemic.

Main outcomes

Under each scenario, model simulations were projected from 2020 to 2034 for 1,000 different parameter sets. The annual number of incident cases (i.e., new infections) and the incidence rate (per 1,000 person-years [PYs]) were estimated for infectious syphilis and reported as the median and the 2.5th–97.5th percentiles as the credible interval (CI). In addition, we evaluated the effectiveness of improving syphilis testing frequency and use of Doxy-P separately by estimating the number needed to treat (NNT) to avert one syphilis infection from the Status Quo scenario. The NNT was estimated as the number of PYs affected by the intervention scenario divided by the averted number of new syphilis infections.[12,36] We also selected a series of optimal intervention scenarios for each subgroup, similar to the health production function.[37] We plotted each intervention scenario by syphilis infections averted in the y-axis and individuals involved in the intervention program

Interventions	HIV-negative/unaware MSM with HIV-PrEP recommended (not on HIV-PrEP)	HIV-negative/unaware MSM actively on HIV-PrEP	MSM diagnosed with HIV
Testing frequency for syphilis			
Status Quo	Every 274 days	Every 143 days	Every 185 days
Low scenario	Every six months	NA[a]	Every six months
Medium scenario	Every four months	Every four months	Every four months
High scenario	Every three months	Every three months	Every three months
Percentage of MSM using Doxy-P (%)			
Status Quo	0%	0%	0%
Low scenario	3.2%	9.8%	6.5%
Medium scenario	6.5%	19.6%	13.0%
High scenario[b]	12.9%	39.2%	26.0%

Note: MSM: men who have sex with men; HIV-PrEP: pre-exposure prophylaxis for HIV; Doxy-P: Doxycycline pre/post-exposure prophylaxis for syphilis prevention. [a]NA: Not applicable since the testing frequency under the Low scenario is smaller than Status Quo. [b]The percentage of MSM using Doxy-P was increased from 0% (Status Quo) to 25% (Low), 50% (Medium), and 100% (High) of the targeted level, where the targeted level was determined by the proportion in each subgroup that was eligible for DoxyPEP study, using data from the Momentum Health Study Phase II.

Table 2: **Description of intervention scenarios for improving syphilis testing and Doxy-P coverage among the MSM population in BC.**

(total PYs divided by the intervention period) in the x-axis. Starting from the intervention with the smallest NNT as the first optimal intervention, the next optimal intervention was selected based on the smallest incremental NNT compared to the optimal intervention selected before.

Sensitivity analysis

We conducted a univariate sensitivity analysis by estimating the sensitivity coefficients for the syphilis incidence rate under the Status Quo scenario at the end of 2034. The sign of the sensitivity coefficients shows whether the coefficient is positively or negatively associated with the changes in the outcome, and their magnitude reflects how sensitive the outcome is to the change in parameters.[12,38] We also tested the robustness of interventions by varying some parameters with uncertainties: (1) we assumed that the annual new enrollment of active HIV-PrEP users would decrease to a quarter of 2021 level by 2025; (2) we assumed that MSM no longer use condoms once on HIV-PrEP after 2020, in comparison to the assumption under the Status Quo scenario that MSM decreased condom use from 33.4% to 19.0% after on HIV-PrEP; (3) we assumed that MSM have 20.0% more partners once on HIV-PrEP than the number under the Status Quo scenario; and (4) we assumed that the effectiveness of Doxy-P would be as low as 41.0% for all the simulations, which was the lower bound of the 95% confidence interval of the estimated effectiveness of Doxy-PEP.[18]

Ethics

This study received approval from the University of British Columbia ethics review committee at the St Paul's Hospital, Providence Health Care site (H18-00949). Some parameters were estimated based on data from the Momentum Health Study Phase II, which received approval from the University of British Columbia ethics review committee (H16-01226), Simon Fraser University (2011s0691), and the University of Victoria (11–459).

Role of the funding source

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Results

Under the Status Quo scenario, our model estimated that the annual number of syphilis incident cases among MSM was 815 (CI: 769–852) in 2020, peaked in 2023 (892 [791–992]), and then decreased to 434 (245–702) in 2034. The syphilis incidence rate would be 16.1 (14.2–17.9) per 1,000 PYs at the peak in 2023 and decrease to 6.7 (3.8–10.9) per 1,000 PYs in 2034, corresponding to a 56.8% reduction from the 15.6 (15.0–16.0) per 1,000 PYs in 2019 (Supporting Information in Supplementary Tables S6 and S7).

Counterfactual scenarios

Fig. 2 shows syphilis incident cases and rates under counterfactual scenarios relating to the HIV-PrEP program compared to the Status Quo scenario at the end of 2034. Without HIV-PrEP implementation, in 2034, the syphilis incidence rate would increase to 42.4 (32.0–51.8) per 1,000 PYs, along with a 168.1% (128.1%-217.2%) increase from 11,173 (8,878–13,875) to 30,043 (25,598–33,368) in the number of cumulative incident cases compared to the Status Quo (Fig. 2b, Supporting Information in Supplementary Table S9). If the testing frequency for syphilis among those on HIV-PrEP was the same as those not on HIV-PrEP (approximately nine months): the syphilis incidence rate would increase to 64.1 (44.7–86.4) per 1,000 PYs in 2034, and approximately a 220.1% (181.3%-259.5%) increase in the cumulative number of incident cases to 35,775 (27,793–44,249) from the Status Quo scenario (Fig. 2b, Supporting Information in Supplementary Table S9). The model estimated that the syphilis incidence rate in 2034 would be 11.5 (5.9–22.4) per 1,000 PYs if MSM on HIV-PrEP no longer used condoms after 2020 and 4.6 (2.4–7.9) if 400 more MSM were actively receiving HIV-PrEP each year (Fig. 2b).

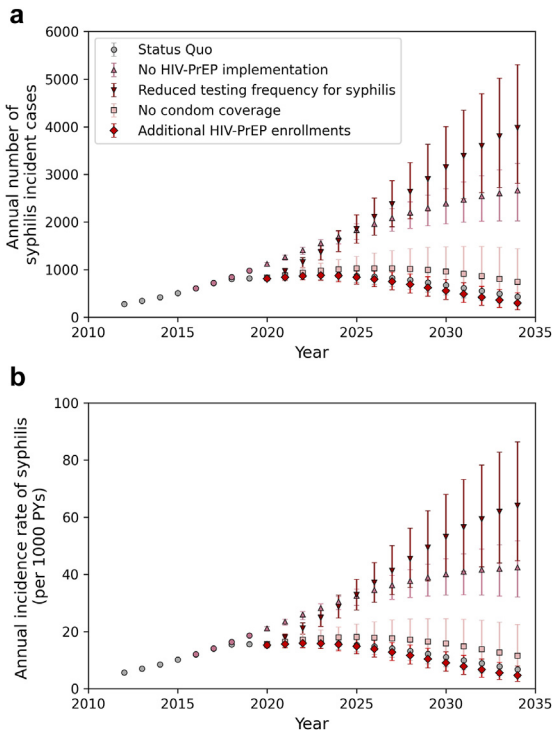

Fig. 2: Annual number of syphilis incident cases (a) and incidence rate (b) under the Status Quo scenario and other counterfactual scenarios.

Interventions to curb the syphilis epidemic

Fig. 3 shows the estimated annual syphilis incidence rates under intervention scenarios with either improved syphilis testing frequency or the introduction of Doxy-P usage between 2020 and 2034, focusing on different subgroups of the MSM population. By improving testing frequency alone, if focusing on HIV-negative/unaware MSM with HIV-PrEP recommended (not on HIV-PrEP) under the Low scenario, the syphilis incidence rate was estimated at 0.6 (0.3–1.0) per 1,000 PYs, representing a 91.5% decrease from the Status Quo in 2034 (6.7 [3.8–10.9] per 1,000 PYs). For MSM diagnosed with HIV, the syphilis incidence rate under the Medium scenario was estimated at 0.7 (0.3–1.3) per 1,000 PYs (90.0% decrease from the Status Quo). If focusing on HIV-negative/unaware actively on HIV-PrEP under the High scenario, the syphilis incidence rate was estimated at 1.5 (0.7–3.0) per 1,000 PYs (77.3% decrease from the Status Quo) (Fig. 3a–c).

Implementing Doxy-P alone, in our environment where over 5,200 MSM (in 2019) were already on HIV-PrEP, would reduce the syphilis incidence rates but not as much as improving the testing frequency (Fig. 3d–f). Under the High scenario (100% coverage of the proportion in each subgroup eligible for Doxy-P as shown in Table 2), the syphilis incidence rate in 2034 was estimated at 1.4 (0.5–3.4) per 1,000 PYs if focusing on MSM diagnosed with HIV, 2.6 (1.2–5.1) per 1,000 PYs if focusing on HIV-negative/unaware MSM actively on HIV-PrEP, and 3.0 (1.6–5.5) per 1,000 PYs if focusing on HIV-negative/unaware MSM with HIV-PrEP recommended (not on HIV-PrEP) (Supporting Information in Supplementary Table S11). These rates represent a 79.7%, 61.7%, and 56.0% decrease, respectively, from the Status Quo.

Fig. 4 shows the impact of interventions that combine improving syphilis testing frequency and Doxy-P implementation on the annual syphilis incidence rate. Improving testing frequency only among those using Doxy-P would reduce the annual syphilis incidence rates to slightly lower than those observed with only Doxy-P (Fig. 4a–c). For example, if focusing on MSM diagnosed with HIV, HIV-negative/unaware MSM actively on HIV-PrEP, and HIV-negative/unaware MSM with HIV-PrEP recommended (not on HIV-PrEP) under the High scenario, the syphilis incidence rate reduced to 1.0 (0.4–2.1), 2.3 (1.1–4.3), and 2.4 (1.4–3.9) per 1,000 PYs, respectively in 2034 (Supporting Information in Supplementary Table S12). In addition, increasing syphilis testing frequency for all MSM in each subgroup and implementing Doxy-P under the High scenario would lower syphilis incidence rates to 0.0 (0.0-0.1), 0.8 (0.3–1.8), and 0.0 (0.0-0.1), if focusing on HIV-negative/unaware MSM with HIV-PrEP recommended (not on HIV-PrEP), HIV-negative/unaware MSM actively on HIV-PrEP, and MSM diagnosed with HIV, respectively (Fig. 4d–f).

Effectiveness of the interventions to curb the syphilis epidemic

Estimates of the effectiveness (NNT) of different interventions for 2020–2029 are shown in Fig. 5. Improving syphilis testing frequency only among MSM using Doxy-P yielded the best effectiveness (lowest NNT) compared to the other three interventions. This intervention was more effective if focusing on MSM

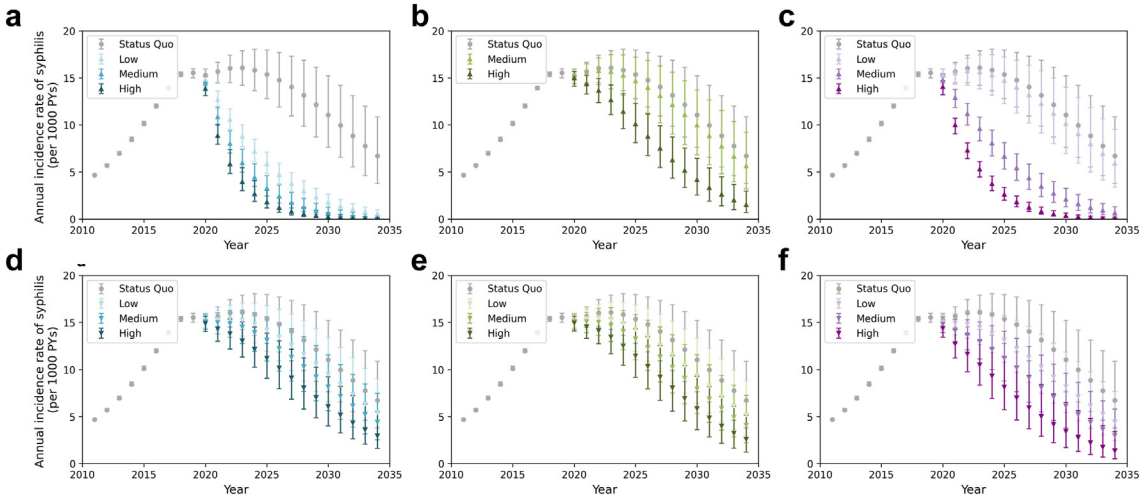

Fig. 3: Annual syphilis incidence rate under different intervention scenarios: improving syphilis testing frequency alone to every six months (Low), every four months (Medium), and every three months (High) (a–c) and implementing Doxy-P alone from 0% coverage in 2019 to 25% (Low), 50% (Medium), and 100% (High) of the target level (d–f), shown in Table 2. Target groups are HIV-negative/unaware MSM with HIV-PrEP recommended (not on HIV-PrEP) (blue), HIV-negative/unaware MSM actively on HIV-PrEP (green), and MSM diagnosed with HIV (purple).

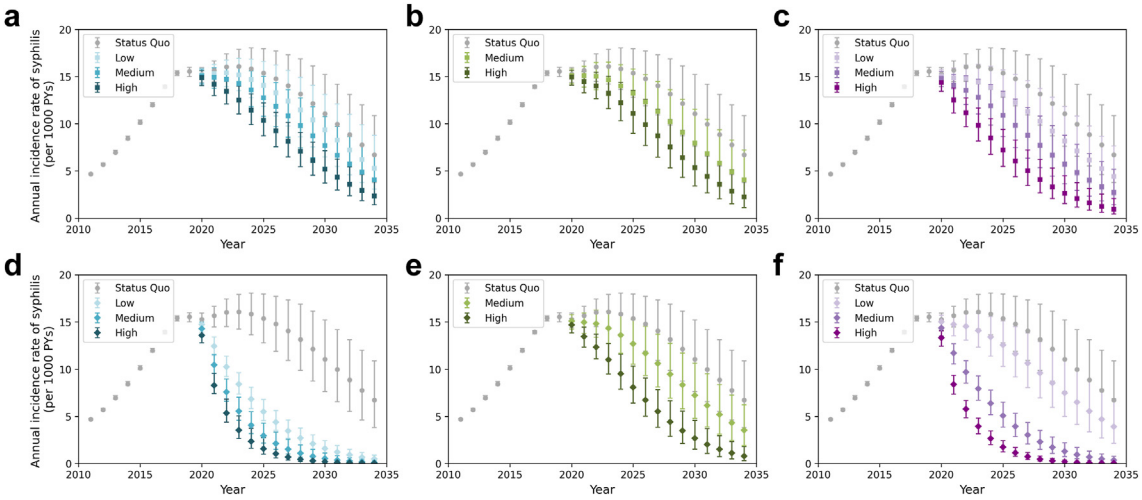

Fig. 4: Annual syphilis incidence rate under combined interventions: improving syphilis testing frequency among MSM using Doxy-P (a–c); and combining syphilis testing frequency and Doxy-P implementation (d–f). The testing frequency and Doxy-P implementation under the Low/Medium/High scenario were the same as under the scenarios if improving testing or implementing Doxy-P alone, as shown in Table 2. Target groups are HIV-negative/unaware MSM with HIV-PrEP recommended (not on HIV-PrEP) (blue), HIV-negative/unaware MSM on HIV-PrEP (green), and MSM diagnosed with HIV (purple).

diagnosed with HIV (NNT: 2.7 [1.9–4.5] under the Low scenario). Within the same subgroup, Doxy-P alone would be more effective (NNT ranged between 2.7–20.1) than improving syphilis testing frequency alone (NNT in the range 8.4–288.7). For each intervention strategy, it is always more effective to target MSM diagnosed with HIV than the other two subgroups, except for the Low scenario which only improved the syphilis testing frequency marginally from the Status Quo scenario.

Fig. 6 shows the optimal series of intervention scenarios for 2020–2029, focusing on different subgroups. The optimal scenario was the scenario with the lowest NNT. For example, suppose we focused on HIV-negative/unaware MSM with HIV-PrEP recommended (not on HIV-PrEP). In this case, priority should be given to the strategy that improves syphilis testing frequency among individuals using Doxy-P under the Medium scenario (NNT: 11.0). If more resources can be allocated, the next priority will be implementing Doxy-P and improving their testing frequency to the High level based on the incremental NNT as 12.2, which indicates that besides MSM enrolled, an additional 12.2 MSM staying under the intervention scenario for one year can avert one syphilis case (Fig. 6a). Similarly, suppose we focused on HIV-negative/unaware MSM actively on HIV-PrEP. In this case, priority should be given to the intervention implementing Doxy-P under the Low scenario, followed by the combined interventions under the High scenario (Fig. 6b). Lastly, if we focused on MSM diagnosed with HIV, then, priority should be given to the intervention that improves syphilis testing frequency only among those using Doxy-P under the Low scenario, and we should expand to other interventions along the curve depending on available resources (Fig. 6c).

Sensitivity analyses

We performed a univariate sensitivity analysis by estimating the sensitivity coefficients on the syphilis incidence rate in 2034 under the Status Quo scenario. The top ten parameters with the highest sensitivity coefficients are shown in Fig. 7. The most sensitive parameter was the syphilis transmission probability per UAS partner per year (β_S), which shows that higher values for this parameter were associated with an increase in the syphilis incidence rate (sensitivity coefficient 25.2 [20.3–31.7]; Supporting Information in Supplementary Table S14).

We also evaluated the robustness and the impact of improving syphilis testing frequency among MSM on Doxy-P on syphilis incidence rates by assuming: (1) fewer MSM on HIV-PrEP; (2) no condom use among MSM actively on HIV-PrEP; (3) more partners among MSM actively on HIV-PrEP; and (4) lower effectiveness of Doxy-P. The syphilis incidence rates in 2034 under each scenario are shown in Fig. 8a–c. A significant reduction in the syphilis incidence rates was achievable under the High scenario if focusing on MSM diagnosed with HIV, regardless of less condom use or more partners (Supporting Information in Supplementary Table S16).

Discussion

Our results demonstrated that the syphilis incidence among MSM was estimated to decrease by half in 2034 under the Status Quo, solely based on increased syphilis

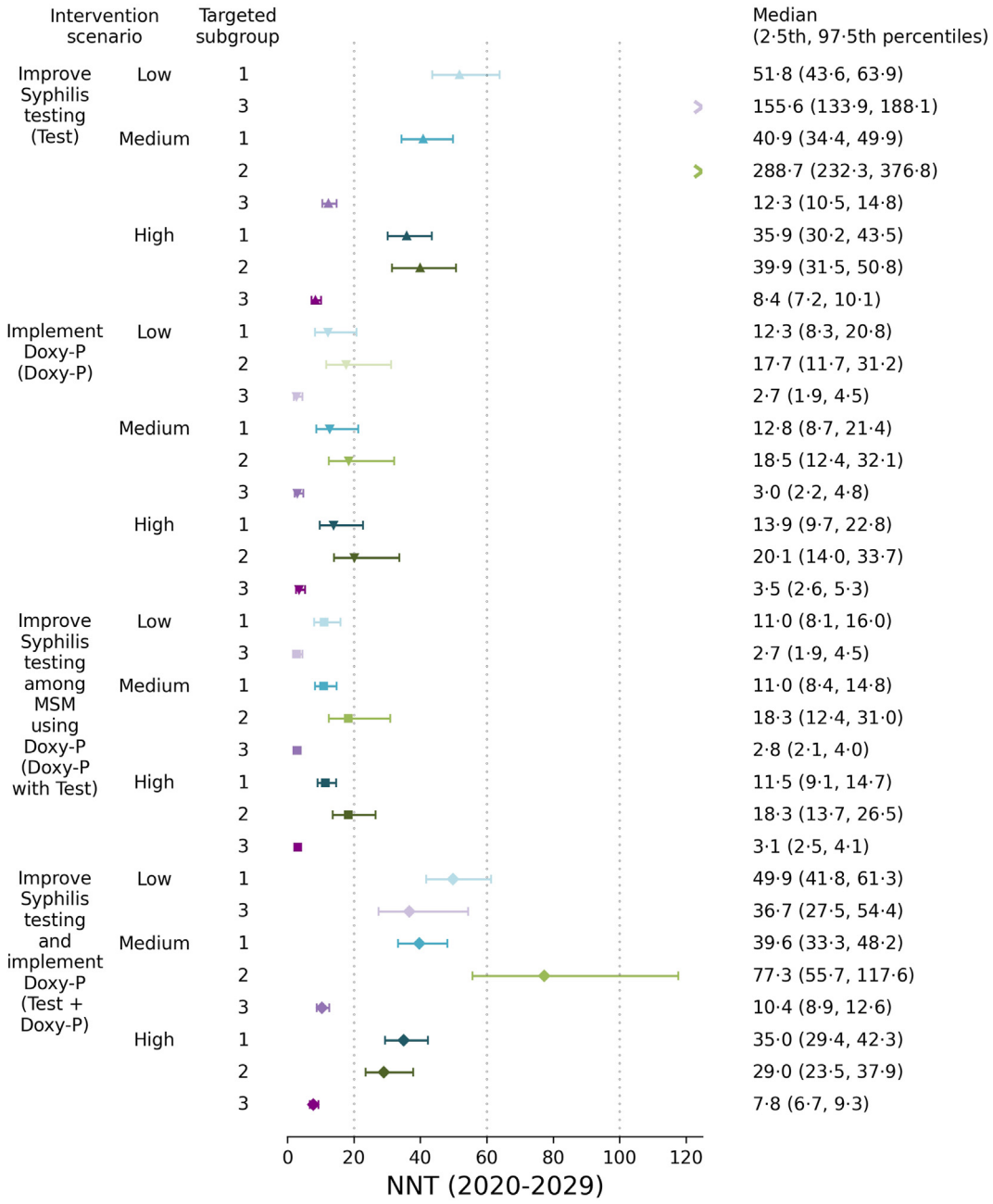

Fig. 5: Estimates of the effectiveness (NNT) of each intervention for the period 2020–2029 for different subgroups: Subgroup 1 - HIV-negative/unaware MSM with HIV-PrEP recommended (not on HIV-PrEP) (blue); Subgroup 2 - HIV-negative/unaware MSM actively on HIV-PrEP (green); Subgroup 3 - MSM diagnosed with HIV (purple). Note: We do not have improved syphilis testing intervention under the Low scenario for Subgroup 2 since the testing frequency under the Low scenario is smaller than the Status Quo.

testing among MSM with higher syphilis acquisition risk due to more than tripled number of MSM actively on HIV-PrEP (Table 1). Without enhanced syphilis testing offered by the HIV-PrEP program, the syphilis incidence is expected to increase dramatically. Further reduction in syphilis incidence is required to end syphilis as a major public concern,[39] which can be achieved by improving syphilis testing frequency and implementing Doxy-P among all subgroups of the MSM. However, we have shown that increasing these interventions, as per the High scenario among MSM diagnosed with HIV, could significantly reduce the syphilis incidence rates from the Status Quo. Though Doxy-P usage alone decreased the syphilis incidence

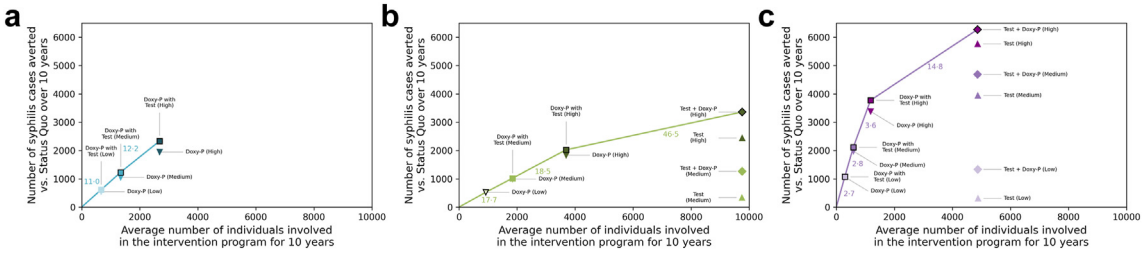

Fig. 6: Optimal series of intervention scenarios for each subgroup (markers with black edges along the solid line) for the period 2020–2029 focusing on different subgroups a: HIV-negative/unaware MSM with HIV-PrEP recommended (not on HIV-PrEP); b: HIV-negative/unaware MSM actively on HIV-PrEP; c: MSM diagnosed with HIV. The intervention scenarios and the short name used in the figure are: improve syphilis testing (Test), implement Doxy-P (Doxy-P), improve syphilis testing among MSM using Doxy-P (Doxy-P with test), and improve syphilis testing and implement Doxy-P (Test + Doxy-P). The numbers along the line are incremental NNTs compared to the next optimal intervention scenario.

rates, the decrease was relatively smaller than the combined interventions. Note that our model did not consider that Doxy-P could also have a preventive effect on other bacterial STIs.[18] Nonetheless, Doxy-P was substantially more effective than improving syphilis testing frequency alone. For most subgroups, the optimal intervention was improving syphilis testing frequency among MSM using Doxy-P.

Our findings concur with previous modelling studies that showed the preventive effect of scaling up syphilis testing.[40,41] Increasing syphilis testing frequency among high-risk MSM can vastly reduce the duration of infectiousness and the number of infectious MSM. Even though higher testing frequency means that more syphilis-infected individuals will be diagnosed, treated, and become susceptible to reinfection, the estimated number of treated MSM each year was much smaller than the susceptible population, and its impact on increasing the number of infections was negligible. We estimated that the HIV-PrEP program in BC likely played an essential role in increasing STI testing frequency as recommended once on HIV-PrEP, similar to other studies.[15] Still, questions remain on how the testing frequency can be improved among the MSM

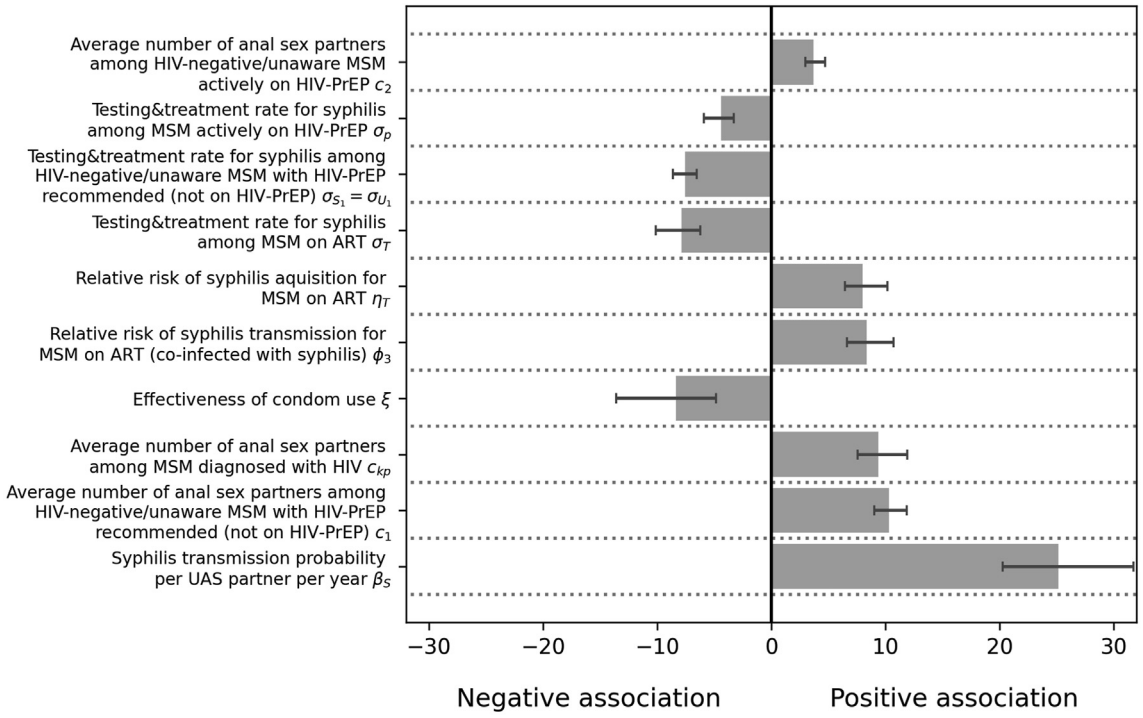

Fig. 7: Univariate sensitivity analyses under the Status Quo scenario for the syphilis incidence rate for the top ten parameters with the highest sensitivity coefficients.

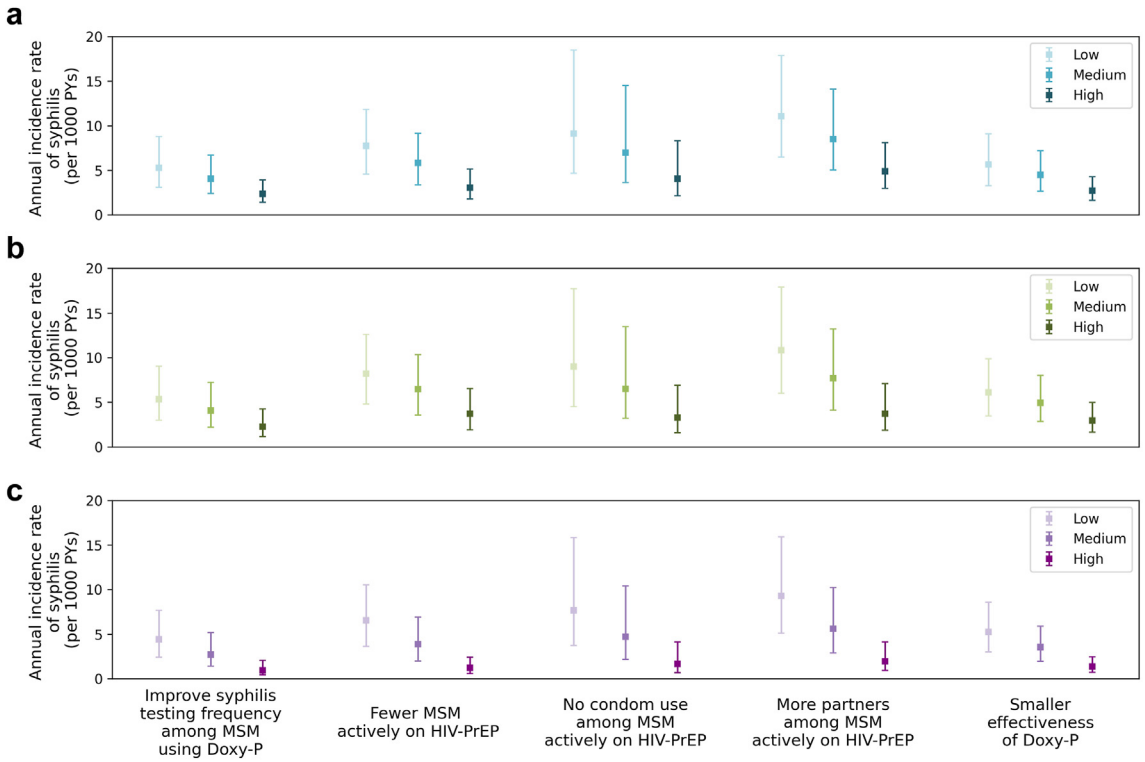

Fig. 8: Sensitivity analyses for the impact of the intervention improved syphilis testing frequency among MSM using Doxy-P on syphilis incidence rate: (a) targeting HIV-negative/unaware MSM, with HIV-PrEP recommended (not on HIV-PrEP) (blue), (b) targeting HIV-negative/unaware MSM actively on HIV-PrEP (green); and (c) targeting MSM diagnosed with HIV (purple) under different assumptions: fewer MSM on HIV-PrEP; no condom use among MSM on HIV-PrEP; more partners among MSM on HIV-PrEP; and lower effectiveness of Doxy-P.

population to the target level, which may only be achievable for specific subgroups like those diagnosed with HIV or those on HIV-PrEP who are already linked to care. Novel testing methods like the currently available GetChecked Online service (a free online STI testing service offered by the BC Centre for Disease Control) and the recently approved dual point-of-care testing kit for HIV and syphilis, albeit varying sensitivity, may be helpful to overcome the challenge of increasing syphilis testing among MSM less linked to care.[42,43] In addition, campaigns to encourage HIV-negative/unaware MSM with HIV-PrEP recommended (not on HIV-PrEP) to enroll in the HIV-PrEP program will also be helpful to improve syphilis testing.

Our model indicated that Doxy-P could be an effective complementary strategy to curb the syphilis epidemic in BC. After accounting for the reduction in syphilis incidence and the effectiveness of the tested interventions, the priority intervention should be improving syphilis testing frequency among those using Doxy-P, focusing on MSM diagnosed with HIV, which may be easier to implement since most of this population are highly engaged in care. Primary care guidelines for HIV care in BC recommend syphilis testing for MSM living with HIV every three to six months.[34] However, this testing level has not been achieved under the Status Quo based on recent data.[33] Promoting more frequent syphilis testing and prescribing Doxy-P in this subgroup would likely help on both fronts. Meanwhile, public health agencies like the San Francisco Department of Health and the Australian Society for HIV, Viral Hepatitis and Sexual Health Medicine have developed guidelines promoting Doxy-PEP use.[20,44] Unlike *Neisseria gonorrhoeae*, *Mycoplasma genitalium*, or other pathogenic bacterial species, there is a lack of evidence regarding the doxycycline resistance in *Treponema pallidum*, which is considered unlikely to occur.[18,45,46] Nonetheless, longitudinal evidence is required to understand the safety and antimicrobial resistance of long-term doxycycline use. Ongoing randomized trials should help characterize the potential concerns for antimicrobial resistance in the context of Doxy-P and develop guidelines for monitoring for doxycycline resistance in clinical practice.[47,48]

Our model is unique with relevant implications. First, our model integrated data from multiple sources to replicate HIV and syphilis epidemics and their interactions in BC,[11,16,24–27] thus allowing us to assess the

feasibility of our interventions in various risk groups within the MSM population. Secondly, we accounted for the fast expansion of HIV-PrEP uptake in BC since 2018, unlike other studies that did not consider HIV-PrEP or considered a hypothetical scenario with HIV-PrEP.[40,41] We estimated that the current HIV-PrEP program significantly reduced the syphilis rate compared to a scenario with no HIV-PrEP implementation. In addition, we stratified the MSM population by HIV-PrEP eligibility, HIV-PrEP use, and HIV status, accounting for the heterogeneity of the MSM population in HIV/syphilis risk and healthcare access. This stratification allowed us to identify the particularities of the different population subgroups and evaluate the impact and effectiveness of each intervention.

Our study also has some limitations. Our model was calibrated for the period 2011–2019, accounting for the expansion of the HIV-PrEP program in BC and the fast increase in syphilis diagnoses in 2019. However, the Status Quo scenario, which kept the parameters the same as in 2019 with further expansion of the HIV-PrEP program, no longer represents the real-life setting due to the COVID-19 pandemic since 2020, which has caused dramatic changes in behaviours such as testing frequency, PrEP uptake or whether to have unprotected anal sex with multiple partners.[49–51] The interpretation of our results should focus on the difference between the Status Quo scenario and the interventions. Next, we highlighted the degree of uncertainty from some parameters and model assumptions, for example, the number of anal sex partners or the effectiveness of HIV-PrEP/Doxy-P associated with adherence to the prescription and retention in the program. Our sensitivity analyses showed the impact of the assumptions made for the estimated parameters and the combined interventions on syphilis incident rates. Furthermore, even though syphilis is easily transmitted via oral sex, we do not have information regarding how many syphilis infections were acquired through oral sex only or the probability of syphilis transmission via oral sex per partner. Therefore, we simplified our model by only considering the probability of syphilis transmission per UAS partner per year, calibrated to match the overall syphilis diagnosis. Moreover, a diagnosis of any bacterial STI in the past 12 months was used to determine a target proportion for Doxy-P implementation. The dynamics of the eligibility for Doxy-P in real life based on the same condition, depending on the testing frequency and the epidemic not only of syphilis but of other bacterial STIs, was not considered. In our model, the impact of Doxy-P was evaluated based on different percentages of MSM using Doxy-P in each subgroup, which can be determined in different ways. Furthermore, due to the lack of costing information, we could not evaluate the cost-effectiveness of each intervention, which is critical given the limited allocated budget for healthcare in BC. As a substitute, the series of optimal interventions was determined based on the number of individuals involved in the intervention program instead of the cost. In addition, our model did not incorporate the effect of psychosocial health determinants (e.g., mental health, substance use, violence, discrimination, and stigma), which are significant drivers of the syphilis epidemic among MSM.[52] Although these determinants are pivotal in understanding syphilis transmission in this population, they were omitted due to lack of data. Lastly, we did not model the complexity related to the sexual network of MSM or the heterogeneity in risk behaviours within subgroups such as HIV-negative/unaware MSM actively on HIV-PrEP since it is beyond the scope of this study. However, if data becomes available, the next step is to use network analysis or agent-based modelling to address these co-epidemics.

In conclusion, our model provided relevant data to inform public health policies addressing the syphilis epidemic among MSM in BC and similar settings. The HIV-PrEP program in BC played a crucial role in increasing syphilis testing frequency among high-risk MSM and reducing syphilis transmission among MSM. In addition, we showed that Doxy-P implementation could be an effective complementary strategy to reduce syphilis incidence, especially among MSM diagnosed with HIV.

Contributors

Concept and design: BTT, JZ, JD, VDL; Acquisition, verification, and analysis of data: JZ, VDL; Interpretation of the modelling results: BTT, JZ, VDL; Drafting of the manuscript: BTT, JZ VDL; Critical revision of the manuscript for important intellectual content: BTT, JZ, JS, JD, MH, JW, TG, DMM, JSGM, VDL; Administrative, technical, or material support: JSGM, VDL. All authors have read and approved the final manuscript.

Data sharing statement

The British Columbia Centre for Excellence in HIV/AIDS (BC-CfE) is prohibited from making individual-level data available publicly due to provisions in our service contracts, institutional policy, and ethical requirements. To facilitate research, we make such data available via data access requests. Some BC-CfE data is unavailable externally due to prohibitions in service contracts with our funders or data providers. Institutional policies stipulate that all external data requests require collaboration with a BC-CfE researcher. For more information or to make a request, please contact Mark Helberg, Senior Director, Internal and External Relations and Strategic Development, at mhelberg@bccfe.ca.

Declaration of interests

JSGM is the Executive Director and Physician-in-Chief of the BC Centre for Excellence in HIV/AIDS, a provincial program serving all BC health authorities and based at St. Paul's Hospital-Providence Health Care. JSGM's Treatment as Prevention® (TasP®) research, paid to his institution, has received support from the BC Ministry of Health, Health Canada, Canadian Institutes of Health Research, Public Health Agency of Canada, Genome Canada, Genome BC, Vancouver Coastal Health, and Vancouver General Hospital Foundation. Institutional grants have been provided by Gilead, Merck, and ViiV Healthcare. VDL received honoraria to present at the 2023 CROI (Conference on Retroviruses and Opportunistic Infections) ViiV Healthcare Ambassador Program. JS is supported by a Canadian HIV Trials Network postdoctoral fellowship award and a Michael Smith Foundation for Health Research trainee award. MH has received research funding for an investigator-initiated study from Gilead Life Sciences and Merck. MH has also received

honoraria for advisory boards, and speaking engagements paid to his institution. TG's institution has received investigator-initiated research grants from Gilead and Merck. The other authors declare that they have no competing interests.

Acknowledgements

This work was supported by a grant from the Canadian Institutes of Health Research (PJT-156147) to VDL. We thank the participants of the British Columbia Centre for Excellence in HIV/AIDS Drug Treatment Program, physicians, nurses, social workers, and volunteers who support them.

Disclaimer: All inferences, opinions, and conclusions drawn in this model simulation are those of the authors and do not reflect the opinions or policies of the Data Steward(s).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2024.100725.

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