Supplementary Material

This supplementary material describes specific details of the individual-based syphilis transmission and sexual behavior model. The size of the simulated population is constant, with individuals remaining in the population over the course of a simulation; and with their sexual behavior, HIV status, and clinical behavior fixed. The model tracks every individual and sexual partnership in a population of gay men over time with state variables describing the HIV status, disease progression, level of sexual activity, partnership availability, and current sexual partners updated daily. Our model is calibrated using data from surveys of gay sexual behavior [1, 2] to be representative of the increasing syphilis incidence in the state of Victoria, Australia over the period 1998 to 2007. Although we do not track HIV transmission, 10% of the gay male population was designated as HIV-positive with ~60% of them on antiretroviral therapy (ART) (see Table in main text).

Each person's sexual activity is determined by the average number of sexual partnerships they have per year. Individuals are classified as 'low-activity' if they have less than 10 partnerships per year, otherwise they are classified as 'high activity'. The model simulates a dynamic sexual partnership network that is updated daily and assumes homogeneous sexual mixing. Gay men can participate in casual partnerships (lasting up to one day), form long-term (regular) partnerships, or engage in group sex. Group size, the frequency, and the number of sexual encounters within a group sex event are determined probabilistically. Sexual behavior (condom use and frequency of sexual acts) within a partnership is also simulated according to probabilistically-inferred rates dependent on partnership type, as defined in the Table.

Population demographics, sexual partnership dynamics, and sexual behavior

Our model population is made up of 30,000 gay men of whom 10% are HIV-positive with 60% of the HIV-positive men on antiretroviral treatment (ART). These values are consistent with the demographics of Victorian gay populations [1]. As we are focused on syphilis transmission, the HIV status and treatment characteristics of each person are fixed for the duration of a model simulation.

The sexual activity of each individual is determined by their HIV status and the number of casual partnerships they have per year. Individuals in the model population may engage in three types of sexual partnerships: regular, casual, and group sex. Regular partnerships are long-term partnerships between two gay men with a duration that is geometrically distributed with a mean of 4 years. Casual partnerships have duration of one day and all men can have a casual relationship concurrently with a regular partnership. Group sex partnerships have the same characteristics as casual partnerships except they occur in a group sex setting.

The distributions of the number of casual partners per year for HIV-negative and HIV-positive men were obtained from the 'Health In Men' (HIM) study [3] and the 'Positive Health' (PH) study [3], respectively. In these studies the number of casual partnerships per year is categorized into 1-2, 3-5, 6-11, 12-50, and > 50 casual partnerships every six months. We double these to get the number of partnerships per year and set the maximum number of partnerships to 120. When the population is initialized in our model HIV-negative and positive individuals are randomly assigned a category for the number of sexual partnerships based on these distributions. The actual number of casual partnerships for each individual is then randomly determined uniformly from their assigned category. In our model gay men who have less than 10 casual partnerships

are designated to be ‘low activity’ with the others labeled to be ‘high activity’. For Australian populations approximately 50% of gay men are low activity.

Group sex activity is also incorporated in the model. Almost all gay men engage in group sex at least once in their lifetime, with many men engaging in it infrequently or once off [2, 4]. However, in our model the sexual activity of each individual is fixed for the duration of a model simulation. The proportion of HIV-negative and positive gay men who regularly engage in group sex is estimated to be 17% and 30%, respectively [1]. In our model only high activity gay men are designated to engage in group sex; thus we randomly assign 34% and 60% of HIV-negative and positive high activity men in our model population so that the overall population proportion agrees with these estimates. However, when a high activity individual is randomly assigned to be someone who engages in group sex the number of casual partnerships they have per year is decreased by the average number of group sex partnerships for the population (described below). Hence their overall number of casual sexual partnerships includes the average number of group sex partnerships they have per year.

In the model simulations, when someone is available to form a casual partnership (see below) another person is randomly selected from the pool of available people (if any) and the partnership is stored. If neither of the two people in a casual partnership also has a regular partner then the partnership can become regular with probability 0.2. This is calibrated so that the overall probability of an individual being in a regular partnership is 50% to match behavioral data [1]. When someone is in a regular partnership they are still available to form a casual

partnership. However, in the model individuals can only have one casual partnership per day unless they are engaging in a group sex session.

From the population of gay men available to engage in group sex, groups of males are formed. The size of these groups g_s is given by a generalized Pareto distribution with probability distribution function

$$f(x) = \left(\frac{1}{\sigma}\right) e^{-(x-\theta)/\sigma}$$

for $x > \theta$ where $\sigma = 1.9$ and $\theta = 3$. These parameters are set so that the average and median group size is 4.4 and 4 respectively, matching available behavioral data [2, 4]. The average number of sexual partnerships p_g formed by each individual in the group is uniformly selected from between 1 and $\min(g_s - 1, 10)$. Within a group, casual partnerships are formed randomly with a probability equal to $\min\left(1, p_g/(g_s - 1)\right)$. Given the distribution for the group size the average number of group sex partners a gay man who engages in group sex has per year is approximately 10.

After someone engages in group sex there is a gap time where they are not available to form new partnerships. This gap time for each individual is uniformly distributed between 0 and $730/n_g$ days where n_g is the average number of group sex sessions an individual has per year.

The transmission of syphilis within a partnership depends on the frequency of anal and oral intercourse within a partnership and whether a condom has been effectively used. The probability of anal and oral intercourse during a day in a regular partnership are given by $p_a^r = f_a^r/7$ and $p_o^r = f_o^r/7$, respectively where f_a^r and f_o^r are the average number of anal and

oral acts per week respectively. Within casual and group sex partnerships there is a probability of once off anal and oral sex during the partnership. In the model we assume there is no condom usage during oral sex but there is a probability of condoms being used during anal sex which is dependent on the serostatus of each partner and the probability of disclosure (see Table in main text). The effectiveness of a condom in preventing the transmission of syphilis from an infected person to a susceptible partner is denoted by ε. If a condom is used during anal intercourse then the infectiousness β of an infected partner is reduced to $(1-\varepsilon)\beta$.

Disease stages and clinical characteristics

The disease progression of infected individuals is described in the main text and shown in Figure 1a. Individuals are designated to be infectious if they are in the incubating, primary, secondary, early latent or recurrent infectious stages of syphilis with the probability of transmission to a susceptible partner changing depending on the stage of syphilis and the sexual behavior within the partnership (see Table in main text). It is assumed that the infectiousness of an individual is constant while they are in each disease stage. Infected individuals are given a fixed duration for their incubating, primary, secondary, and early latent stages. These time periods are randomly assigned uniformly at the time of infection from the ranges specified in the Table in the main text. Individuals progress through the late latent, remission, and recurrent stages of syphilis probabilistically with a probability equal to the inverse of the average duration in each stage. When individuals progress to tertiary syphilis they remain there unless they receive treatment. Individuals who are treated in the early infectious stages are assumed to become immediately

susceptible to re-infection, while those who are treated in the later stages of syphilis are immune to re-infection for an average duration of 5 years.

Background testing and treatment

To model the testing and treatment of gay men, individuals are tested randomly each day with a probability per day that depends on the sexual behavior and HIV status of each individual. For the purposes of testing and the targeting of interventions four sub-populations of gay men are considered: these are high activity gay men, gay men who engage in group sex, HIV-positive gay men on ART, and the low activity gay population. These sub-populations are not mutually exclusive: if an individual is HIV-positive and on ART then they will be in one of the sub-populations describing their sexual activity and also in the HIV-positive and on ART sub-population.

For each of these sub-populations there is a different value for the testing probability, which is determined by four parameters: the duration of the testing/screening period d_t; the proportion of the population tested p_c during this period (coverage); the frequency of testing (average number of tests) for each individual f_t during this period; and the gap time between testing periods g_t. Each sub-population has different values of p_t, f_t, d_t, and g_t representing different background testing rates or the targeting of specific testing interventions. The probability of being tested during the testing period is given by $p_t = p_c f_t / d_t$ and zero during the gap time between testing periods.

Surveys of Australian gay men show that there is a proportion p_t^n of gay men who are unwilling to undergo testing for syphilis. For gay men who are willing to get tested, the probability of testing per day is rescaled by dividing by $(1 - p_t^n)$ so that the overall probability for the entire sub-population equals p_t. For individuals who are HIV-positive and on ART their probability of being screened per day is given by

$$p_t = 1 - (1 - p_t^s)(1 - p_t^h)$$

where p_t^s is the probability of testing for the sexual activity sub-population they belong to and p_t^h is the probability of testing because they are HIV-positive and on ART.

When an infected individual is tested there is a probability $(1 - t_s)$, where t_s is the test sensitivity, of a miss diagnosis. Assuming all positively diagnosed individuals are effectively treated, the probability per day that a gay male infected with syphilis is treated equals $(1 - t_s)p_t$.

Background testing: Each of the sub-populations has a different background rate of testing in the absence of specific interventions. The percentage of gay men in each sub-population who test for syphilis at least once each year is estimated from surveys of gay men [1] and listed in the Table in the main text. These estimates determine the proportion of men p_c tested in each subpopulation. For background testing we set $d_t = 365$ and $g_t = 0$ (i.e. gay men can be tested all year every year with no period of no testing). HIV-positive men are tested more frequently than negative men; thus for background testing we estimate f_t to be 3 for HIV positive gay men on ART while $f_t = 1$ for the rest of the population. These values of p_c, f_t, d_t, and g_t for each sub-population remain fixed in our model unless a specific screening intervention is targeted at the men in that sub-population.

Screening interventions

To model and compare the impact of particular screening interventions the values of $p_c, f_t, d_t,$ and g_t for each sub-population and the implementation of screening are changed. The particular interventions and their implementation investigated with our model are listed and described below. These interventions can be targeted at the whole population of gay men by changing the values of $p_c, f_t, d_t,$ and g_t for each sub-population or focused on particular sub-populations by only changing the corresponding values of $p_c, f_t, d_t,$ and g_t for that sub-population.

Increasing coverage: To model an increase in the coverage of gay men tested per year the value of p_c is increased from the background value with $f_t, d_t,$ and g_t remaining fixed. The maximum value of p_c is $(1 - p_t^n)$ as p_t^n never test for syphilis. However, the impact of increasing the coverage to 100% of gay men being tested at least once per year can be determined by setting $p_c = 1$.

Increase frequency of testing: To model an increase in testing frequency the value of f_t is increased for each sub-population group while p_c, d_t, and g_t remain at their background values.

Synchronized or 'blitz' testing: Modeling of synchronized testing is implemented by setting d_t to the duration of the synchronized testing or 'blitz' and g_t to the time period between testing blitzes. The value of p_c is changed to the proportion of men tested during a blitz while f_t equals the average number times men are tested in a blitz. For example an intervention that tests 80% of

gay men during a one month period twice every year would be implemented by setting $p_c = 0.8, f_c = 1, d_c = 31,$ and $g_c = 151$. In our model we assume that testing only occurs during blitz periods with no screening happening between blitzes.

Follow-up testing: We model 'follow-up' testing where previously tested gay men are encouraged to return for another test after a certain time period (e.g. through personal contact via mail or a phone call). The proportion of men who return for another test after being contacted is given by p_c. The time period after contact that a male returns for a follow-up test is given by d_c while g_c equals the time duration since their previous test to the time they are encouraged to come back for a follow test. For this intervention the value of f_c is set to one.

This intervention is implemented by performing background screening on the population. When an individual is tested due to this background screening they will not be tested until they are reminded to return for another test after g_c days, if they are tested within the following d_c days they are again reminded to return after g_c days. This pattern continues until they miss being tested during the $d_c$testing period. If a gay male does not get tested during the follow-up testing period then they return to being tested at the background rate.

Contact tracing: The implementation of contact tracing in the model is carried out differently to the other interventions described above. When an individual is tested and positively diagnosed for syphilis due to background testing, a proportion of the regular and casual partners they had during a fixed time period before their diagnosis are contacted and tested within two weeks after the individual's diagnosis with a probability $p_c = 1/14$. To reflect the practical difficulty in

tracing casual partnerships, the proportion of casual partners tested, and the preceding time period for which they are traced, is less than that for regular partners.

Model initialization and running of simulations:

The model population is initialized by randomly assigning the HIV status, sexual activity, average number of partners, and treatment seeking status for each individual. Initially there are no partnerships in the population but everyone is available to form partnerships. Everyone in the population is susceptible and there are no syphilis infections present. The model was run for 5 years, to stabilize the partnership dynamics, prior to designating 10 individuals to be infectious to establish an epidemic. The syphilis transmission and disease progression was then tracked for 10 years (corresponding to the years 1998 to 2007).

As described in the main text, the realistic biological and behavioral parameters used in the model led to simulations that were well-calibrated to match the number of syphilis diagnoses in Victoria, Australia. Out of 50 simulations, the 10 simulations that best fit the epidemic data (according to a Pearson chi-squared test) were selected to forecast the impact of screening interventions (Fig. S1b). The random number seeds generated in Matlab® R2008a for each of these interventions were stored so that the first 15 years prior to the introduction of an intervention for these simulations was repeated and direct comparisons between interventions could be made.

Screening strategies that follow-up men who have previously been treated for syphilis were investigated, assuming that 50%, 70%, or 90% of men return for re-testing every 6 or 12 months.

Supplementary Material Figures

Figure S1: (a) Schematic diagram of the stages and disease progression of syphilis included in the model. Infectious syphilis includes the incubating, primary, secondary, early latent and recurrent stages. **(b)** The number of infectious syphilis diagnoses in the state of Victoria, Australia (blue discs, data) compared with 10 model-based simulations (red) and median (of 50) simulations (black) over the 10 year period from 1998 to 2007.

Figure S1a

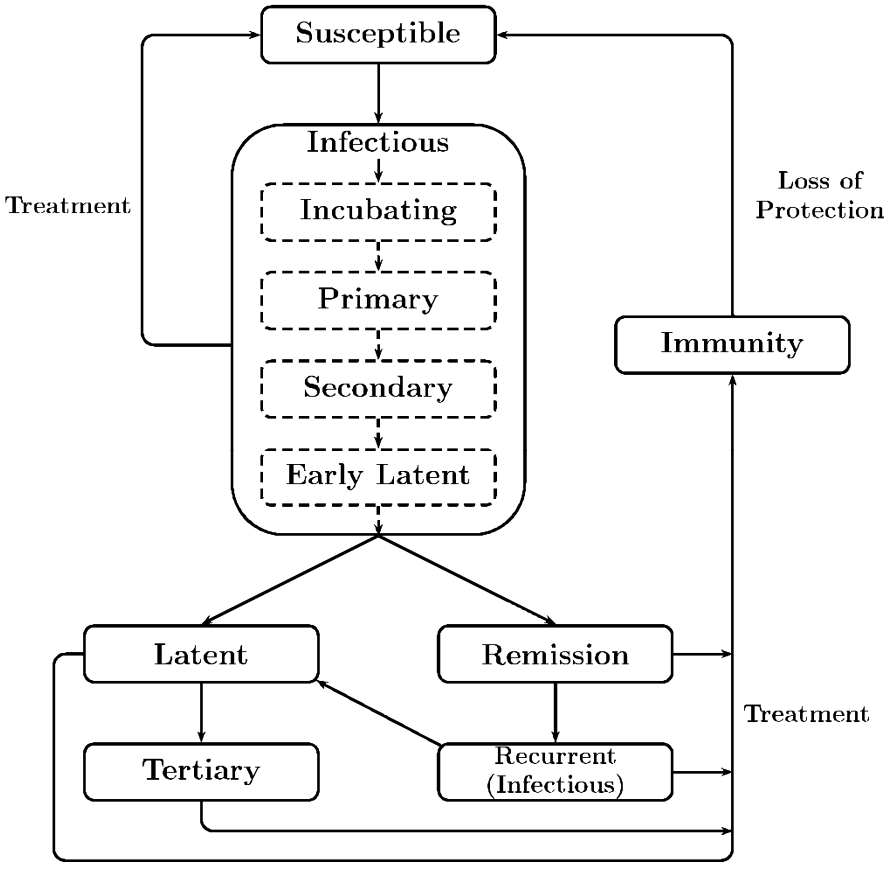
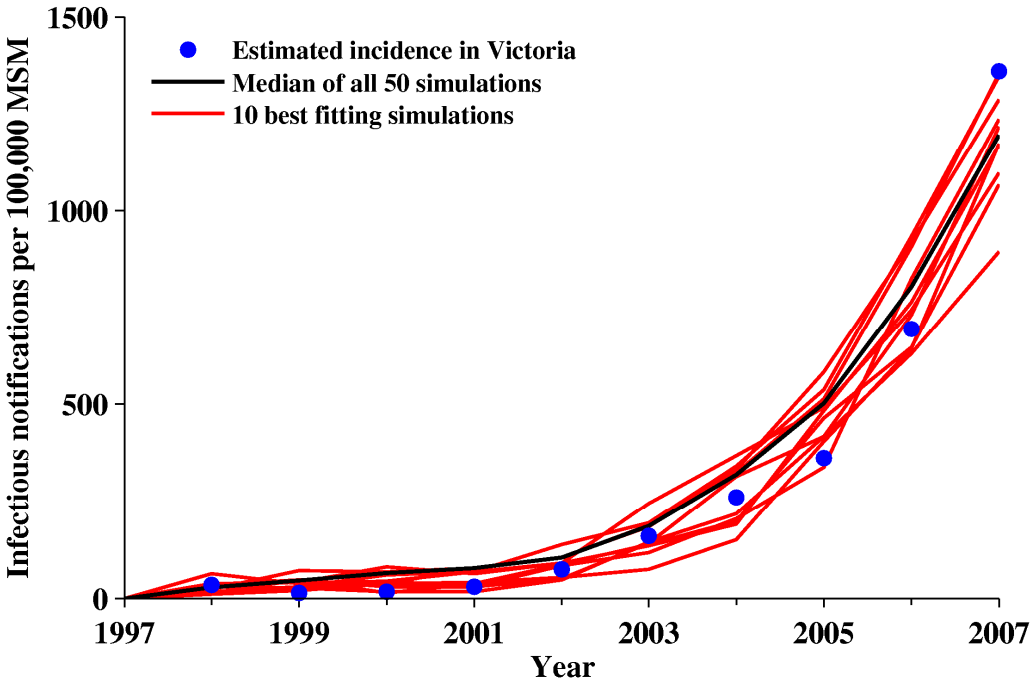


Figure S1b


Estimated incidence in Victoria
Median of all 50 simulations
10 best fitting simulations
Infectious notifications per 100,000 MSM
1500
1000
500
0
1997
1999
2001
2003
2005
2007
Year

References for Supplementary Material

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4. Prestage GP, Hudson J, Down I, et al. Gay Men Who Engage in Group Sex are at Increased Risk of HIV Infection and Onward Transmission. AIDS behav, in press, doi:10.1007/s10461-008-9460-7, 2009