Mathematical Models of HIV Epidemics in Australia and South East Asia

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This thesis consists of a series of publications that address timely public health questions in the field of mathematical epidemiology of HIV/AIDS and sexually transmissible infections (STIs). Mathematical epidemiology requires the forecasting of epidemic trajectories coupled with degrees of uncertainty. This study commenced with the development of new software and utilisation of techniques from a variety of disciplines to assist the conduct of uncertainty and sensitivity analyses. A user-friendly software package was developed and also used in the subsequent projects of this study. The number of HIV diagnoses in Australia has been increasing over the past decade and it was timely for a detailed analysis to be conducted. This study investigated the differing trends observed in three States of Australia: New South Wales, Queensland, and Victoria. The model included epidemiological, clinical, behavioural, and biological data to analyse and identify the differences in each State. It found that the only way to fit the data was to incorporate changes in other STIs as interactive biological cofactors. This model was then extended to examine the impact of testing and early treatment of HIV as a means of preventing new HIV infections. It was found that increasing testing rates for HIV can have a significant impact on reducing further secondary infections. This has since become a topic of very large international interest. Since syphilis epidemics have resurged and could facilitate HIV transmission, possible public health intervention strategies were simulated using a detailed individual-based model. This formed the foundation for Australia's National Gay Men's Syphilis Action Plan (NGMSAP). This study then examined the potential benefits in HIV incidence that could be due to the implementation of the NGMSAP. Lastly, this study examined an important current issue for neighbouring countries in the region, namely, the impact of universal HIV treatment access in Southeast Asia on the development of drug resistance. This model-based investigation found that a high prevalence of drug resistance can potentially develop, however, increased treatment access will likely reduce the incidence of new HIV infections. It also found that regular viral load tests can mitigate the prevalence of drug resistance in the population.

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Preface

The main chapters of this thesis have been reproduced from papers that have been published or under peer-review. The citations to these papers are provided at the start of each chapter, and pdf files of each paper have been provided on the CD found at the end of the thesis. The CD also includes a copy of the SaSAT software package. At the time of writing, Chapter 5 had not yet been published but was submitted for peer-review at an international scientific journal. Content of all chapters appear as published but minor alterations were made to the format of the papers; these include the placement of figures and tables and references to supplementary material now refer to the appropriate appendix. Reference styles were also changed to be made consistent throughout the thesis.

Introduction

Overview

Epidemiology is the study of incidence and prevalence of diseases affecting the health of a population, with the goal to indentify the factors responsible for, or contributing to the disease [1]. From the earliest origins of medicine, to the present, the epidemiology of diseases has been studied. Hippocrates is the first recorded person to investigate rational explanations for diseases. He coined the terms endemic and epidemic, and made observations between diseases and environmental factors [2].

Perhaps the next major advance came in medieval times. In the *Canon of Medicine* [3], Avicenna, discovered the contagious nature of some diseases, and started the practice of quarantine to limit the spread of diseases. This marked a significant turning point in the treatment and prevention of infectious diseases.

The study of epidemics continued through the ages, with major epidemics such as the Black Death of the 14th century, to the flu epidemic of 1918, both responsible for millions of deaths [4-5]. Methods of control and research have led to the eradication of some diseases such as smallpox that had plagued humans for centuries [6-7]. Recently, mathematics has had a role in the fight against disease.

History of Mathematical Analyses of Epidemics

The use of mathematics to analyse and study epidemics first begins In 1760, when Daniel Bernoulli applied mathematics to analyse an outbreak of smallpox [8]. In his paper *Essai d'une nouvelle analyse de la mortalite causee par la petite verole*, Bernoulli aimed to inform public health policy at the time to

adopt variolation (infecting healthy children with mild smallpox, thus giving them immunity later in life). At the time there was a debate that variolation was dangerous and whether it would provide any benefit to the community. To show the effectiveness of variolation, Bernoulli, preformed a mathematical analysis using life tables to compare the average life expectancy of a child living in a smallpox afflicted state against living in a non-afflicted state. He then looked at the introduction of variolation, testing several scenarios in which variolation was 100% effective and risk free. In this scenario, he showed that variolation would increase life expectancy by 3 years. He then looked at the scenario in which one in 200 inoculated individuals died as a result of variolation, under this assumption, the increase in the average life expectancy was only one month shorter than the ideal case in which no deaths occur from inoculation.

It is not known if Bernoulli's efforts were successful in convincing governments of the time to adopt variolation, however England began variolation around 1750, and introduced compulsory vaccination for infants in 1853. This reduced the susceptible population and decreased the length and severity of smallpox outbreaks, such that by the end of the 19th century, smallpox had disappeared from England [9].

The use of mathematics in epidemiology became stagnant over the next few hundred years, until the 19th century. It was then that William Farr [10], began to use statistics to analyse epidemics. Farr studied the cholera epidemics that plagued London in 1849, 1853 and 1866. Using various pieces of information collected about victims, he was able to show correlations between victims and their water suppliers. Farr, in collaboration with John Snow, helped disprove the miasmic theory of disease.

Mathematical epidemiology continued to be developed in the early 20th century through the work of Hamer and Ross. In 1906, Hamer [11] postulated that the rate of contact between susceptible and

infectious individuals was significant and formulated this idea in a discrete–time model. This idea of contact between susceptible and infected individuals would become a key concept in epidemiological modelling. Then in 1908, using Hamer's ideas, Ross [12-14] developed a continuous-time model to investigate malaria.

The next major development in the field of mathematical epidemiology was the work by Kermack and McKendrick. In 1927 [15], they published their work which introduced the use of ordinary differential equations to model an epidemic. The model consists of three coupled nonlinear ordinary differential equations. This is the standard S-I-R model, which has become the foundation of modern mathematical modelling. Where each equation corresponds to a stage of infection, (S)usceptible – those that have no immunity to the disease and are capable of being infected, (I)nfected – those that have become infected, and (R)emoved/recovered – those who are no longer infected and are no longer susceptible to infection.

$$\frac{dx}{dt} = -\kappa xy$$
$$\frac{dy}{dt} = \kappa xy - ly$$
$$\frac{dz}{dt} = ly$$

In this set of equations x denotes the number of people in the susceptible population, y denotes the number in the infected population, and z is the number in the removed/recovered population. Individuals get infected at a rate κ, which denotes the transmission probability of infection. The symbol l denotes the rate that infected individuals are removed or recovered from the infected population. This simple set of ordinary differential equations would lay the foundations of more complicated models to come.

In this paper they also introduce the idea of a threshold density. The threshold density is dependent on the infectivity, recovery and death rates. If the density of the population was equal to or below the threshold density, then the introduction one or more infected individuals would not give rise to an epidemic. If the population density exceeds the threshold value, then an epidemic will occur. This threshold density theory is recognised as one of the fundamental concepts of modern mathematical epidemiology.

Another important concept is the basic reproduction rate often denoted as R_0, which is related to the threshold density. This is the average number of secondary infections caused by an infected individual. It was first introduced by MacDonald in 1952 [16], while investigating population models for malaria. If R_0 is greater than 1, then a disease can lead to an epidemic, if it is less than 1, the number of new infections is not enough to maintain an epidemic.

Kermack and McKendrick's work remained almost untouched for the next 50 years, until 1979 when Anderson and May [17] resurrected their work. More complicated versions of Kermack and McKendrick's equations are now used to model several different diseases, and to help model control strategies [18-20]. Anderson and May also built upon the R_0 equation for S-I-R type models, relating R_0 to the number of contacts with infected individuals (c), the transmission probability of the disease (β), and the duration of the infection (D) [21-22] by the following equation:

$$R_0 = c\beta D$$

Then in 1991, Anderson and May complied their seminal book, *Infectious Diseases of Humans: Dynamics and Control* [23]. This book discusses the public health methods for dealing with a wide range of

infectious diseases, from malaria to AIDS and how the application of mathematical models can be an effective tool in understanding and controlling epidemics.

HIV/AIDS Modelling

During the late 1970s and early 1980s, a new virus emerged – HIV. During the early days of the HIV epidemic, mathematical models helped provide public health officials and other researchers with valuable insights. Anderson and May were responsible for much of the early modelling of HIV transmission. In 1987 [22], they used modelling to investigate the transmission dynamics of HIV. Using simple models, they were able to determine some of the essential relations between parameters, and help identify data needed for making more detailed models and predictions for the future.

During the 1990s, there was a shift in focus on modelling. With the development of new and improved drugs, new models were needed to investigate the effects of potential vaccines, and the distribution of new treatments. In 1993, McLean and Blower [24], developed a model to investigate imperfect vaccines. At the time, several potential vaccines were in phase I or phase II trials. The authors used their model to investigate the implications of vaccines, with different sets of imperfections. They focused on three aspects of vaccines: 'take' – proportion of individuals in which the vaccine protects, 'degree' – the level of protection offered by the vaccine, and 'duration' – the length of time that the vaccine remains effective. The authors then analysed the impact of each potential imperfection on a simulated population using their model. This enabled them to identify possible sensitivities of vaccines without the need for large and expensive clinical trials.

In 1994, Blower and McLean [25] continued to investigate the impact of HIV vaccines with a model that investigated the probability of eradicating HIV in San Francisco. One of the questions asked in the paper

was, how vaccines may change behaviour? The authors looked at the effect of increased risky behaviour as a result of prophylactic vaccines. The results of their model suggest that to eradicate HIV in San Francisco, a highly effective vaccine along with high vaccine coverage is needed. However, eradication is unlikely if there are no reductions in risky behaviour. In fact, under some scenarios, vaccination could lead to a larger epidemic.

A major change in the clinical and epidemiological landscape of HIV occurred in 1996 with the introduction of Highly Active Antiretroviral Therapy (HAART) keeping people alive longer[26]. Consequently, models began to adapt to reflect the introduction of HAART. Many were developed and used to explore epidemiological outcomes associated with its use in diverse settings (e.g. [27-30]).

In a model applied to an Australian setting, Law et al. [31], investigated the effect of antiretroviral therapy (ART) on HIV incidence. Specifically they examined the decrease in infectiousness conferred by treatment, against the increase in risky behaviour, such as decreased condom use. Their findings suggest that an increase in unsafe sex may counteract any reductions of new HIV infections associated with ART.

In 2003, the World Health Organisation launched an initiative to provide ART for three million people living with AIDS by 2005. In resource poor countries, where the number of people living with AIDS outnumbers the available treatment, difficult questions were asked about the best strategy to distribute treatment effectively, with the most impact to prevent future infections. To answer these questions, Wilson and Blower [32-33], modelled different drug allocation strategies. The models considered many strategies, by focusing on equity, ethics, and epidemiological criteria, with the aim of finding the most effective distribution strategy. The papers conclude that the best epidemiological strategy, would to distribute drugs to the major cities, as these act as hubs to each of the smaller communities.

Models of the Asian HIV Epidemic

As HIV spread throughout the world, differences in the epidemiology of an HIV became more apparent depending on the country or region. We now look at efforts to model the HIV epidemic in Asia. While the prevalence of HIV/AIDS in Asian countries is much lower than compared with African countries, it is still moderate when compared to western countries, and due to the size of population in Asia, the number of infected cases is still alarmingly high. However, there have been few attempts to create models for this region.

In 1994, Mastro et al. [34], developed a simple mathematical model to estimate the female-to-male transmission probability of HIV in Thailand. This model does not rely on any ordinary differential equations, but instead uses statistics gathered from a survey of military conscripts in Thailand. Using this data, the authors were able to gain an estimate of the transmission probability. This was important since most of the research of HIV/AIDS had been focused on the Western or African world, it was not known if the transmission probability was the same for the Asian, due to environmental and genetic differences. The authors determined that the female-to-male transmission was much larger than estimates from North America.

Then in 1995, Busenburg, Cooke, and Hsieh [35] developed a more rigorous model for the Asian setting. Extending the principles set out by Kermack and McKendrick [36], the authors here designed a model that concentrated on heterosexual contact, and did not include any homosexual contact, or injecting drug use. They performed a rigorous mathematical analysis of this model, studying equilibrium points, and determining an expression for R_0. However, the paper is largely theoretical and did not use epidemiological data to provide any predictions.

In 2004, a study done by Tim Brown and Weewat Peerapatanapokin [37], presented the Asian Epidemic Model (AEM). The model focuses on the route of HIV spread outlined by Weniger et al in *The epidemiology of HIV infection and AIDS in Thailand* [38]. The model divides the population into nine compartments: males who are clients of sex workers (SW), males who are not clients of SWs, lower risk general population females, direct SWs, indirect SWs, high risk injecting drug users (IDU), low risk IDUs, male sex workers, and men who have sex with men (MSM) who are not SWs. The premise is that epidemics in Asia follow the following pattern: starts in MSM and spreads to IDU population, it then moves to the SW population, and from there is spread to the general population. The strength of the AEM is that it is semi-empirical and must use specific data associated with HIV prevalence in each of the identified groups. Some of the disadvantages of this model are that it does require a lot of data, which may not be readily available. Also, because it relies on such specific data, a full uncertainty and sensitivity analysis cannot be performed. However, this model has been applied with some success in Thailand [39] and Cambodia [40] and many other countries for their evaluation – although peer-review publications are not available.

A more rigorous model was developed in 2006, by Bacaër, Abdurahman, and Ye [41]. The focus of this model is to investigate the effects of sex workers and injecting drug users in Yunnan province, China. These two groups are of particular importance in the Asian setting, with the HIV/AIDS epidemic largely contained in these groups. The model stratifies the population into 18 groups, nine each for males and females. The authors were able to determine an approximation for R_0, based on the two routes of infection – commercial sex, and needle sharing. This enabled the critical values of condom use and clean needle use to be determined. The authors then used data from Yunnan province in China, focusing on the main city of Kunming. Based on their analysis, they determined that IDUs were

responsible for new infections, and that targeting the IDU population was crucial to reducing HIV transmission.

Modelling ART Resistance

With the scale-up of HAART in most countries, a new concern arose. Many resource poor countries are only able to provide a single treatment therapy, such as the General Pharmaceutical Organisation's GPO-VIR, consisting of stavudine, lamivudine, and nevirapine, to its citizens. Without alternative treatment therapies, the risk of developing treatment failure increases, as does the risk of transmitting drug resistant strains. This concern has resulted in a shift in focus in more recent models to predict the development of drug resistance, and the possible effects on the population. The following papers discuss the approaches taken to address this problem.

In 2000 Blower, Gershengorn, and Grant [42] produced the first paper that mathematically analysed the emergence of drug resistance. It focused on the homosexual population of San Francisco, which at the time had an HIV prevalence of 30%, 50% of whom were receiving antiretroviral therapy. HAART had only been widely available since 1996, and protease inhibitors had only been recently developed at this time. The full epidemiological implications of treatment were not known, and there were questions of whether the treatment would encourage risky behaviour and result in more new infections, or if mass treatment would lead to the spread of drug resistant strains. The authors developed a mathematical model, comprising of five ordinary differential equations. They made several assumptions regarding the characteristics of the drug resistant strains. Drug resistance had only recently emerged and little was known about the properties of drug resistant strains. To help overcome the lack of data, the authors

applied uncertainty and sensitivity analysis. They found that the emergence of drug resistant strains can lead to a high prevalence of drug resistant infections. However, they noted that increasing the usage of ART would lead to lower death rates from AIDS and also a significant decrease in incidence of infection, and that the emergence of drug resistant strains had little impact on this decrease.

By 2005, more knowledge had been gained on drug resistant strains. A review paper by Blower et al [43], discussed whether the planned ART rollout for Africa is likely to result in an epidemic of drug resistant virus. The World Health Organisation (WHO) is concerned with the emergence of drug resistant virus, since in many resource poor settings only a few treatment regimens are available. As such, the WHO has developed a surveillance system to detect when transmitted drug resistance has reached 5%, 5-15% and greater than 15%. They reviewed the data obtained on drug resistance, and how mathematical models have been used to predict the emergence of drug resistant HIV. This paper then makes a ten year prediction on the impact of ART on reducing HIV transmission, the transmission of drug resistance, and the level of acquired drug resistance. Based on the results, the authors concluded that the impact of ART on reducing HIV transmission and prevalence is likely to be undetectable, unless there are significant changes in behaviour. They also found that the level of transmitted resistance is likely to remain below the WHO's 5% threshold. Lastly, they found that the majority of drug resistant cases are likely to arise from acquired resistance. From these finding they recommended that surveillance for transmitted resistance is unnecessary for the next decade. Instead, it is proposed that patients on treatment should be monitored for acquired resistance.

The development of drug resistance is still of some concern and has meant that it was necessary to factor it in to new models of drug distribution. As previously discussed, the 2006 paper by Wilson, Kahn,

and Blower [33] investigated strategies to distribute ART in a resource poor setting. The authors focused on the South African province of KwaZulu-Natal, and examine drug allocation strategies that varied from distributing the drugs only to the capital city of Durban, to distributing the drugs to rural areas around Durban. This paper also accounted for the development of drug resistance and the levels of transmitted resistance that would occur using different drug allocation strategies. An important and surprising finding of this paper is that the level of transmitted resistance was found to be lower if ART was distributed in Durban only. This is surprising because it was expected that concentrating ART in one location would lead to more transmitted resistance. However, the authors do point out that the model was set from 2004 to 2008. In the short time period, it is likely that levels of acquired resistance were low, and likely to increase over longer time periods, which would in turn lead to more transmitted resistance.

In 2007, Vardavas and Blower [44] investigated the emergence of transmitted resistance to anti-retroviral medication for HIV. To do this they derived stochastic equations of the evolution of drug-resistant strains using data gathered from Botswana. To fully analyse the situation, they focused on two key drivers relating to transmitted resistance: 1) the fitness of the resistant strain, and 2) the rate of acquired resistance. The first relates to the new resistant strains' ability to compete with the wild-type drug susceptible strain. The second driver relates to how the resistant strains develop in the first place. The authors were able to show that time until transmitted drug resistance was detectable, is largely determined by the fitness of drug resistant strains relative to the wild-type strain. If the relative fitness is low, then the rate of acquired resistance was a negligible factor. Acquired resistance became more important as the relative fitness was increased. Overall, they determined that it was unlikely that the level of transmitted resistance could be detected for several years using the WHO 5% threshold.

Syphilis

Mathematical models have also been applied to other sexually transmitted diseases such as herpes simplex virus type 2 [45-47], gonorrhoea [48], and Chlamydia [49-50]. All of these models apply the same principles of mathematical modelling, with adjustments made to cater for the specific diseases. For this thesis, we shall focus on only syphilis infection.

Syphilis, caused by the bacteria *Treponema pallidum*, is a sexually transmitted disease that has been afflicting humans for several centuries with one of the first reports of an outbreak occurring in the late 15th century [51-52]. It was not until the relatively recent discovery of antibiotics that an effective treatment was available.

Treponema pallidum infection can also play a role in the spread of HIV. Studies have shown that there may be a link between syphilis and an increased probability of transmission of HIV [53-60]. The sores caused by syphilis provide an easier means for HIV to enter the body, while also acting as areas where the viremia can concentrate, thus increasing the probability of transmission. Because of this link, it is important for HIV models to consider the presence of other STIs within the population.

Several mathematical models have been developed to analyse syphilis epidemics and evaluate the impact of control measures in reducing the spread of an epidemic. In 1996 Oxman et al [61] used a simple multi-compartment model implemented within Microsoft Excel. In this investigation they sought to use modelling to gain an insight into the transmission dynamics of a syphilis epidemic. They used empirically gathered data to parameterise the model, specifically behavioural data such as partner exchange rates. From this they were able to determine that an epidemic can result from adding a core of individuals with very high partner exchange rates. Using the results from their model, they concluded

that transmission dynamics are likely to have a large influence on the control of a syphilis epidemic, and that these dynamics should be considered in designing effective prevention and control strategies.

A year later, Garnett et al [62] also produced a model based investigation into syphilis transmission. In this model, the authors used a multi-ordinary differential equation model, with each equation corresponding to a stage in the natural history of syphilis. They parameterised their model using several sources of clinical, epidemiological and behavioural information. From their analysis, they were able to assess several aspects of a syphilis epidemic, such as the endemic prevalence of syphilis in a population, and the impact of treatment.

Thesis Outline

There are two parts to mathematical modelling; the first is the development and the implementation of a model and the second and perhaps most important, is the analysis of the results. Although models differ in structure and goal, often the results that they produce can be subjected to similar types of analyses. In Chapter 1 of this thesis, the development of the Sampling and Sensitivity Analyses Tools (SaSAT) software program is described. The key objective of SaSAT was to make it as easy as possible for a modeller to generate large sets of parameters for sensitivity analysis. It also provides several different statistical measures for analysing results, all within the one program, and is independent of model type.

SaSAT was presented as a poster at the Epidemics1 conference in Asilomar, California. It has since found wide use among several modelling groups around the world and has been recognised as a useful tool in the field [63]. One of the first applications of SaSAT was to perform analyses on the HIV epidemic in Australia.

During the 1990s, the number of reported HIV cases in Australia was declining for several consecutive years [64]. However, from 2000 to the present steady increase in HIV notifications has been observed. This was a worrying trend and it was important to ascertain the key drivers of this resurgence.

Modelling provided an opportunity to investigate the several key factors that were believed to have contributed to this rise in HIV notifications. Chapter 2 outlines the model that was developed to investigate this increase of HIV notifications. More specifically, investigating the possible explanations for the different rates of increase in HIV in the three largest Australian states of New South Wales, Queensland and Victoria. The model was the basis of a report [65] that received some media attention [66-67]. The findings of this project helped set public health guidelines for the future, with a new focus on the importance of other STIs and the role that they could play in the HIV epidemic.

While not only good at analysing the previous events of the HIV epidemic in Australia, modelling was also helpful in evaluating strategies to lessen the number of new infections. In Chapter 3, the same model presented in the report was reconfigured to project into the future and predict the impact of different levels of testing. For example, encouraging more people to test each year, and how that would impact the future of the epidemic, assuming that behaviour changes upon diagnosis.

An important finding from the previous work was the impact that untreated STIs could have on HIV incidence. The model was not equipped to look at the transmission of STIs in detail, and their impact on HIV. Over the same time period, syphilis was found to have increased dramatically. Work then began on developing a model focusing on syphilis among MSM.

Victoria observed the largest increase in syphilis [68] in Australia, and therefore it was decided to apply Victorian data to parameterise the model. This would be a larger more complicated model that would

allow us to investigate more complex interactions between individuals. For example, different sexual activity levels for each person, which leads to different types of partnerships that can form.

This model was then employed to evaluate different intervention strategies to control syphilis. A report was produced on behalf of the Blood-Borne Virus and STI Subcommittee (BBVSS) [69]. The findings of the report were then implemented into a National strategy to control the spread of infectious syphilis.

There has been some speculation that syphilis infection can facilitate the transmission of HIV [54]. It follows that interventions targeting syphilis may have an added benefit of helping reduce incidence in HIV. In Chapter 5, we explore what possible impacts a set of syphilis interventions may have on HIV incidence. Using an updated version of the model developed for the BBVSS, we were able to gauge the impact of several different syphilis interventions on HIV incidence.

Lastly in Chapter 6, we analyse the potential problem faced by countries in South-East Asia - the development of anti-retroviral (ARV) drug resistance. With many countries in this region beginning or having already started the scale-up of ARVs, making treatment available to all who are eligible according to the WHO guidelines [70]. In these developing countries, access to treatment is usually limited to a few different drugs, and also regular viral load testing to monitor the effectiveness of treatment is not always possible, thus the potential for the development of drug resistance can be high. The development of drug resistance can lead to the transmission of drug resistant strains. The presence of drug resistant strains among treatment naive individuals can greatly reduce the effectiveness of the available treatment. With our model, we explored the impact that these undetectable resistant strains can have on an epidemic. We also evaluate how different frequencies of viral load testing would be expected to reduce transmitted resistance among the population.

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Chapter 1: Sampling and Sensitivity Analysis Tools for Computation Modelling

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Author contributions

AH developed the graphics user interface code for SaSAT, developed the software package, wrote code for functions implemented in SaSAT, wrote the User Guide, performed analyses with the example model, produced all figures, and contributed to the Outline of Software section. DR and DW contributed to the overall conceptualisation and design of the project, developed code for the uncertainty and sensitivity algorithms. DR contributed to preparation of the manuscript. DW designed the example model, prepared the manuscript, and supervised the software design.

Abstract

SaSAT (Sampling and Sensitivity Analysis Tools) is a user-friendly software package for applying uncertainty and sensitivity analyses to mathematical and computational models of arbitrary complexity and context. The toolbox is built in Matlab®, a numerical mathematical software package, and utilises algorithms contained in the Matlab® Statistics Toolbox. However, Matlab® is not required to use SaSAT as the software package is provided as an executable file with all the necessary supplementary files. The SaSAT package is also designed to work seamlessly with Microsoft Excel but no functionality is forfeited if that software is not available. A comprehensive suite of tools is provided to enable the following tasks to be easily performed: efficient and equitable sampling of parameter space by various methodologies; calculation of correlation coefficients; regression analysis; factor prioritisation; and graphical output of results, including response surfaces, tornado plots, and scatterplots. Use of SaSAT is exemplified by application to a simple epidemic model. To our knowledge, a number of the methods available in SaSAT for performing sensitivity analyses have not previously been used in epidemiological modelling and their usefulness in this context is demonstrated.

Introduction

Mathematical and computational models today play a key role in almost every branch of science. The rapid advances in computer technology have led to increasingly more complex models as performance more like the real systems being investigated is sought. As a result, uncertainty and sensitivity analyses for quantifying the range of variability in model responses and for identifying the key factors giving rise to model outcomes have become essential for determining model robustness and reliability and for ensuring transparency [1]. Furthermore, as it is not uncommon for models to have dozens or even hundreds of independent predictors, these analyses usually constitute the first and primary approach for establishing mechanistic insights to the observed responses.

The challenge in conducting uncertainty analysis for models with moderate to large numbers of parameters is to explore the multi-dimensional parameter space in an equitable and computationally efficient way. Latin hypercube sampling (LHS), a type of stratified Monte Carlo sampling [2, 3] that is an extension of Latin Square sampling [4, 5] first proposed by McKay at al. [6] and further developed and introduced by Iman et al. [1-3], is a sophisticated and efficient method for achieving equitable sampling of all predictors simultaneously. Uncertainty analyses in this context use parameter samples generated by LHS as inputs in an independent external model; each sample may produce a different model response/outcome. Sensitivity analysis may then be conducted to rank the predictors (input parameters) in terms of their contribution to the uncertainty in each of the responses (model outcomes). This can be achieved in several ways involving primarily the calculation of correlation coefficients and regression analysis [1, 7], and variance-based methods [8].

In response to our need to conduct these analyses for numerous and diverse modelling exercises, we were motivated to develop a suite of tools, assembled behind a user-friendly interface, that would facilitate this process. We have named this toolbox SaSAT for "Sampling and Sensitivity Analysis Tools".

The toolbox was developed in the widely used mathematical software package Matlab® (The Mathworks, Inc., MA, USA) and utilises the industrial strength algorithms built into this package and the Matlab® Statistics Toolbox. It enables uncertainty analysis to be applied to models of arbitrary complexity, using the LHS method for sampling the input parameter space. SaSAT is independent of the model being applied; SaSAT generates input parameter samples for an external model and then uses these samples in conjunction with outputs (responses) generated from the external model to perform sensitivity analyses. A variety of methods are available for conducting sensitivity analyses including the calculation of correlation coefficients, standardised and non-standardised linear regression, logistic regression, Kolmogorov-Smirnov test, and factor prioritization by reduction of variance. The option to import data from, and export data to, Microsoft Excel or Matlab® is provided but not requisite. The results of analyses can be output in a variety of graphical and text-based formats.

While the utility of the toolbox is not confined to any particular discipline or modelling paradigm, the last two or three decades have seen remarkable growth in the use and importance of mathematical modelling in the epidemiological context (the primary context for modelling by the authors). However, many of the methods for uncertainty and sensitivity analysis that have been used extensively in other disciplines have not been widely used in epidemiological modelling. This paper provides a description of the SaSAT toolbox and the methods it employs, and exemplifies its use by application to a simple epidemic model with intervention. But SaSAT can be used in conjunction with theoretical or computational models applied to any discipline. Online supplementary material to this paper provides the freely downloadable full version of the SaSAT software for use by other practitioners.

Description of methods

In this section we provide a very brief overview and description of the sampling and sensitivity analysis

methods used in SaSAT. A user manual for the software is provided as supplementary material. Note that we use the terms parameter, predictor, explanatory variable, factor interchangeably, as well as outcome, output variable, and response.

Sampling methods and uncertainty analysis

Uncertainty analyses explore parameter ranges rather than simply focusing on specific parameter values. They are used to determine the degree of uncertainty in model outcomes that is due to uncertainty in the input parameters. Each input parameter for a model can be defined to have an appropriate probability density function associated with it. Then, the computational model can be simulated by sampling a single value from each parameter's distribution. Many samples should be taken and many simulations should be run, producing variable output values. The variation in the output can then be explored as it relates to the variation in the input. There are various approaches that could be taken to sample from the parameter distributions. Ideally one should vary all (*M*) model parameters simultaneously in the *M*-dimensional parameter space in an efficient manner. SaSAT provides random sampling, full factorial sampling, and Latin Hypercube Sampling.

Random sampling

The first obvious sampling approach is random sampling whereby each parameter's distribution is used to draw *N* values randomly. This is generally vastly superior to univariate approaches to uncertainty and sensitivity analyses, but it is not the most efficient way to sample the parameter space. In Figure 1a we present one instance of random sampling of two parameters.

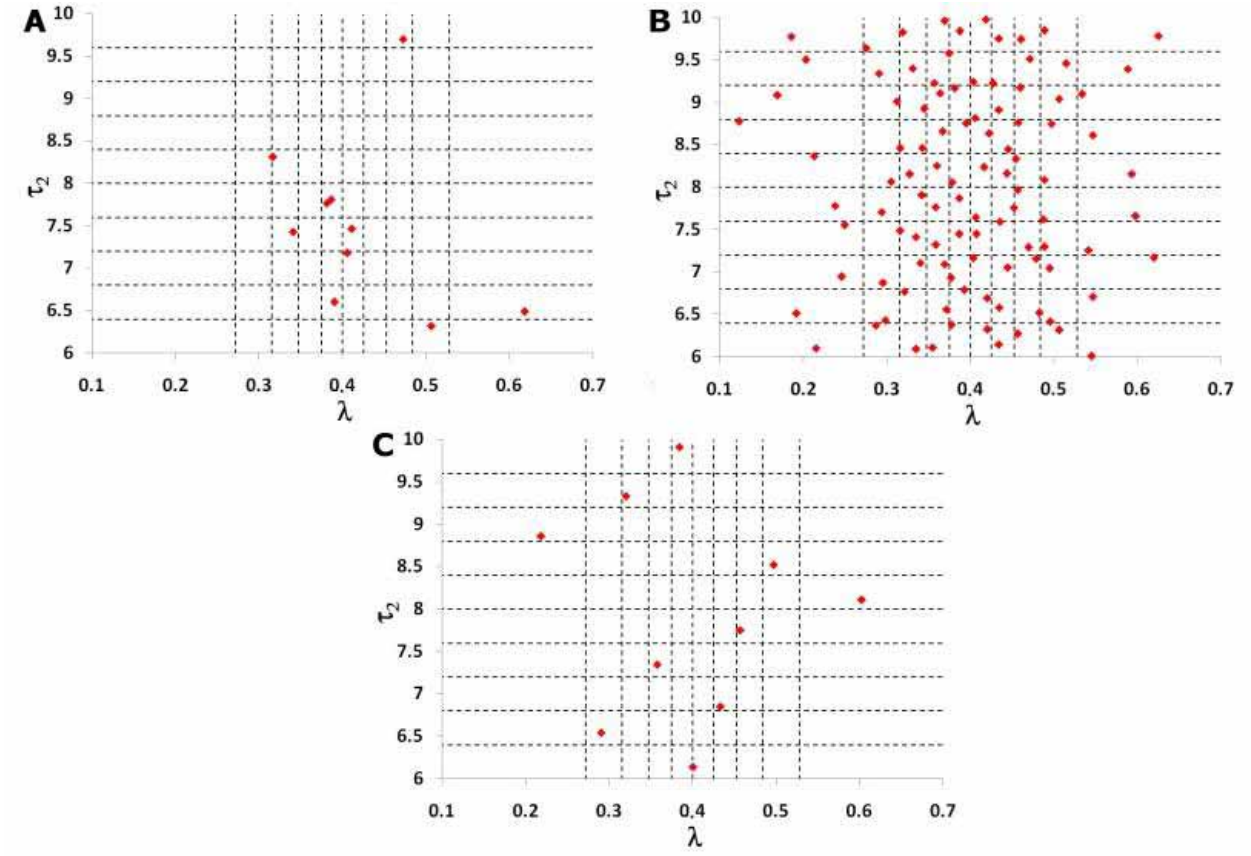

Figure 1: Examples of the three different sampling schemes: **(a)** random sampling, **(b)** full factorial sampling, and **(c)** Latin Hypercube Sampling, for a simple case of 10 samples (samples for $\tau_2 \sim U(6,10)$ and $\lambda \sim N(0.4,0.1)$ are shown). In random sampling, there are regions of the parameter space that are not sampled and other regions that are heavily sampled; in full factorial sampling, a random value is chosen in each interval for each parameter and every possible combination of parameter values is chosen; in Latin Hypercube Sampling, a value is chosen once and only once from every interval of every parameter (it is efficient and adequately samples the entire parameter space).

Full factorial sampling

The full factorial sampling scheme uses a value from every sampling interval for each possible combination of parameters (see Figure 1b for an illustrative example). This approach has the advantage of exploring the entire parameter space but is extremely computationally inefficient and time-consuming and thus not feasible for all models. If there are *M* parameters and each one has *N* values (or its distribution is divided into *N* equiprobable intervals), then the total number of parameter sets and model simulations is N^M (for example, 20 parameters and 100 samples per distribution would result in 10^{40} unique combinations, which is essentially unfeasible for most practical models). However, on

occasion full factorial sampling can be feasible and useful, such as when there are a small number of parameters and few samples required.

Latin hypercube sampling

More efficient and refined statistical techniques have been applied to sampling. Currently, the standard sampling technique employed is Latin Hypercube Sampling and this was introduced to the field of disease modelling (the field of our research) by Blower [9]. For each parameter a probability density function is defined and stratified into *N* equiprobable serial intervals. A single value is then selected randomly from every interval and this is done for every parameter. In this way, an input value from each sampling interval is used only once in the analysis but the entire parameter space is equitably sampled in an efficient manner [1, 9-11]. Distributions of the outcome variables can then be derived directly by running the model *N* times with each of the sampled parameter sets. The algorithm for the Latin Hypercube Sampling methodology is described clearly in [9]. Figure 1c and Figure 2 illustrate how the probability density functions are divided into equiprobable intervals and provide an example of the sampling.

Sensitivity analyses for continuous variables

Sensitivity analysis is used to determine how the uncertainty in the output from computational models can be apportioned to sources of variability in the model inputs [9, 12]. A good sensitivity analysis will extend an uncertainty analysis by identifying which parameters are important (due to the variability in their uncertainty) in contributing to the variability in the outcome variable [1]. A description of the sensitivity analysis methods available in SaSAT is now provided.

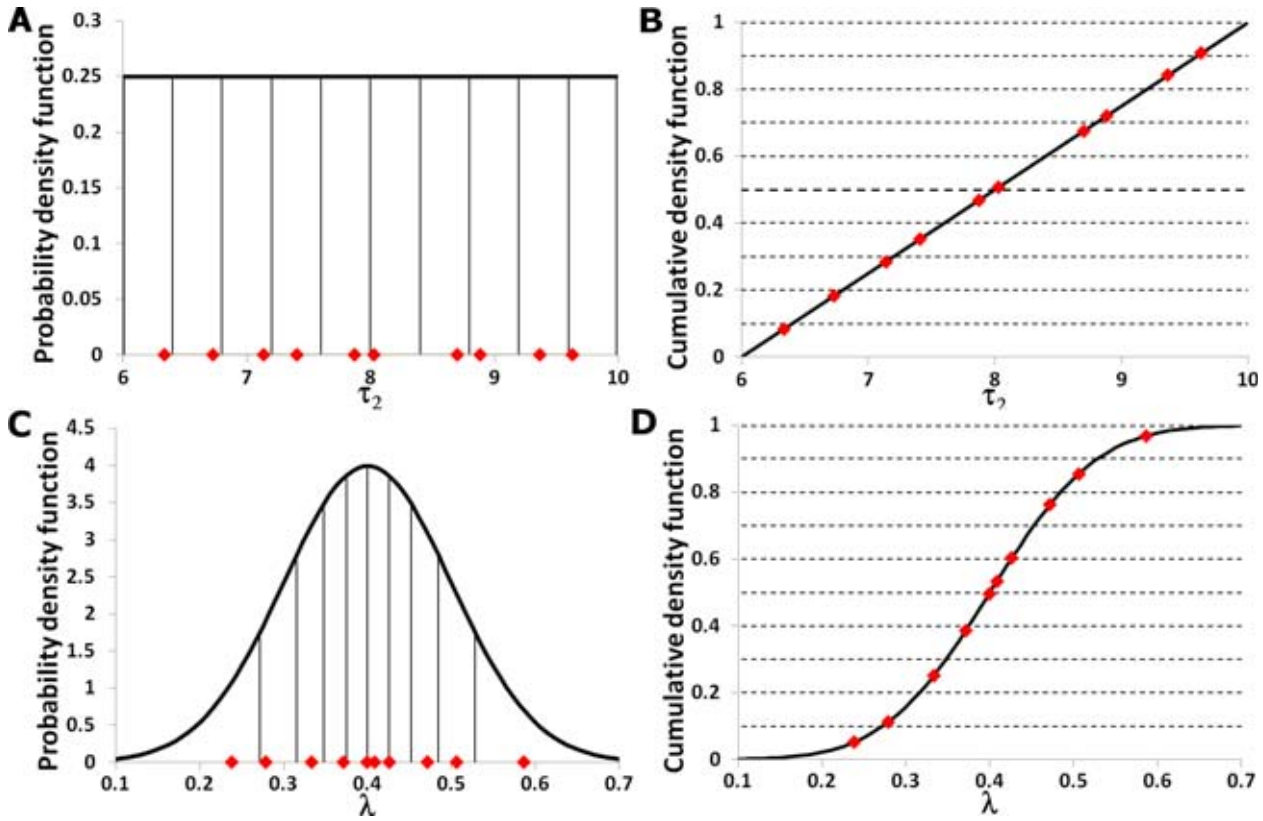

Figure 2: Examples of the probability density functions (**(a)** and **(c)**) and cumulative density functions (**(b)** and **(d)**) associated with parameters used in Figure 1; the black vertical lines divide the probability density functions into areas of equal probability. The red diamonds depict the location of the samples taken. Since these samples are generated using Latin Hypercube sampling there is one sample for each area of equal probability. The example distributions are: **(a)** A uniform distribution of the parameter τ_2, **(b)** the cumulative density function of τ_2, **(c)** a normal distribution function for the parameter λ, and **(d)** cumulative density function of λ.

Correlation coefficients

The association, or relationship, between two different kinds of variables or measurements is often of considerable interest. The standard measure of ascertaining such associations is the correlation coefficient; it is given as a value between -1 and +1 which indicates the degree to which two variables (e.g., an input parameter and output variable) are linearly related. If the relationship is perfectly linear (such that all data points lie perfectly on a straight line), the correlation coefficient is +1 if there is a positive correlation and -1 if the line has a negative slope. A correlation coefficient of zero means that there is no linear relationship between the variables. SaSAT provides three types of correlation

coefficients, namely: Pearson; Spearman; and Partial Rank. These correlation coefficients depend on the variability of variables. Therefore it should be noted that if a predictor is highly important but has only a single point estimate then it will not have correlation with outcome variability, but if it is given a wide uncertainty range then it may have a large correlation coefficient (if there is an association). Raw samples can be used in these analyses and do not need to be standardized.

Interpretation of the Pearson correlation coefficient assumes both variables follow a Normal distribution and that the relationship between the variables is a linear one. It is the simplest of correlation measures and is described in all basic statistics textbooks (e.g., [13]). When the assumption of normality is not justified, and/or the relationship between the variables is non-linear, a non-parametric measure such as the Spearman Rank Correlation Coefficient is more appropriate. By assigning ranks to data (positioning each datum point on an ordinal scale in relation to all other data points), any outliers can also be incorporated without heavily biasing the calculated relationship. This measure assesses how well an arbitrary monotonic function describes the relationship between two variables, without making any assumptions about the frequency distribution of the variables. Such measures are powerful when only a single pair of variables is to be investigated. However, quite often measurements of different kinds will occur in batches. This is especially the case in the analysis of most computational models that have many input parameters and various outcome variables. Here, the relationship between each input parameter with each outcome variable is desired. Specifically, each relationship should be ascertained whilst also acknowledging that there are various other contributing factors (input parameters). Simple correlation analyses could be carried out by taking the pairing of each outcome variable and each input parameter in turn, but it would be unwieldy and would fail to reveal more complicated patterns of relationships that might exist between the outcome variables and several variables simultaneously. Therefore, an extension is required and the appropriate extension for handling groups of variables is

partial correlation. For example, one may want to know how A was related to B when controlling for the effects of C, D, and E. Partial rank correlation coefficients (PRCCs) are the most general and appropriate method in this case. We recommend calculating PRCCs for most applications. The method of calculating PRCCs for the purpose of sensitivity analysis was first developed for risk analysis in various systems [2-5, 14]. Blower pioneered its application to disease transmission models [9, 15-22]. Because the outcome variables of dynamic models are time dependent, PRCCs should be calculated over the outcome time-course to determine whether they also change substantially with time. The interpretation of PRCCs assumes a monotonic relationship between the variables. Thus, it is also important to examine scatter-plots of each model parameter versus each predicted outcome variable to check for monotonicity and discontinuities [4, 9, 23]. PRCCs are useful for identifying the most important parameters but not for quantifying how much change occurs in the outcome variable by changing the value of the input parameter. However, because they have a sign (positive or negative) PRCCs can indicate the direction of change in the outcome variable if there is an increase or decrease in the input parameter. This can be further explored with regression and response surface analyses.

Regression

When the relationship between variables is not monotonic or when measurements are arbitrarily or irregularly distributed, regression analysis is more appropriate than simple correlation coefficients. A regression equation provides an expression of the relationship between two (or more) variables algebraically and indicates the extent to which a dependent variable can be predicted by knowing the values of other variables, or the extent of the association with other variables. In effect, the regression model is a surrogate for the true computational model. Accordingly, the coefficient of determination, R^2, should be calculated with all regression models and the regression analysis should not be used if R^2 is low (arbitrarily, less than ~0.6). R^2 indicates the proportion of the variability in the data set that is

explained by the fitted model and is calculated as the ratio of the sum of squares of the residuals to the total sum of squares. The adjusted R^2 statistic is a modification of R^2 that adjusts for the number of explanatory terms in the model. R^2 will tend to increase with the number of terms in the statistical model and therefore cannot be used as a meaningful comparator of models with different numbers of covariants (e.g., linear versus quadratic). The adjusted R^2, however, increases only if the new term improves the model more than would be expected by chance and is therefore preferable for making such comparisons. Both R^2 and adjusted R^2 measures are provided in SaSAT.

Regression analysis seeks to relate a response, or output variable, to a number of predictors or input variables that affect it. Although higher-order polynomial expressions can be used, constructing linear regression equations with interaction terms or full quadratic responses is recommended. This is in order to include direct effects of each input variable and also variable cross interactions and nonlinearities; that is, the effect of each input variable is directly accounted for by linear terms as a first-order approximation but we also include the effects of second-order nonlinearities associated with each variable and possible interactions between variables. The generalized form of the full second-order regression model is:

$$Y = \beta_0 + \sum_{i=1}^{m} \beta_i X_i + \sum_{i=1}^{m} \beta_{ii} X_i^{\,2} + \sum_{i=1}^{m-1} \sum_{j=i+1}^{m} \beta_{ij} X_i X_j \,,$$

where Y is the dependent response variable, the X_i's are the predictor (input parameter) variables, and the β's are regression coefficients.

One of the values of regression analysis is that results can be inspected visually. If there is only a single explanatory input variable for an outcome variable of interest, then the regression equation can be plotted graphically as a curve; if there are two explanatory variables then a three dimensional surface can be plotted. For greater than two explanatory variables the resulting regression equation is a hypersurface. Although hypersurfaces cannot be shown graphically, contour plots can be generated by

taking level slices, fixing certain parameters. Further, complex relationships and interactions between outputs and input parameters are simplified in an easily interpreted manner [24, 25]. Cross-products of input parameters reveal interaction effects of model input parameters, and squared or higher order terms allow curvature of the hypersurface. Obviously this can best be presented and understood when the dominant two predicting parameters are used so that the hypersurface is a visualised surface.

Although regression analysis can be useful to predict a response based on the values of the explanatory variables, the coefficients of the regression expression do not provide mechanistic insight nor do they indicate which parameters are most influential in affecting the outcome variable. This is due to differences in the magnitudes and variability of explanatory variables, and because the variables will usually be associated with different units. These are referred to as unstandardized variables and regression analysis applied to unstandardized variables yields unstandardized coefficients. The independent and dependent variables can be standardized by subtracting the mean and dividing by the standard deviation of the values of the unstandardized variables yielding standardized variables with mean of zero and variance of one. Regression analysis on standardized variables produces standardized coefficients [26], which represent the change in the response variable that results from a change of one standard deviation in the corresponding explanatory variable. While it must be noted that there is no reason why a change of one standard deviation in one variable should be comparable with one standard deviation in another variable, standardized coefficients enable the order of importance of the explanatory variables to be determined (in much the same way as PRCCs). Standardized coefficients should be interpreted carefully – indeed, unstandardized measures are often more informative. Standardized coefficients take values between -1 and +1; a standardized coefficient of +/-1 means that the predictor variable perfectly describes the response variable and a value of zero means that the predictor variable has no influence in predicting the response variable. Standardized regression coefficients should not, however, be considered to be equivalent to PRCCs. They both take values in the

same range (-1 to +1), can be used to rank parameter importance, and have similar interpretations at the extremes but they are evaluated differently and measure different quantities. Consequently, PRCCs and standardized regression coefficients will differ in value and may differ slightly in ranking when analysing the same data. The magnitude of standardized regression coefficients will typically be lower than PRCCs and should not be used alone for determining variable importance when there are large numbers of explanatory variables. However, the regression equation can provide more meaningful sensitivity than correlation coefficients as it can be shown that an x% decrease in one parameter can be offset by a y% increase/decrease in another, simply by exploring the coefficients of the regression equation. It must be noted that this is true for the statistical model, which is a surrogate for the actual model. The degree to which such claims can be inferred to the true model is determined by the coefficient of determination, R_2.

Factor prioritization by reduction of variance

Factor prioritization is a broad term denoting a group of statistical methodologies for ranking the importance of variables in contributing to particular outcomes. Variance-based measures for factor prioritization have yet to be used in many computational modelling fields, , although they are popular in some disciplines [27-34]. The objective of reduction of variance is to identify the factor which, if determined (that is, fixed to its true, albeit unknown, value), would lead to the greatest reduction in the variance of the output variable of interest. The second most important factor in reducing the outcome is then determined etc., until all independent input factors are ranked. The concept of importance is thus explicitly linked to a reduction of the variance of the outcome. Reduction of variance can be described conceptually by the following question: for a generic model,

$$Y = f\left(X_1, \ldots, X_M\right),$$

how would the uncertainty in Y change if a particular independent variable X_i could be fixed as a constant? This resultant variation is denoted by $V_{\mathbf{X}\sim i}\left(Y\middle| X_i = x_i^*\right)$. We expect that having fixed one source of variation $\left(X_i\right)$, the resulting variance $V_{\mathbf{X}\sim i}\left(Y\middle| X_i = x_i^*\right)$ would be smaller than the total or unconditional variance $V\left(Y\right)$. Hence, $V_{\mathbf{X}\sim i}\left(Y\middle| X_i = x_i^*\right)$ can be used as a measure of the importance of X_i ; the smaller $V_{\mathbf{X}\sim i}\left(Y\middle| X_i = x_i^*\right)$, the more X_i is influential. However, this is based on sensitivity with respect to the position of a single point $X_i = x_i^*$ for each input variable, and it is also possible to design a model for which $V_{\mathbf{X}\sim i}\left(Y\middle| X_i = x_i^*\right)$ at particular x_i^* values is greater than the unconditional variance, $V\left(Y\right)$ [35]. In general, it is also not possible to obtain a precise factor prioritization, as this would imply knowing the true value of each factor. The reduction of variance methodology is therefore applied to rank parameters in terms of their direct contribution to uncertainty in the outcome. The factor of greatest importance is determined to be that, which when fixed, will on average result in the greatest reduction in variance in the outcome. "On average" specifies in this case that the variation of the outcome factor should be averaged over the defined distribution of the specific input factor, removing the dependence on x_i^*. This is written as $E_{X_i}\left(V_{\mathbf{X}\sim i}\left(Y\middle| X_i\right)\right)$ and will always be less than or equal to $V(Y)$; in fact,

$$E_{X_i}\left(V_{\mathbf{X}\sim i}\left(Y\middle| X_i\right)\right)+V_{X_i}\left(E_{\mathbf{X}\sim i}\left(Y\middle| X_i\right)\right)=V(Y).$$

A small $E_{X_i}\left(V_{\mathbf{X}\sim i}\left(Y\middle| X_i\right)\right)$, or a large $V_{X_i}\left(E_{\mathbf{X}\sim i}\left(Y\middle| X_i\right)\right)$ implies that X_i is an important factor. Then, a first order sensitivity index of X_i on Y can be defined as

$$S_i = \frac{V_{X_i}\left(E_{\mathbf{X}\sim i}\left(Y\middle| X_i\right)\right)}{V(Y)}.$$

Conveniently, the sensitivity index takes values between 0 and 1. A high value of S_i implies that X_i is an important variable. Variance based measures, such as the sensitivity index just defined, are concise, and easy to understand and communicate. This is an appropriate measure of sensitivity to use to rank the input factors in order of importance even if the input factors are correlated [36]. Furthermore, this method is completely 'model-free'. The sensitivity index is also very easy to interpret; S_i can be interpreted as being the proportion of the total variance attributable to variable X_i. In practice, this measure is calculated by using the input variables and output variables and fitting a surrogate model, such as a regression equation; a regression model is used in our SaSAT application. Therefore, one must check that the coefficient of determination is sufficiently large for this method to be reliable (an R^2 value for the chosen regression model can be calculated in SaSAT).

Sensitivity analyses for binary outputs: logistic regression

Binomial logistic regression is a form of regression, which is used when the response variable is dichotomous (0/1; the independent predictor variables can be of any type). It is used very extensively in the medical, biological, and social sciences [37-41]. Logistic regression analysis can be used for any dichotomous response; for example, whether or not disease or death occurs. Any outcome can be considered dichotomous by distinguishing values that lie above or below a particular threshold. Depending on the context these may be thought of qualitatively as "favourable" or "unfavourable" outcomes. Logistic regression entails calculating the probability of an event occurring, given the values of various predictors. The logistic regression analysis determines the importance of each predictor in influencing the particular outcome. In SaSAT, we calculate the coefficients (β_i) of the generalized linear model that uses the logit link function,

$$\text{logit}\left(p_i\right) = \ln\left(\frac{p_i}{1-p_i}\right) = \beta_0 + \beta_1 X_{1,i} + \beta_2 X_{2,i} + \ldots + \beta_m X_{m,i},\ i = 1\ldots n,$$

where $p_i = E\left(Y \middle| X_i\right) = \Pr\left(Y_i = 1\right)$ and the X 's are the covariates; the solution for the coefficients is determined by maximizing the conditional log-likelihood of the model given the data. We also calculate the odds ratio (with 95% confidence interval) and p-value associated with the odds ratio.

There is no precise way to calculate R^2 for logistic regression models. A number of methods are used to calculate a pseudo-R^2, but there is no consensus on which method is best. In SaSAT, R^2 is calculated by performing bivariate regression on the observed dependent and predicted values [42].

Sensitivity analyses for binary outputs: Kolmogorov-Smirnov

Like binomial logistic regression, the Smirnov two-sample test (two-sided version) [43-46] can also be used when the response variable is dichotomous or upon dividing a continuous or multiple discrete response into two categories. Each model simulation is classified according to the specification of the 'acceptable' model behaviour; simulations are allocated to either set *A* if the model output lies within the specified constraints, and set to A' otherwise. The Smirnov two-sample test is performed for each predictor variable independently, analysing the maximum distance $d_{\max}$ between the cumulative distributions of the specific predictor variables in the *A* and A' sets. The test statistic is $d_{\max}$, the maximum distance between the two cumulative distribution functions, and is used to test the null hypothesis that the distribution functions of the populations from which the samples have been drawn are identical. P-values for the test statistics are calculated by permutation of the exact distribution whenever possible [46-48]. The smaller the p-value (or equivalently the larger $d_{\max}\left(x_i\right)$), the more important is the predictor variable, X_i, in driving the behaviour of the model.

Overview of software

SaSAT has been designed to offer users an easy to use package containing all the statistical analysis tools described above. They have been brought together under a simple and accessible graphical user interface (GUI). The GUI and functionality was designed and programmed using MATLAB® (version 7.4.0.287, Mathworks, MA, USA), and makes use of MATLAB®'s native functions. However, the user is not required to have any programming knowledge or even experience with MATLAB® as SaSAT stands alone as an independent software package compiled as an executable. SaSAT is able to read and write MS-Excel and/or MATLAB® '*.mat' files, and can convert between them, but it is not requisite to own either Excel or Matlab.

The opening screen presents the main menu (Figure 3a), which acts as a hub from which each of four modules can be accessed. SaSAT's User Guide [see additional file 1] is available via the Help tab at the top of the window, enabling quick access to helpful guides on the various utilities. A typical process in a computational modelling exercise would entail the sequence of steps shown in Figure 3b. The model (input) parameter sets generated in steps 1 and 2 are used to externally simulate the model (step 3). The output from the external model, along with the input values, will then be brought back to SaSAT for sensitivity analyses (steps 4 and 5).

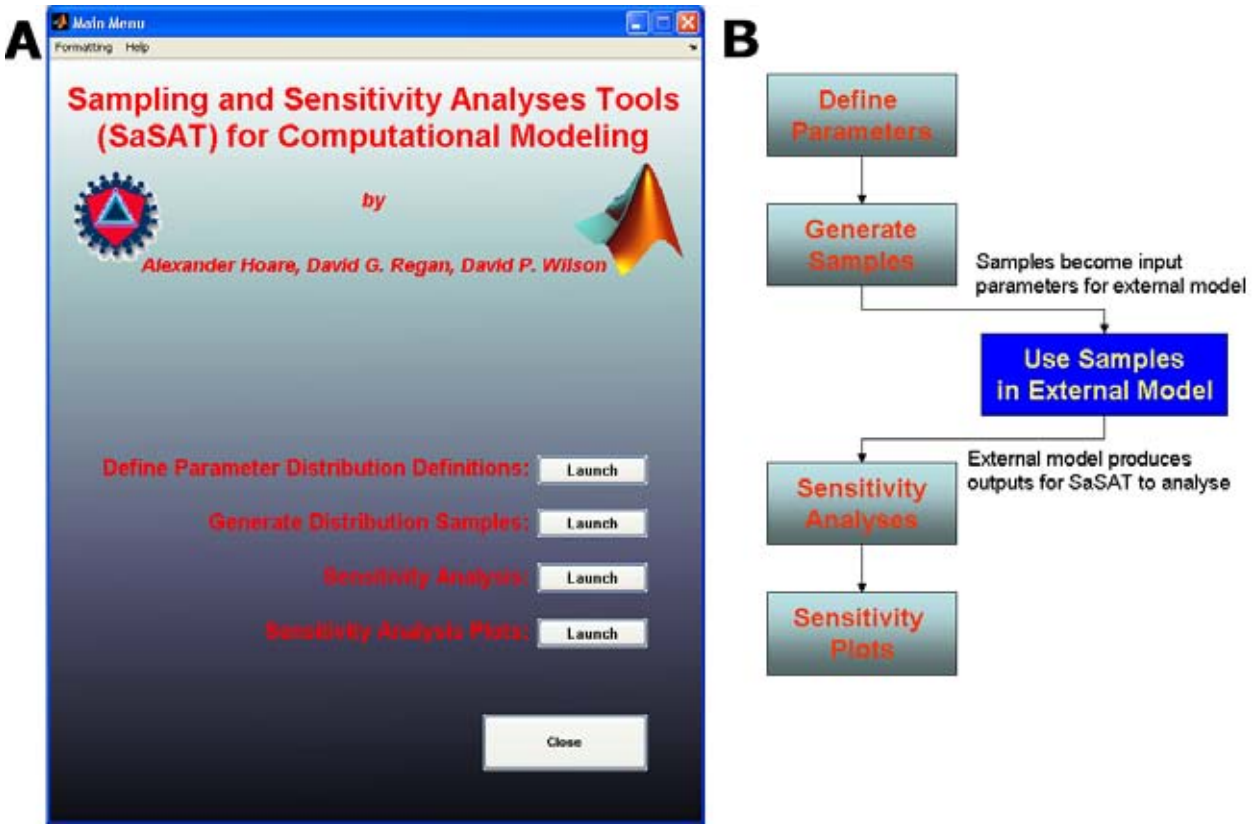

Figure 3: (a) The main menu of SaSAT, showing options to enter the four utilities; **(b)** a flow chart describing the typical process of a modelling exercise when using SaSAT with an external computational model, beginning with the user assigning parameter definitions for each parameter used by their model via the SaSAT '*Define Parameter Distribution*' utility. This is followed by using the '*Generate Distribution Samples*' utility to generate samples for each parameter, the user then employs these samples in their external computational model. Finally the user can analyse the results generated by their computational model, using the '*Sensitivity Analysis*' and '*Sensitivity Analysis Plots*' utility.

Define parameter distributions

The '*Define Parameter Distribution*' utility (interface shown in Figure 4a) allows users to assign various distribution functions to their model parameters. SaSAT provides sixteen distributions, nine basic distributions: 1) Constant, 2) Uniform, 3) Normal, 4) Triangular, 5) Gamma, 6) Lognormal, 7) Exponential, 8) Weibull, and 9) Beta; and seven additional distributions have also been included, which allow dependencies upon previously defined parameters. When data is available to inform the choice of distribution, the parameter assignment is easily made. However, in the absence of data to inform on the distribution for a given parameter, we recommend using either a uniform distribution or a triangular distribution peaked at the median and relatively broad range between the minimum and maximum

values as guided by literature or expert opinion. When all parameters have been defined, a definition file can be saved for later use (such as sample generation).

Generate distribution samples

Typically, the next step after defining parameter distributions is to generate samples from those distributions. This is easily achieved using the '*Generate Distribution Samples*' utility (interface shown in Figure 4b). Three different sampling techniques are offered: 1) Random, 2) Latin Hypercube, and 3) Full Factorial, from which the user can choose. Once a distribution method has been selected, the user need only select the definition file (created in the previous step using the '*Define Parameter Distribution*' utility), the destination file for the samples to be stored, and the number of samples desired, and a parameter samples file will be generated. There are several options available, such as viewing and saving a plot of each parameter's distribution. Once a samples file is created, the user may then proceed to producing results from their external model using the samples file as an input for setting the parameter values.

Sensitivity analyses

The '*Sensitivity Analysis Utility*' (interface shown in Figure 4c) provides a suite of powerful sensitivity analysis tools for calculating: 1) Pearson Correlation Coefficients, 2) Spearman Correlation Coefficients, 3) Partial Rank Correlation Coefficients, 4) Unstandardized Regression, 5) Standardized Regression, 6) Logistic Regression, 7) Kolmogorov-Smirnov test, and 8) Factor Prioritization by Reduction of Variance. The results of these analyses can be shown directly on the screen, or saved to a file for later inspection allowing users to identify key relationships between parameters and outcome variables.

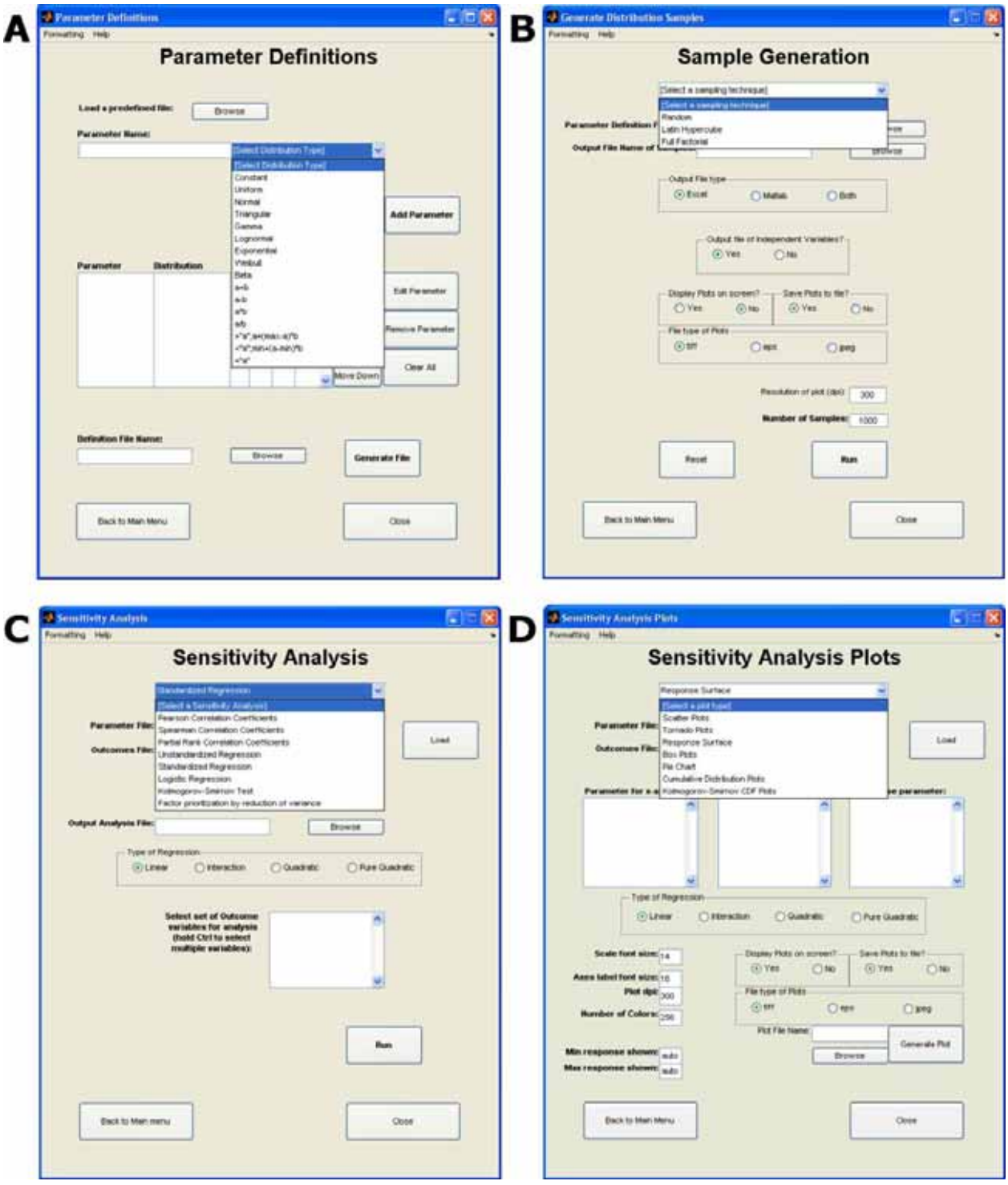

Figure 4: Screenshots of each of SaSAT's four different utilities: **(a)** The *Define Parameter Distribution Definition* utility, showing all of the different types of distributions available, **(b)** The *Generate Distribution Samples* utility, displaying the different types of sampling techniques in the drop down menu, **(c)** the *Sensitivity Analyses* utility, showing all the sensitivity analyses that the user is able to perform, **(d)** the *Sensitivity Analysis Plots* utility showing each of the seven different plot types.

Sensitivity analyses plots

The last utility, '*Sensitivity Analyses Plots'* (interface shown in Figure 4d) offers users the ability to visually display some results from the sensitivity analyses. Users can create: 1) Scatter plots, 2) Tornado plots, 3) Response surface plots, 4) Box plots, 5) Pie charts, 6) Cumulative distribution plots, 7) Kolmogorov-Smirnov CDF plots. Options are provided for altering many properties of figures (e.g., font sizes, image resolution, etc.). The user is also provided the option to save each plot as either a *.tiff, *.eps, or *.jpeg file, in order to produce images of suitable quality for publication.

A simple epidemiological example

To illustrate the usefulness of SaSAT, we apply it to a simple theoretical model of disease transmission with intervention. In the earliest stages of an emerging respiratory epidemic, such as SARS or avian influenza, the number of infected people is likely to rise quickly (exponentially) and if the disease sequelae of the infections are very serious, health officials will attempt intervention strategies, such as isolating infected individuals, to reduce further transmission. We present a 'time-delay' mathematical model for such an epidemic. In this model, the disease has an incubation period of τ_1 days in which the infection is asymptomatic and non-transmissible. Following the incubation period, infected people are infectious for a period of τ_2 days, after which they are no longer infectious (either due to recovery from infection or death). During the infectious period an infected person may be admitted to a health care facility for isolation and is therefore removed from the cohort of infectious people. We assume that the rate of colonization of infection is dependent on the number of current infectious people *I*(*t*), and the infectivity rate λ (λ is a function of the number of susceptible people that each infectious person is in

contact with on average each day, the duration of time over which the contact is established, and the probability of transmission over that contact time). Under these conditions, the rate of entry of people into the incubation stage is λI (known as the force of infection); we assume that susceptible people are not in limited supply in the early stages of the epidemic. In this model λ is the average number of new infections per infectious person per day. We model the change between disease stages as a step-wise rate, i.e., after exactly τ_1 days of incubation individuals become infectious and are then removed from the system after an infectious period of a further τ_2 days. If $1/\gamma$ is the average time from the onset of infectiousness until isolation, then the rate of change in the number of infectious people at time *t* is given by

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \lambda I\left(t-\tau_1\right) - \lambda e^{-\gamma\tau_2} I\left(t-\tau_1-\tau_2\right) - \gamma I\left(t\right).$$

The exponential term arises from the fact that infected people are removed at a rate γ over τ_2 days [50]. See Figure 5 for a schematic diagram of the model structure. Mathematical stability and threshold analyses (not shown) reveal that the critical threshold for controlling the epidemic is

$$R_0 = \left(1-e^{-\gamma\tau_2}\right)\lambda/\gamma\,.$$

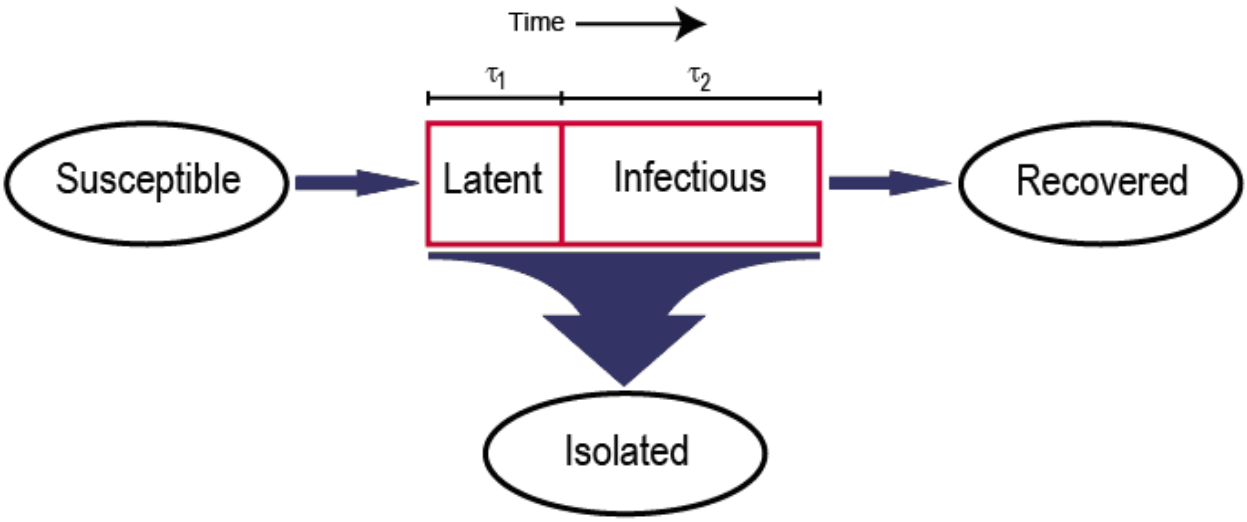

Figure 5: Schematic diagram of the framework of our illustrative theoretical epidemic model.

This threshold parameter, known as the basic reproduction number [49], is independent of τ_1 (the incubation period). But at the beginning of the epidemic, if there is no removal of infectious people before natural removal by recovery or death (that is, if $\gamma = 0$), the threshold parameter becomes $R_0 = \lambda\tau_2$. If the infectious period (τ_2) is long and there is significant removal of infectious people $(\gamma > 0)$, then the threshold criterion reduces to $R_0 = \lambda/\gamma$. Intuitively, both of these limiting cases represent the average number of days that someone is infectious multiplied by the average number of people to whom they will transmit infection per day.

In order to contain (and effectively eliminate) an epidemic an intervention could involve attempting to quarantine infected individuals sufficiently quickly such that $\gamma > \lambda$. The sooner such an intervention is implemented, the greater the number of new infections that will be prevented. Therefore, an appropriate outcome indicator of the effectiveness of such an intervention strategy is the cumulative total number of infections over the entire course of the epidemic, which we denote as the 'attack

number'. This quantity is calculated numerically from computer simulation. To investigate various interventions of quarantining, we model the steady increase from no isolation to a maximum of *p*% of infectious people that are isolated after an average of τ_3 days of symptoms and this level of quarantining is maintained after *T* days. That is, $\gamma(t) = \begin{cases} pt/(\tau_3 T), & t < T \\ p/\tau_3, & t \geq T \end{cases}$, where *t* is the time from the beginning of infectiousness of the first infected person (infectiousness could relate to the onset of symptoms, but not necessarily). Then, provided that $p/\tau_3 > \lambda$ and this quarantine level is sustained, the epidemic will be eradicated.

There are three biological parameters that influence disease dynamics: λ, τ_1, and τ_2 (of which λ and τ_2 are crucial for establishing the epidemic); and there are three intervention parameters crucial for eliminating the epidemic (p, τ_3) and for reducing its epidemiological impact (T). In order to demonstrate this theoretical model and the tools of SaSAT we choose a hypothetical newly emergent disease with an incubation period of $\tau_1 \sim \Gamma(9,1/3)$ which specifies an average of 3 days and standard deviation of 1 day according to a Gamma distribution (Γ); an infectious period of $\tau_2 \sim U(6,10)$ days (i.e., a uniform distribution over the interval 6-10 days); and a transmission rate of $\lambda \sim N(0.4, 0.1)$ new transmissions per day per infectious person (this is a Normal distribution with mean 0.4 and variance 0.1). This translates to an initial R_0 prior to interventions of $R_0 \sim U(6,10) \times N(0.4, 0.1)$ (which has a mean of 3.2 and standard deviation of ~0.93). We also investigate a range of different intervention strategies: isolating (1) 50%, (2) 75%, or (3) 95% of infectious people after an average of (a) 1 day, (b) 2 days, or (c) 3 days of symptoms, and scaling up the intervention to reach the maximal

attainable level after either (i) 1 month, (ii) 2 months, or (iii) 3 months. This leads to a total of 27 intervention strategies.

To simulate the epidemics, samples are required from each of the three biological parameters' distributions. SaSAT's 'Define Parameter Distribution Definitions' utility allows these distributions to be defined simply. Then, SaSAT's 'Generate Distribution Samples' utility provides the choice of random, Latin Hypercube, or full-factorial sampling. Of these, Latin Hypercube Sampling is the most efficient sampling method over the parameter space and we recommend this method for most models. We employed this method here, taking 1000 samples, using the defined parameter file. Independent of SaSAT, this set of 1000 parameter values was used to carry out numerical simulations of the time-courses of the epidemic, and in each case we commenced the epidemic by introducing one infectious person. This was then carried out for each of the 27 interventions (a total of 27,000 simulations). For each simulation the time to eradicate the epidemic and the attack number were recorded. These variables became the main outcome variables used for the sensitivity analyses against the input parameters generated by the Latin Hypercube Sampling procedure.

A research paper that is specifically focused on a particular disease and the impact of different strategies would present various figures (like Figure 6, generated from SaSAT's 'Sensitivity Analysis Plots' utility) and discussion around their comparison. However, for the purposes of this paper in demonstrating SaSAT we chose just one strategy (namely, 2aiii: attaining isolation of 75% of infectious individuals 1 day after symptoms begin, after 3 months from the commencement of the epidemic). The cumulative distribution functions of the distributions of time to eradicate the epidemic and the attack number were produced by SaSAT's 'Sensitivity Plots' utility and shown in Figs. 7a,b. The time until the epidemic was eradicated ranged from 28 to 583 days (99 median, IQR 81-126), and the total number of infections ranged from 2 to 501,263 (190 median, IQR 55-732). For the sake of illustration, if the goal of the

intervention was to reduce the number of infections to less than 100, the importance of parameters in contributing to either less than, or greater than, 100 infections can be analysed with SaSAT by categorising each parameter set as a dichotomous variable. Logistic regression and the Smirnov test were used, within SaSAT's 'Sensitivity Analysis' utility and the results are shown in Table 1. As far as we are aware these methodologies have not previously been used to analyse the results of theoretical epidemic models. It is seen from Table 1 that λ (the infectivity rate) was the most important parameter contributing to whether the goal was achieved or not, followed by τ_2 (infectious period), and then τ_1 (incubation period). These results can be most clearly demonstrated graphically by Kolmogorov-Smirnov CDF plots (Fig. 8).

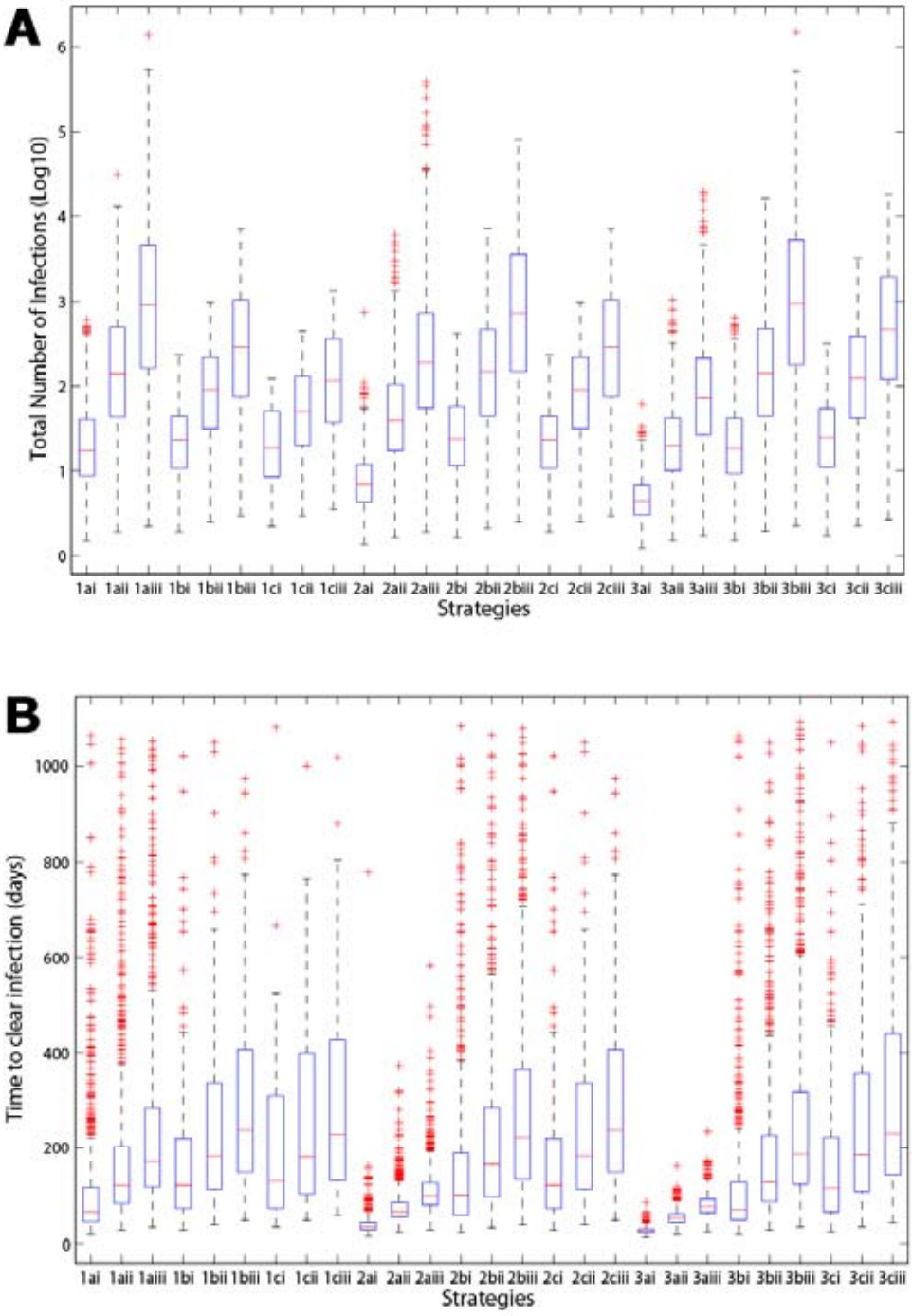

Figure 6: Box plots comparing the 27 different strategies used in the example model, with the whisker length set at 1.5 multiplied by the inter-quartile range, and red '+' showing the outliers: **(a)** the total number of infections caused by each strategy on a log10 scale, **(b)** the total time to clear the infection for each strategy.

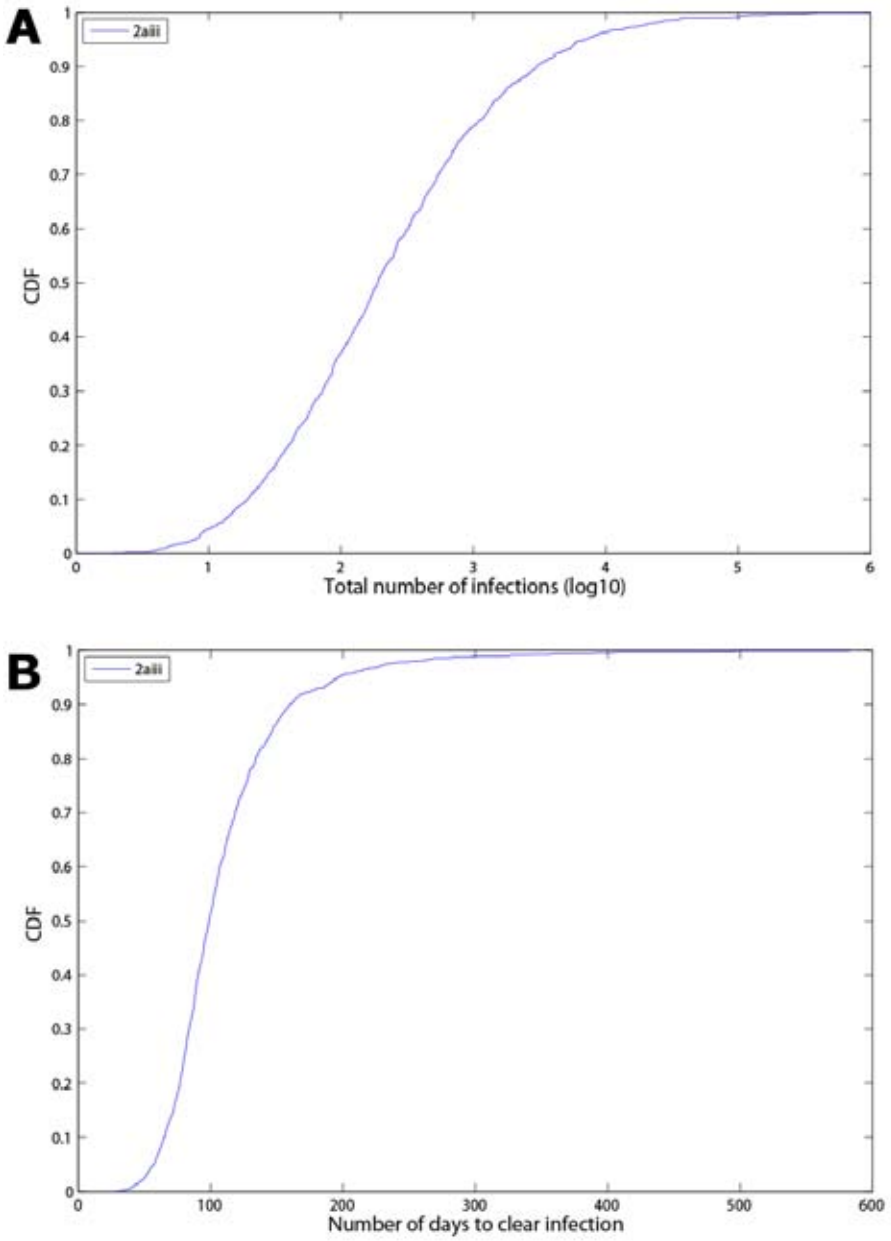

Figure 7: Cumulative density functions of: **(a)** the total number of infections (log10); and **(b)** the number of days to clear the infection, for a single strategy (2aiii: isolating 75% of infectious people after 1 day of infectiousness and achieving this level of intervention after 3 months).

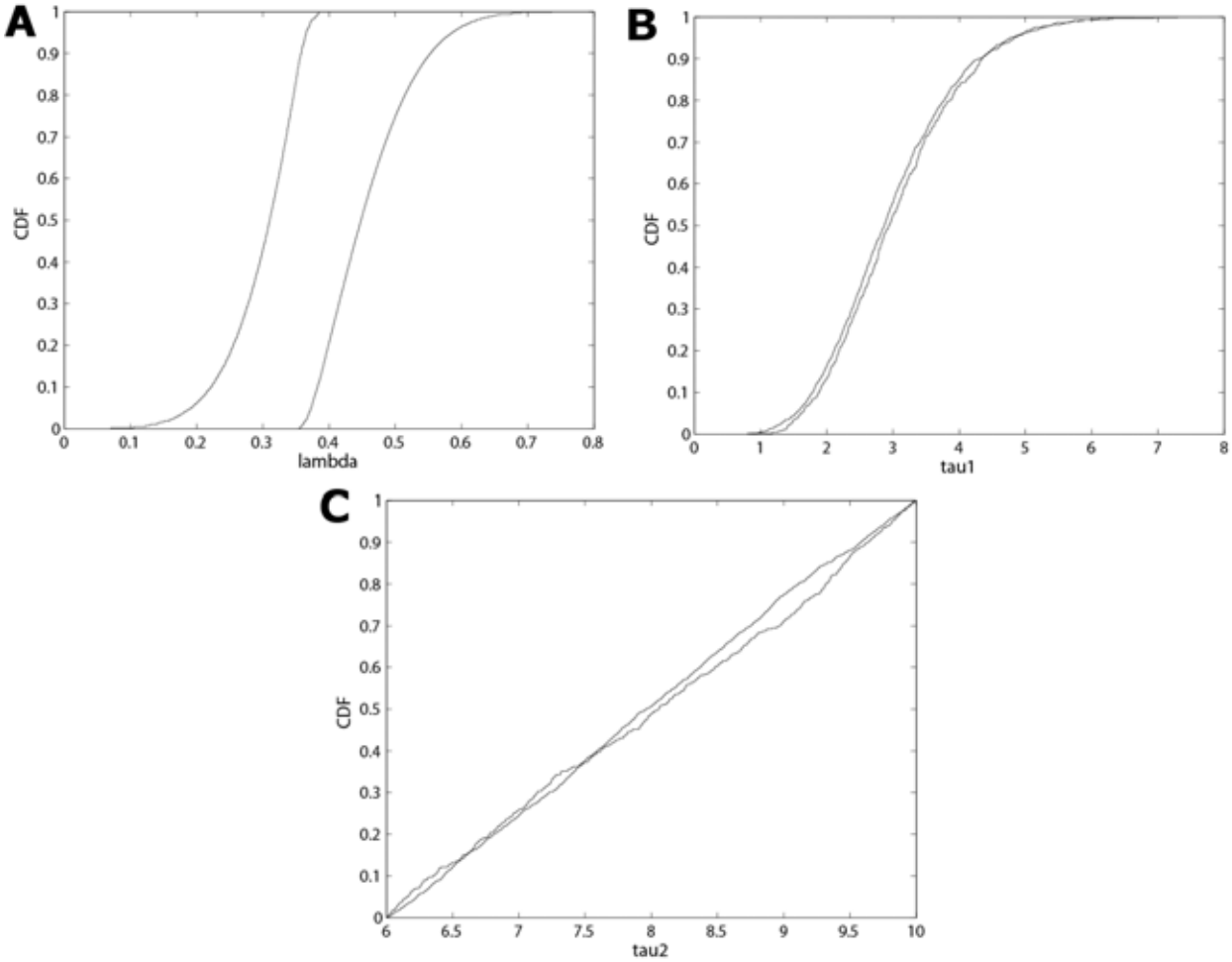

Figure 8: Kolmogorov-Smirnov plots of each parameter displaying the CDFs with the greatest difference between parameter subsets contributing to a 'success' or 'failure' outcome for each parameter (see Table 1): **(a)** λ, showing the largest maximum difference between the two CDFs, **(b)** τ_1, showing very little difference, and **(c)** τ_2, showing little difference similar to τ_1. In this example a 'success' is defined as the total number of infections less than 100 at the end of the epidemic.

Parameter	Logistic Regression (R^2=0.95)	Kolmogorov-Smirnov
infectivity rate (λ)	$p < 0.0001$ odds > 10^8	$p < 0.0001$ maxd = 0.93
incubation period (τ_1)	$p < 0.0001$ odds 3.12 (2.34, 4.17)	$p = 0.57$ maxd = 0.05
infectious period (τ_2)	$p = 0.04$ odds 1.29 (1.01, 1.64)	$p = 0.20$ maxd = 0.07

Table 1: Results of dichotomous variable sensitivity analysis: listing of the most important parameters in determining whether or not less than 100 people are infected by the epidemic (as determined by logistic regression and the Kolmogorov-Smirnov test).

We investigated the existence of any non-monotonic relationships between the attack number and each of the input parameters through SaSAT's 'Sensitivity Plots' utility (e.g. see Figure 9); no non-monotonic relationships were found, and a clear increasing trend was observed for the attack number versus λ, the infectivity rate. Then, it was determined which parameters most influenced the attack number and by how much. To conduct this analysis, SaSAT's 'Sensitivity Analyses' utility was used. The calculation of PRCCs was conducted; these are useful for ranking the importance of parameter-output correlations. Another method that we implemented for ranking was the calculation of standardized regression coefficients; the advantage of these coefficients is the ease of their interpretation in how a change in one parameter can be offset by an appropriate change in another parameter. A third method for ranking the importance of parameters, not previously used in analysis of theoretical epidemic models as far as we are aware, is factor prioritization by reduction of variance. These indicators of importance of parameters provided consistent rankings, as shown in Table 2; we calculated these indices for linear, interaction, pure quadratic and full quadratic response hypersurfaces and they were all in very close agreement (all indices were equivalent to at least 2 decimal places for each statistical model and so we

show results just for the full quadratic case (R^2=0.997)). The rankings for all correlation coefficients can also be shown as a tornado plot (see Figure 10a).

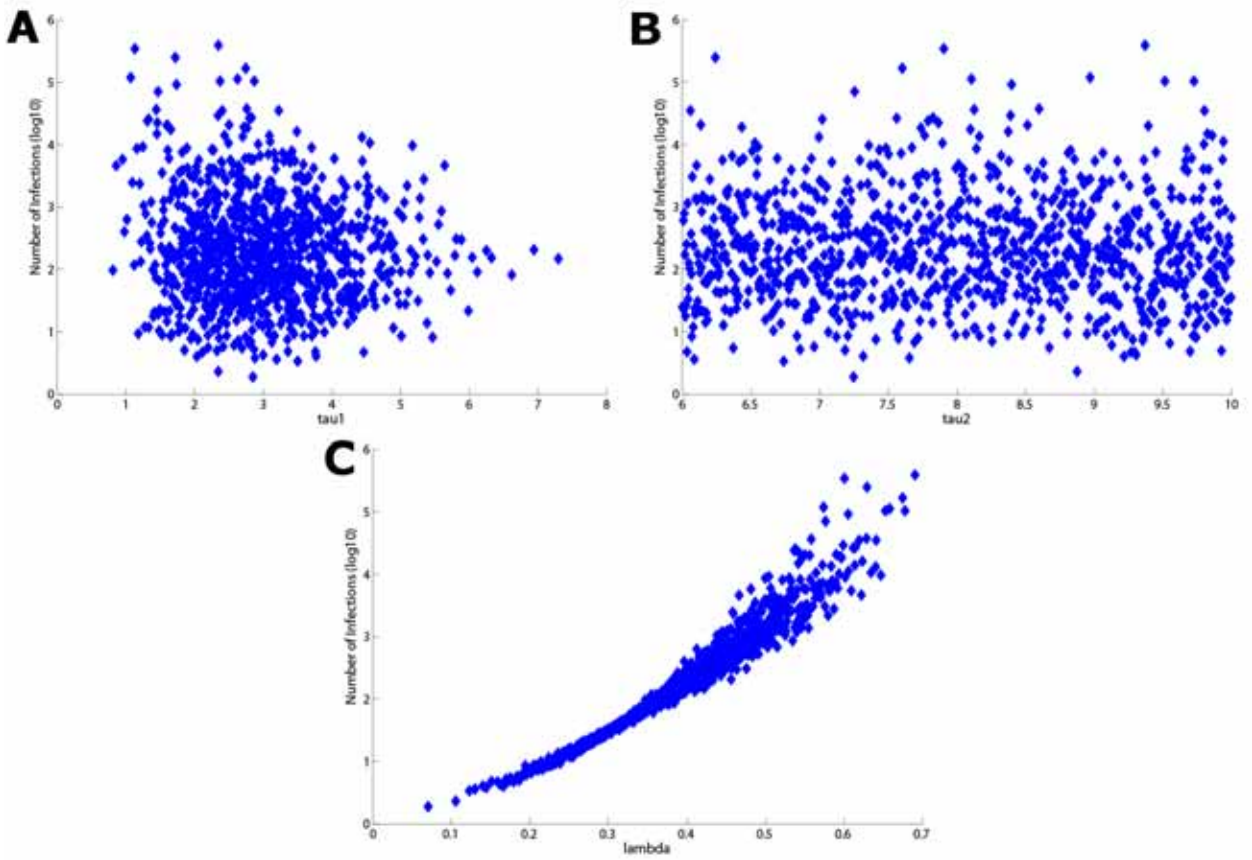

Figure 9: Scatter plots comparing the total number of infections (log10 scale) against each parameter: **(a)** τ_1, shows some weak correlation, **(b)** τ_2, shows little or no correlation, and **(c)** λ, showing a strong correlation (see Table 2 for correlation coefficients).

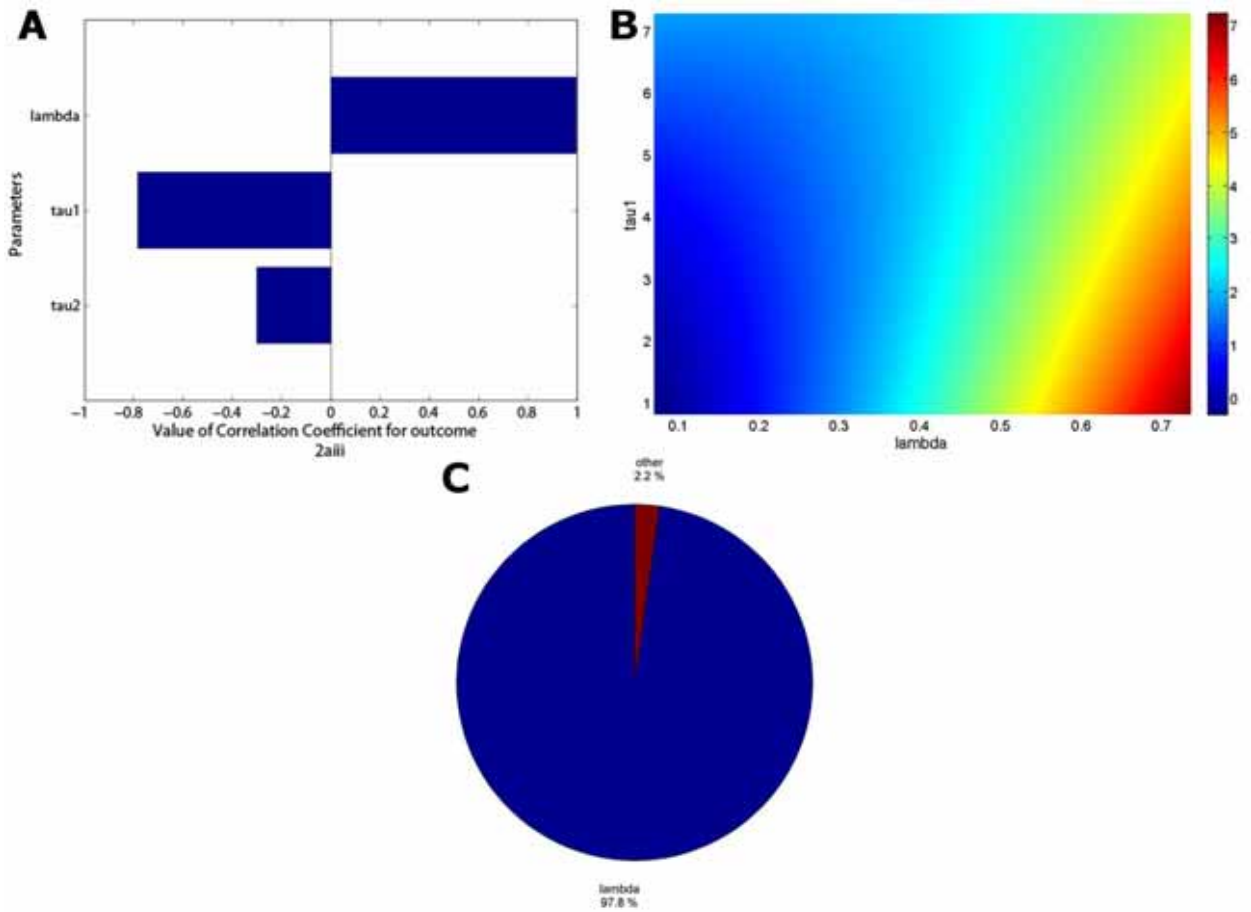

Figure 10: (a) Tornado plot of partial rank correlation coefficients, indicating the importance of each parameter's uncertainty in contributing to the variability in the time to eradicate infection. **(b)** Quadratic response surface (R^2=0.997, indicating extremely strong fit) of the total number of infections over the duration of the epidemic (on log10 scale) as it depends on τ_1 (the incubation period) and λ (the infectivity rate). **(c)** Pie chart of factor prioritization sensitivity indices; this visual representation clearly shows the dominance of the infectivity rate for this model. Note that τ_1 and τ_2 have been combined under the title of 'other', this is because the sensitivity indices of these parameters are both relatively small in magnitude.

Parameter	Partial rank correlation coefficient	Standardized regression coefficient	Sensitivity index (reduction of variance)
infectivity rate (λ)	0.995	0.982	97.7%
incubation period (τ_1)	-0.783	-0.146	2.1%
infectious period (τ_2)	-0.300	-0.025	0.2%

Table 2: Results of sensitivity analysis: impact of the variability in the input variables in influencing variability in the attack number (total cumulative number of infected people), as determined by (i) partial rank correlation coefficients, (ii) standardized regression coefficients, and (iii) factor prioritization by reduction of variance.

The influence of combinations of parameters on outcome variables can be presented visually. Response surface methodology is a powerful approach for investigating the simultaneous influence of multiple parameters on an outcome variable by illustrating (i) how the outcome variable will be affected by a change in parameter values; and (ii) how one parameter must change to offset a change in a second parameter. Figure 10b, from SaSAT's 'Sensitivity Plots' utility shows the pairings of the impact of infectivity rate (λ) and the incubation period (τ_1) on the attack number. Factor prioritization by reduction of variance is a very useful and interpretable measure for sensitivity; it can be represented visually through a pie-chart for example (Fig. 10c).

Conclusions

In this paper we outlined the purpose and the importance of conducting rigorous uncertainty and sensitivity analyses in mathematical and computational modelling. We then presented SaSAT, a user-friendly software package for performing these analyses, and exemplified its use by investigating the impact of strategic interventions in the context of a simple theoretical model of an emergent epidemic.

The various tools provided with SaSAT were used to determine the importance of the three biological parameters (infectivity rate, incubation period and infectious period) in (i) determining whether or not less than 100 people will be infected during the epidemic, and (ii) contributing to the variability in the overall attack number. The various graphical options of SaSAT are demonstrated including: box plots to illustrate the results of the uncertainty analysis; scatter plots for assessing the relationships (including monotonicity) of response variables with respect to input parameters; CDF and tornado plots; and response surfaces for illustrating the results of sensitivity analyses.

The results of the example analyses presented here are for a theoretical model and have no specific “real world” relevance. However, they do illustrate that even for a simple model of only three key parameters, the uncertainty and sensitivity analyses provide clear insights, which may not be intuitively obvious, regarding the relative importance of the parameters and the most effective intervention strategies.

We have highlighted the importance of uncertainty and sensitivity analyses and exemplified this with a relatively simple theoretical model and noted that such analyses are considerably more important for complex models; uncertainty and sensitivity analyses should be considered an essential element of the modelling process regardless of the level of complexity or scientific discipline. Finally, while uncertainty and sensitivity analyses provide an effective means of assessing a model's "trustworthiness", their interpretation assumes model validity which must be determined separately. There are many approaches to model validation but a discussion of this is beyond the scope of the present paper. Here, with the provision of the easy-to-use SaSAT software, modelling practitioners should be enabled to carry out important uncertainty and sensitivity analyses much more extensively.

Acknowledgements

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Chapter 2: Using mathematical modelling to help explain the differential increase in HIV incidence in New South Wales, Victoria, and Queensland: importance of other sexually transmissible infections

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Author Contributions

AH carried out all analyses, produced results and figures, and wrote the manuscript. DPW conceived the analyses, conducted a literature survey, and supervised the technical project. DGR was involved in conceptualization, literature surveys, and manuscript editing. JK was involved with conceptualization, facilitating steering of the project, developing the reference group and manuscript editing. MGL was involved in conceptualization, facilitating steering of the project and the reference group, and manuscript editing. DPW, AH, and DGR developed the model framework.

Abstract

Background: Since 1999, there has been an increase in the number of HIV diagnoses in Australia, predominantly amongst men who have sex with men (MSM), but the magnitude of increase differs between states: ~7% rise in New South Wales, ~96% rise in Victoria, and a ~68% rise in Queensland. ***Methods:*** Epidemiological, clinical, behavioural, and biological data were collated into a mechanistic mathematical model to explore possible reasons for this increase in HIV notifications in MSM. The model was then used to make projections to 2015 under various scenarios.

Results: The model suggests that trends in clinical and behavioural parameters, including increases in unprotected anal intercourse (UAI), cannot explain the magnitude of the observed rise in HIV notifications, without a substantial increase in a 'transmission-increasing' factor. We suggest that a highly plausible biological factor is an increase in the prevalence of other sexually transmitted infections (STIs). It was found that New South Wales required a ~2-fold increase in other STIs to match the data, Victoria needed an ~11-fold increase, and Queensland required a ~9-fold increase. This is consistent with observed trends in Australia for some STIs in recent years. Future projections also indicate that the best way to control the current rise in HIV notifications is to reduce the prevalence of other STIs and to promote condom use, testing for HIV, and initiation of early treatment in MSM diagnosed during primary infection.

Conclusions: Our model can explain the recent rise in HIV notifications with an increase in the prevalence of other STIs. This analysis highlights that further investigation into the causes and impact of other STIs is warranted in Australia, particularly in Victoria.

Introduction

After a steady decline in HIV notifications during the 1990s in Australia, this current decade has seen an increase in the number of notifications, with the majority of cases involving men who have sex with men (MSM). Since 1999 there has been a ~44% increase in notifications among MSM. However, this trend is not uniform across all Australian states. For example, in New South Wales (NSW) there has been a ~7% rise, in Victoria (VIC) there has been a ~96% increase, and a ~68% increase has been observed in Queensland (QLD) [1]. We seek to provide possible explanations for the differences in notifications between these three states, and to predict the future course of the HIV epidemic in these locations. To investigate the differences, we compiled available data from a variety of sources into a single mechanistic framework to understand how the various factors interact, and then estimated their relative importance in yielding an increase in new HIV infections. We developed a mathematical model to evaluate the HIV epidemics in MSM populations in NSW, VIC, and QLD and incorporated data on time-trends in various factors. These factors included: condom usage, proportion of individuals diagnosed in primary HIV infection (PHI) who receive treatment upon diagnosis, proportion of MSM who test for HIV each year, proportion of treated patients with undetectable viral load, average number of sexual partners, and the proportion of MSM who disclose their serostatus. The model also considered other factors such as post-diagnosis behaviour change (possible increase or reduction in the number of casual partnerships), the frequency of sexual acts, and the increase in transmission due to the presence of other STIs. We calibrated the model to match the observed number of HIV notifications in each state in 1999 and conducted rigorous uncertainty and sensitivity analyses.

Methods

Model Structure:

We constructed a deterministic compartmental model [2], formulated as a system of ordinary differential equations, to simulate the HIV epidemic in the MSM population in each state. The modelled population was divided into four main groups: uninfected with HIV (Susceptible), HIV-infected but undiagnosed, diagnosed with HIV-infection, and HIV-infected people on antiretroviral therapy (ART). The HIV-infected population in our model progresses through three stages of disease: from primary infection to chronic infection and eventually to AIDS (see Figure 1). In our model each stage of infection was associated with a different viral load which differentially determined the probability of transmission to a susceptible person [3] during an act of penile-anal intercourse. We assumed that most Australian MSM will engage in both insertive and receptive acts [4]. Thus, we assumed an average transmission probability per act that reflects both insertive and receptive penile-anal intercourse. The model thus comprised ten groups in total (see Figure 1 for a schematic illustration of the model showing the 'flow' of the population between the various disease states).

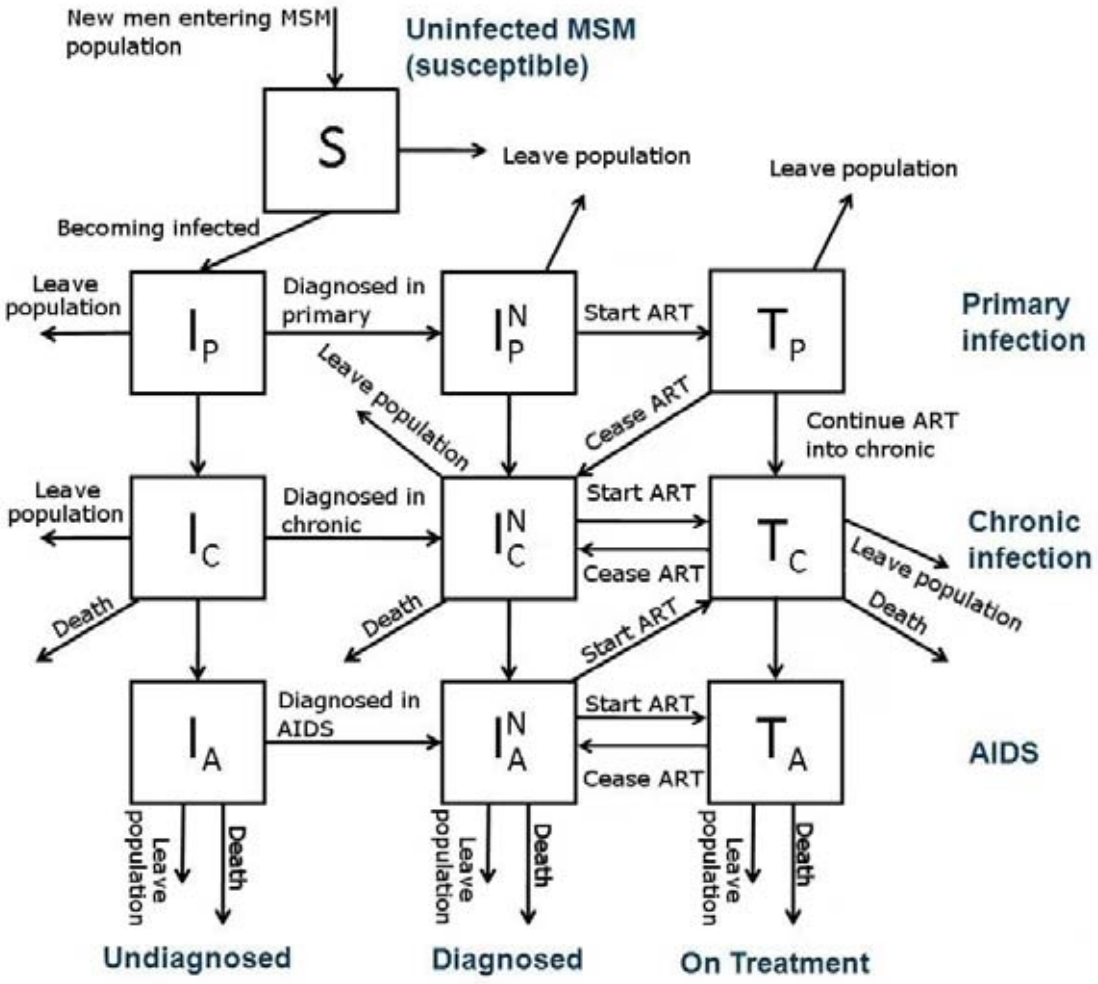
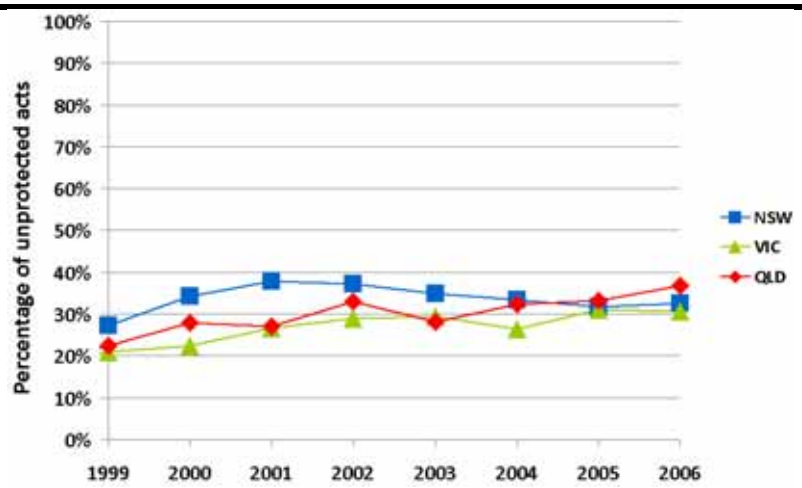
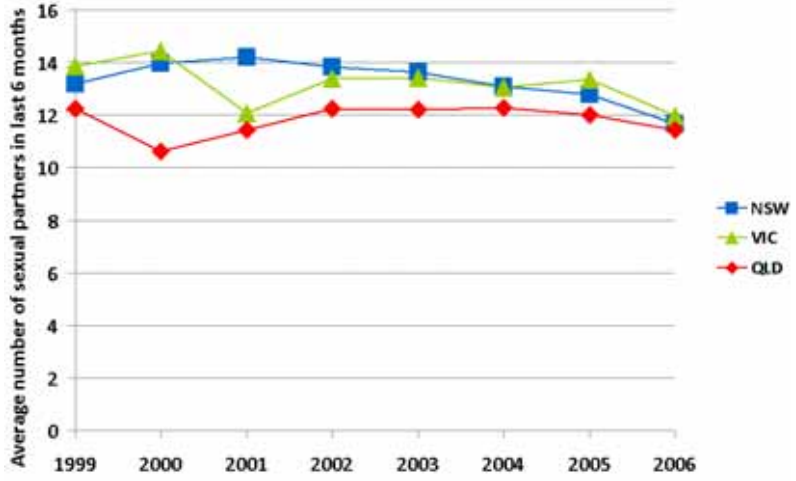
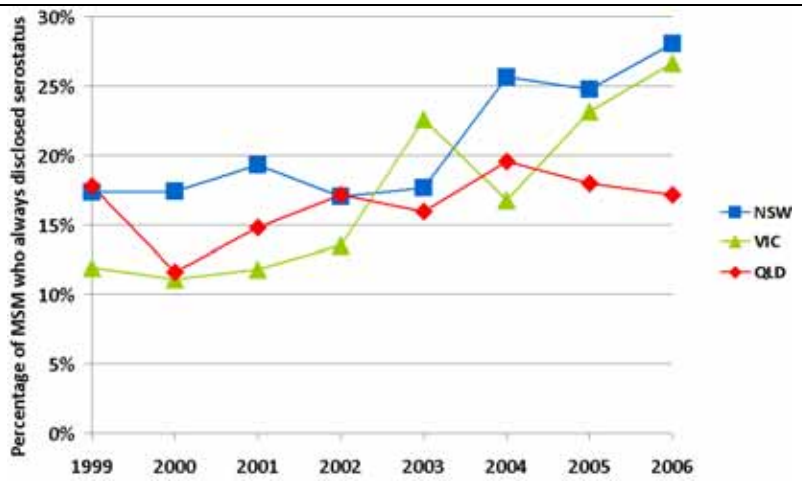


Figure 1: Schematic diagram of our compartmental model structure. Uninfected MSM enter the model as susceptible (S). Upon infection, they move from the susceptible group into undiagnosed primary infection (I_P). From here a certain proportion will get tested and will then move into the diagnosed arm (to I_P^N , I_C^N , or I_A^N depending on disease stage). Those who are not diagnosed will continue to progress through the different disease stages (I_C , or I_A). Once they eventually become diagnosed, a proportion will begin treatment (T_P , T_C , or T_A ; the proportion varies depending on the stage of infection). People can leave each group by 'ageing' out of the population or AIDS-related death once in AIDS stage (or at lower rates in chronic stage).

Parameter estimation and assumptions:

We modelled the population of MSM in Australia, assuming a population size of 150,000-175,000 MSM nationally (~1-2% of the male population; see Appendix for the proportion distributed among each state). Data were gathered on treatment in primary infection [5], HIV testing rates [6-8], number of

casual partners [9-11], condom use [6-8, 12], prevalence of other STIs [13-14], and the rates of disclosure of serostatus amongst partners as reported in behavioural surveys conducted in each state [6-8, 12, 15-16], for the years 1999 to 2006 (see Table 1). We also included other important factors that were not time-dependent and remained constant over the period being modelled. Behaviour change post-diagnosis was one such factor; in this case, a multiplying factor acting on the number of sexual partners (ranging 0.4 – 1.1[10, 17-24]) was applied. This range specifies that there may be an increase or decrease in choosing new partners after HIV diagnosis, but on average there is a decrease in sexual partner acquisition. The frequency of sexual acts between regular partners was also important and ranged between 80–120 acts per year [4]. A complete listing of parameters is given in Table A1 in the Appendix. Available data were insufficient to enable precise estimation of the prevalence of individual STIs in each of the states, and to quantify the impact of these on HIV transmission. Therefore, we did not model STIs individually but made the assumption that a certain proportion of MSM would have another STI, and that the presence of an STI would increase their susceptibility to HIV acquisition. There is strong evidence that both ulcerative and non-ulcerative STIs can increase the probability of HIV transmission by augmenting HIV infectiousness and susceptibility; reciprocally, HIV infection can enhance the transmission of other STIs [25-31]. Several studies (in heterosexuals) estimate the relative risks of HIV infection due to infection with other STIs in the range 2-24, but largely clustering between 2 and 5. We assume that this relative risk is equivalent in MSM and include a 'transmission-increasing' factor of 2-5 if another STI is present [25-31].

Time-dependent Parameter	Graph	Reference
Reported cases of unprotected acts with casual partners		[5-7, 11]
Change in number of sexual partners		[8, 10]
Disclosure of serostatus		[5-7, 11, 14-15]

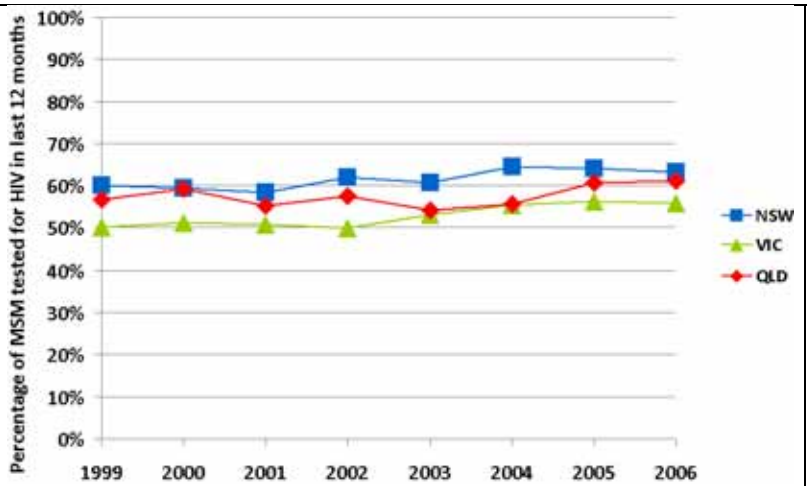
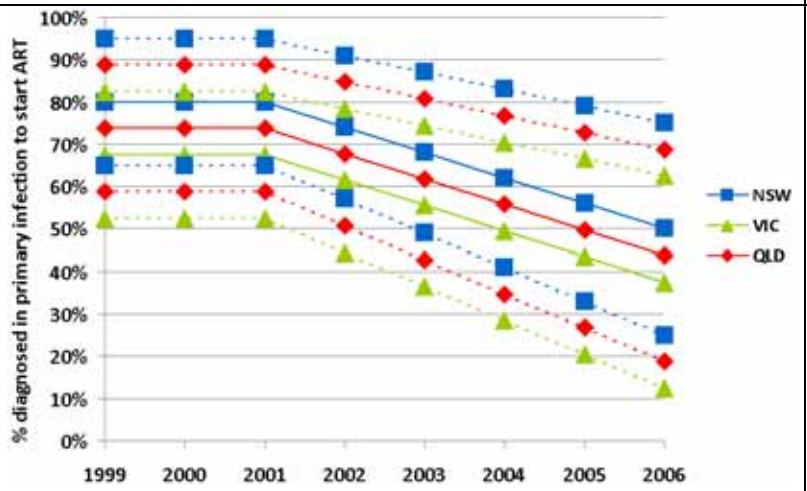
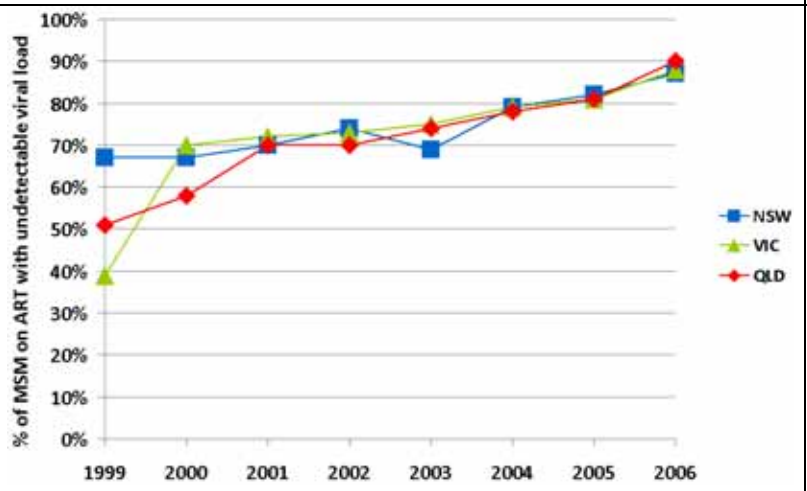
Testing rates		[5-7]
Treatment during primary infection		[42]
Proportion treated who achieve viral suppression		[9, 23, 43]

Table 1: List of time-dependent parameters used in our mathematical model including graphs of changes in these parameters for New South Wales (blue squares), Victoria (green triangles), and Queensland (red diamonds).

In order to model the impact of STIs on HIV transmission, it was necessary to estimate the proportion of MSM with other STIs as well as trends over time and by state. This was problematic for a number of reasons. First, while there have been indications that the prevalence of some STIs, notably syphilis, have been increasing in MSM in Australia, most data are reported only as notifications, not as the proportion of tests that are positive. Furthermore, the National Centre for HIV Social Research reported significant increases in testing (10-20%) in the last few years. Second, much of the published data on STIs in MSM in Australia is from the 'Health in Men' study and the incidence of STIs has decreased in this highly-tested, Sydney-based, HIV-negative cohort over the last few years [15]. Third, there is little data on trends in STI incidence and prevalence in MSM for the other states. Fourth, the most prevalent STI associated with HIV transmission is HSV-2 with prevalence in the HIM cohort estimated at ~23%, masking any trends that might be occurring with other STIs. Of course, HSV-2 is latent for significant proportions of the time in infected people and virus is shred periodically; thus, the effective prevalence of HSV-2 in terms of increasing HIV transmissibility is likely to be lower. Given the uncertainty, we assumed that the average proportion of MSM with STIs (ulcerative or non-ulcerative, that contribute to increasing HIV transmissibility) is in the range 5-15% initially (that is, at 1999). To investigate national HIV trends, we did not distinguish STI rates between states. There is strong evidence of a significant rise in the incidence (and prevalence) of STIs (gonorrhoea and infectious syphilis notifications) in recent years [13-14, 32].

This_contrasts with the declining trends observed in the HIM study. As mentioned above, the HIM cohort is a highly-tested group and may not reflect the wider community. However, recent increases may be explained by increases in STI testing. The main source of STI data comes from the HIV/AIDS, Viral Hepatitis and Sexually Transmissible Infections in Australia Annual Surveillance Report [33], which provides data on new diagnoses each year.

Sampling and sensitivity analysis:

Each parameter used in the model was assigned a uniform distribution between a minimum and maximum value, and Latin Hypercube Sampling [34] was employed to generate 10,000 samples from each distribution for each state. These parameter sets became input values for our model and Monte Carlo filtering was used to remove all parameter sets that could not generate the number of observed notifications in 1999 for each state. This left 4247 simulations for NSW, 3120 for VIC, and 3970 for QLD. These parameter sets then constituted the baseline for running simulations under a number of scenarios. Sensitivity analyses were performed to determine important factors involved in the epidemic. The SaSAT software package [35] was used to generate samples and to perform the sensitivity analyses.

Further filtering was conducted for projecting the HIV epidemic over the next ten years. A regression line was fitted to the notifications data, and only simulations that were within 10% of the regression line at 2006 were selected for projections. This left 1482 simulations for NSW, 443 for VIC, and 799 for QLD. A range of scenarios were simulated to predict the future dynamics of the epidemic including: 1) all parameters remain constant at their 2006 values; 2) all parameters continue on their current trend; and 3) all parameters return to the 1999 values. We also investigated changes in STI prevalence, HIV testing rates, condom usage, and rates of early treatment of MSM diagnosed in primary infection.

Results

Without a change in the prevalence of other STIs, but using the available time-dependent data for all other parameters, our model indicated that the number of HIV diagnoses should have actually

decreased in all three states since 1999 (Fig. 2). This is due to increases in the effectiveness of treatment, increases in testing rates, and a slight decrease in the average number of casual partners, but offset slightly by decreases in condom usage.

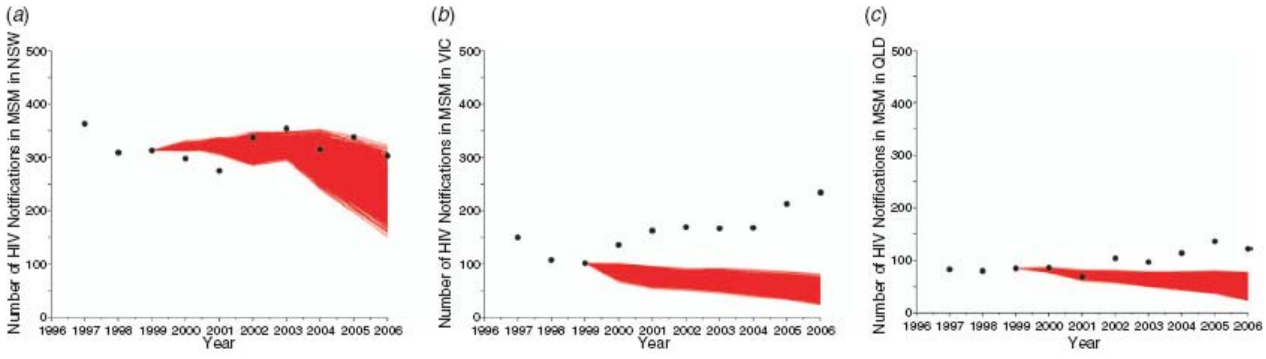


Figure 2: Uncertainty analysis epidemic trajectories of the modelled number of HIV diagnoses if changes in the prevalence of other STIs are not considered. The black dots indicates the number of HIV diagnoses based on the surveillance data, and the red curves represent all simulated time courses for: (a) New South Wales, (b) Victoria, and (c) Queensland.

During the period 1999-2006, NSW experienced a ~7.25% increase in notifications (see Table 2). Without an increase in other STIs, our model suggested that observed changes in condom usage directly resulted in an increase in HIV notifications of ~5.23% and changes in patterns of treatment during primary infection resulted in a ~1.01% increase. That is, these two factors account for a large proportion of the HIV increase in NSW. However, the model indicated that these factors were offset by changes in testing rates, average number of casual partnerships, disclosure of serostatus, and most importantly the proportion of treated MSM that achieve viral suppression. Each of these factors reduces the number of new infections leading to an overall decline in HIV notifications as seen in Figure 2a.

Similarly, in Victoria, the model suggested that a decline in condom usage and treatment in primary infection and changes in testing rates contribute positively to the number of HIV notifications. In contrast to NSW, however, these three factors accounted for a very small proportion of the large observed increase in HIV notifications (Table 2); the impact of these factors was also found to be largely outweighed by the proportion of treated people achieving viral suppression and other key parameters. Overall, without an increase in other STIs, our model yielded a decrease in the number of HIV notifications, in contrast with the observed trend (Figure 2b).

Queensland also experienced a large increase in notifications between 1999 and 2006. In the absence of an increase in other STIs, the most important factors contributing towards the rise for Queensland were again found to be declines in condom use and trends in treatment during primary infection. The model also suggested that changes in testing rates and disclosure of serostatus contributed positively to the rise in HIV notifications. Condom usage was the most influential of these factors contributing to a ~9.45% rise, followed by change in testing rates (~1.73%), treatment during primary infection (~0.69%) and disclosure of serostatus (~0.01%) (Table 2). But when other factors such as treatment effectiveness were included, as for the other states, our model showed that overall Queensland should have experienced a decline in HIV cases (Figure 2c), if the prevalence of other STIs had not risen.

Since our model simulations could not directly account for the number of HIV notifications in all three states, without changes in other STIs, we investigated the extent of the change required to match the notifications data. While the data on the prevalence of STIs among MSM in each state are incomplete, there are clear indications of increases in the incidence of infectious syphilis, Chlamydia, and gonorrhoea in the last few years [13-14, 32]. Therefore, we used our model to estimate the magnitude

of the increase in prevalence of other STIs that would be required in order to match the observed data for each state. We implemented a linear increase in STI prevalence into the model. Figure 3 shows the adjusted simulations with an increasing STI factor. For New South Wales, we found that a 2-fold increase in the prevalence of other STIs from 1999 to 2006 was required to appropriately match the data. Victoria required an increase of ~11-fold for the model simulations to match the data. Queensland required a ~9-fold increase in the prevalence of other STIs for the model simulations to match the data. These required increases are not inconsistent with the trends in notifications of other STIs [13-14, 32]. Where, New South Wales observed an increase in infectious syphilis diagnosis in MSM of from ~50 cases in 1998 to ~450 in 2007. Similarly in Victoria, only 3 cases were diagnosed in 1999, and this grew to just over 400 in 2007. In Queensland, in 2004 there were a total of 114 diagnosis across the whole population, this increased to 237 in2007 [33]. The increases observed are large and are broadly consistent with the increases in STIs needed by our model.

Factor	NSW	VIC	QLD
Number of HIV notifications among MSM in 1999	313	102	85
Percent increase in notifications data from 1999 to 2006 (linear regression)	7.25%	96.43%	67.69%
	Percent increase in HIV notifications due to factor		
Change in condom usage	5.23% (4.48,6.03)	7.89% (6.78,9.13)	9.45% (8.04,10.97)
Change in casual partners	-0.45% (-2.20,-0.74)	-1.23% (-0.86,-1.62)	-0.57% (-0.39,-0.75)
Change in disclosure of serostatus	-0.11% (-0.33,0.07)	-0.14% (-0.42,0.12)	0.01% (0.01,0.03)
Change in testing rates	-0.31% (-0.18,-0.46)	0.17% (0.03,0.41)	1.73% (1.04,2.52)
Change in treatment during primary infection	1.01% (0.43,1.99)	0.52% (0.16,1.15)	0.69% (0.45,2.25)
Change in proportion treated that achieve viral suppression	-25.81% (-32.56,-20.26)	-56.13% (-62.2,-49.3)	-47.01% (-54.45,-39.97)
Change in other STIs required to explain data	~2-fold increase	~11-fold increase	~9-fold increase

Table 2: The percent change in HIV notifications (from 1999 to 2006) that are attributable to various factors.

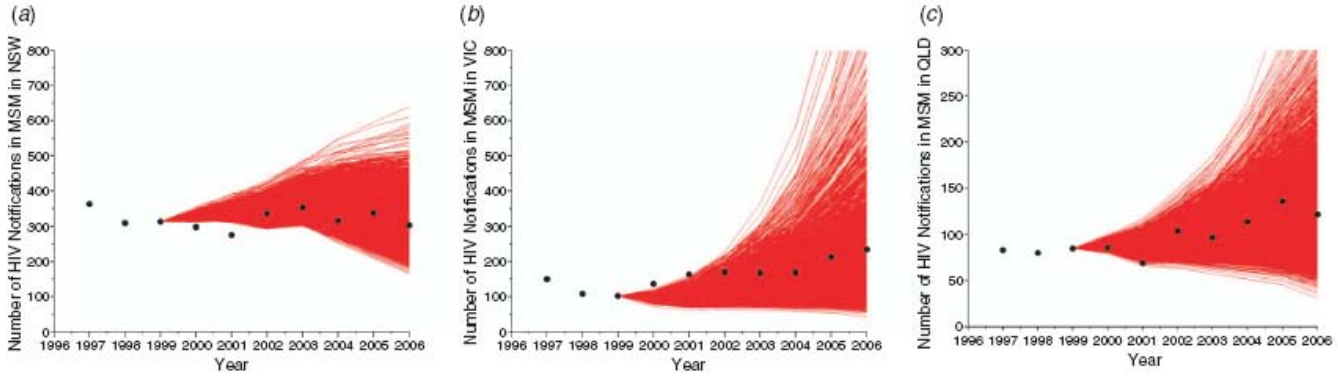


Figure 3: Uncertainty analysis epidemic trajectories of the modelled number of HIV diagnoses if changes in STIs are adjusted for each state. The black dots indicate the number of HIV diagnoses based on the surveillance data, and the red curves represent all simulated time courses for: (a) New South Wales – with a 2-fold increase in other STIs, (b) Victoria – 11-fold increase in other STIs, and (c) Queensland – 9-fold increase in other STIs.

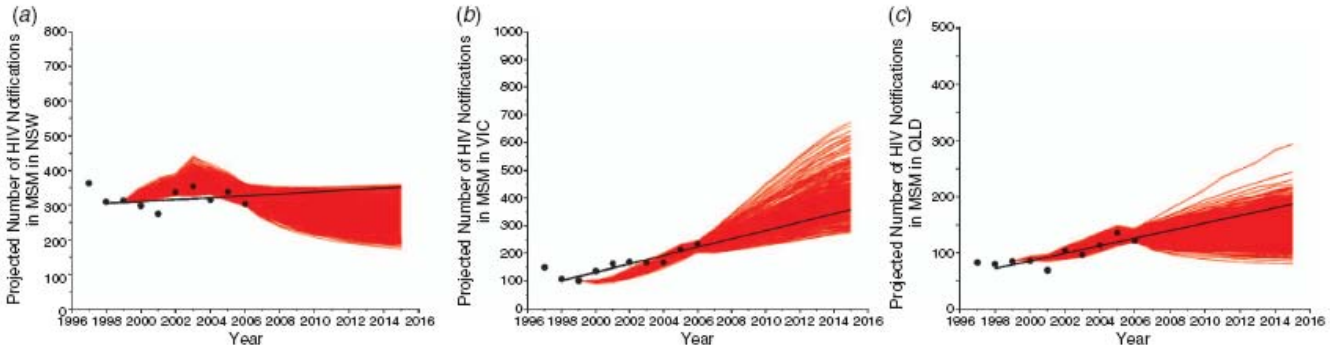


Figure 4: Projected number of HIV notifications to 2015 in the case of parameters remaining constant at 2006 levels. The black dots indicate the surveillance data points, and the black line represents the best-fitting linear regression line through the data points, for: (a) New South Wales, (b) Victoria, and (c) Queensland.

We then used our model to predict the number of new HIV infections, HIV diagnoses, and AIDS deaths until 2015 by simulating the epidemic over this period under a variety of scenarios. We found that, if all parameters remained constant at the 2006 values, there would be an increase in the number of HIV diagnoses in VIC and QLD, whereas there would be a decrease in NSW (Figure 4). HIV prevalence among MSM in NSW decreased from 18.8% (16.9-20.7% IQR) in 1999 to 17.7% (15.6-19.7% IQR) in 2016. However, large increases were observed for VIC, from 7.8% (7.1-8.6% IQR) to 21.4% (18.9-24.6% IQR), and for QLD, from 8.3% (7.5-9.2% IQR) to 12.4% (11.0%-14.0% IQR). The same qualitative result was found if the parameters did not remain constant but continued in the direction of their current trends

(Figure 5); however, if the current trends continued there would be even greater increases in HIV notifications in VIC and QLD (Figure 5). In this scenario, the HIV prevalence was similar with NSW decreasing to 17.3% (15.1-19.7% IQR), VIC increasing to 15.6% (12.1-21.3% IQR), and QLD increasing to 15.9% (13.5-18.7% IQR).

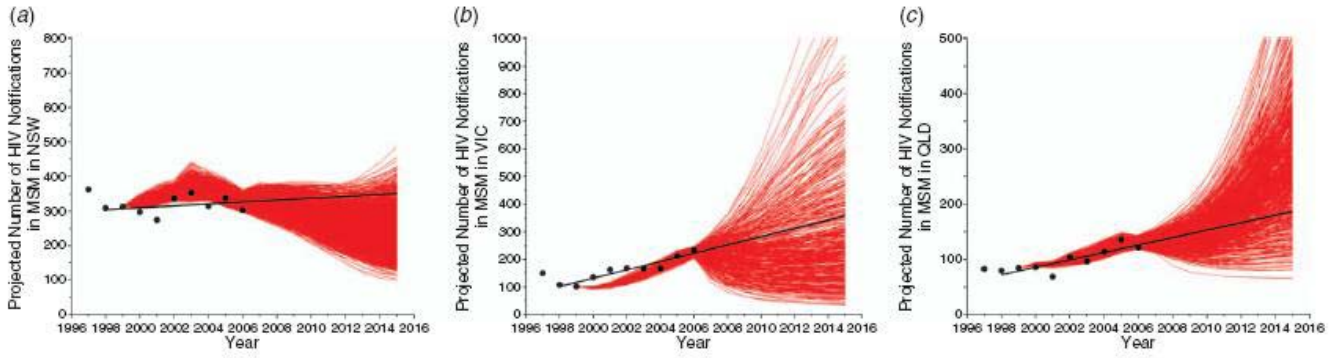
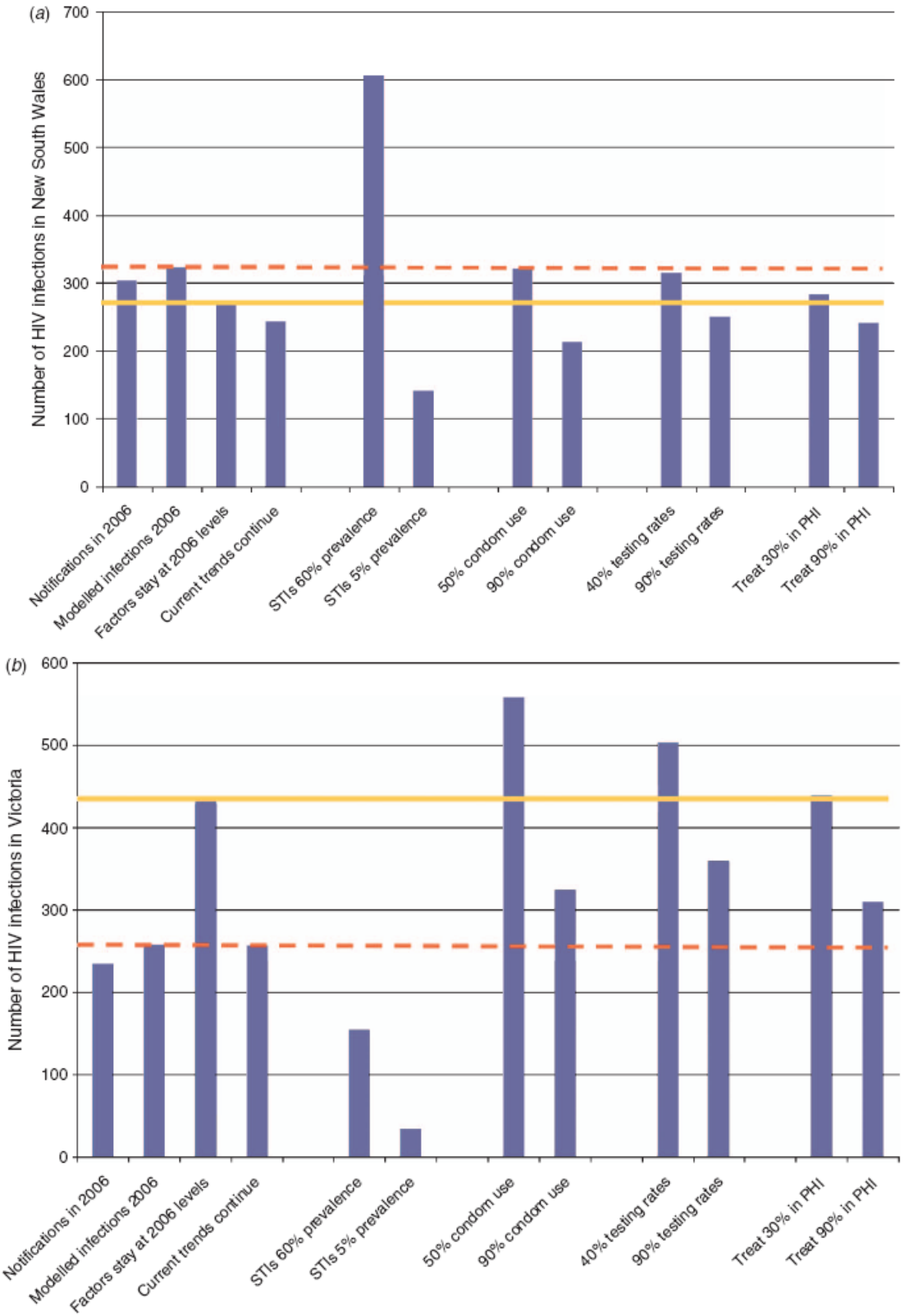


Figure 5: Projected number of HIV notifications to 2015 in the case of all parameters continuing their current trends. The black dots indicate the surveillance data points, and the black line represents the best-fitting linear regression line through the data points, for: (a) New South Wales, (b) Victoria, and (c) Queensland.

We compared the expected impact of different interventions on the projected number of new HIV infections (as distinct from HIV notifications) in 2015 in all three states (Figure 6). We found that the most effective way to reduce the number of new HIV infections was to reduce the prevalence of other STIs. If the prevalence of other STIs was immediately changed to 60%, then New South Wales would see a large increase in new infections, Victoria would see a decrease, and Queensland would see a slight increase over the number expected if all parameters were maintained at their 2006 values. If reduced to 5%, then the epidemic is predicted to decline substantially in all states (Figure 6). Not surprisingly, changes in condom use were also found to be highly influential in determining the future epidemic trajectories. Our projections indicated that if condoms were used in an average of 90% of acts (currently condom usage is ~ 68% in New South Wales, ~69% in Victoria, and ~63% in Queensland [6-8]), significant

declines in HIV cases would be observed in New South Wales and Queensland, but there would still be an increase in HIV cases in Victoria (Figure 6).


(a)
Number of HIV infections in New South Wales
700
600
500
400
300
200
100
0
Notifications in 2006
Modelled infections 2006
Factors stay at 2006 levels
Current trends continue
STIs 60% prevalence
STIs 5% prevalence
50% condom use
90% condom use
40% testing rates
90% testing rates
Treat 30% in PHI
Treat 90% in PHI
(b)
Number of HIV infections in Victoria
600
500
400
300
200
100
0
Notifications in 2006
Modelled infections 2006
Factors stay at 2006 levels
Current trends continue
STIs 60% prevalence
STIs 5% prevalence
50% condom use
90% condom use
40% testing rates
90% testing rates
Treat 30% in PHI
Treat 90% in PHI

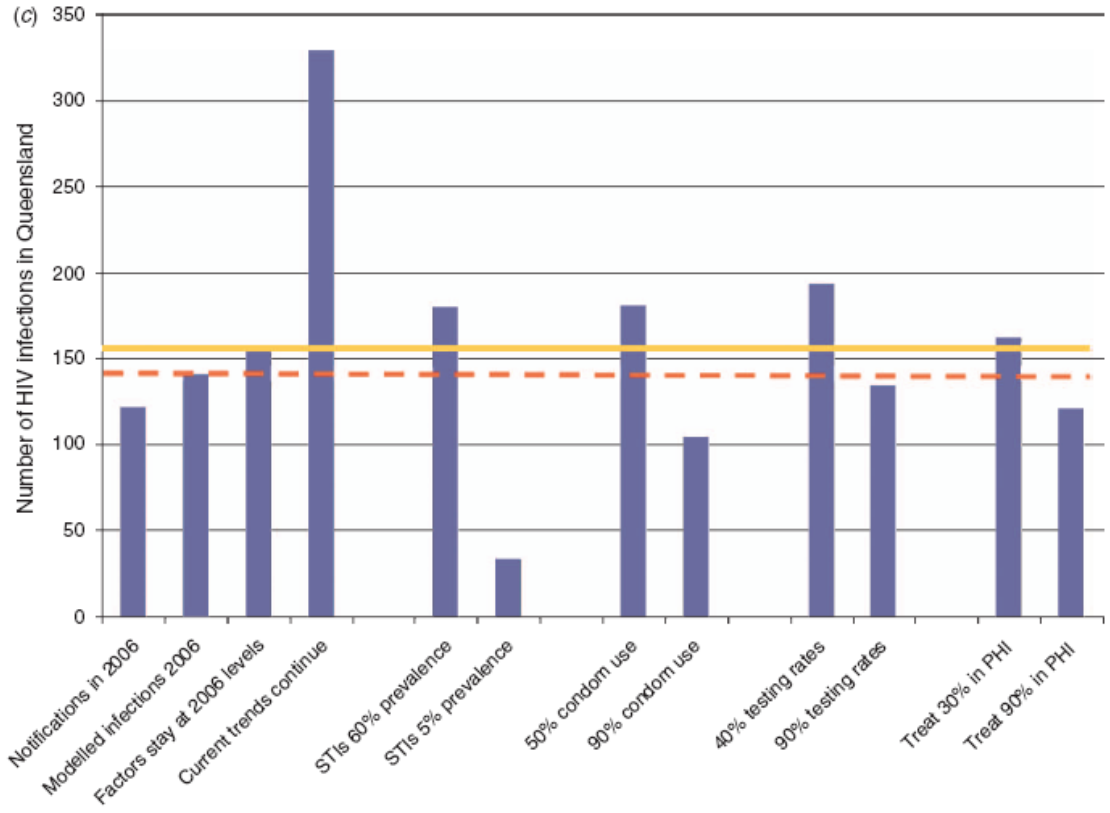


Figure 6: Histograms showing the median number of projected HIV infections (as distinct from notifications) in 2015 for each scenario. The dashed red line corresponds to the number of infections simulated in 2006, and the dashed orange line corresponds to the projected number of infections in 2015 if all parameters remain constant at their 2006 values.

We also investigated the effect of patterns in the treatment of people diagnosed during the primary stage of HIV infection. Although the majority of seroconverters will not be detected with infection during primary infection, if early detection does occur and early treatment is provided then it has the effect of significantly reducing the high viral loads associated with primary infection, and this in turn reduces secondary transmission to others. Our findings indicate that increasing the proportion of people diagnosed in primary infection who receive treatment will lead to reductions in the number of new HIV cases. We investigated several coverage levels of treatment of people diagnosed in primary infection. Currently, ~30-50% of people diagnosed in primary infection receive treatment. If this was

increased to 90%, then decreases would be seen in both New South Wales and Queensland. Victoria would still see an increase over the number of infections in 2006, but the numbers would be considerably lower than if all parameters were to remain constant. Treating 90% of people diagnosed in primary infection may be feasible; high treatment in primary infection was achieved in Australia during the late 1990s. The qualitative implications of this result are that any effort to increase treatment during primary HIV infection is likely to be beneficial at the population level. Of course, the degree of success in treating early infection is dependent on the number of people that are diagnosed early in their infection. Therefore, the rate of testing for HIV is highly important.

Increasing testing for HIV is beneficial in reducing further HIV transmissions because sexual behaviour generally changes upon diagnosis (to decrease transmission to partners). We found that increasing testing rates decreases the incidence of HIV. Currently ~63% of MSM in New South Wales test for HIV each year, ~56% in Victoria, and ~61% in Queensland; testing rates have increased in all states since the levels in 1999 (of 60%, 50%, and 56% respectively). This suggests that it is feasible to continue to increase testing rates. However, the maximum increase attainable is unknown. We investigated testing rates of 40%, 50%, 60%, 70%, 80%, and 90%. Although testing 90% of MSM each year is likely to be unfeasible, we found that increasing testing has the potential to be highly beneficial in reducing the overall incidence of HIV in Australia (see Figure 6).

Discussion

It was found that changes in condom use contributed to increases in HIV notifications in all three states. According to the data gathered from the gay periodic surveys [6-8], in all three states there has been a

slight increase in the percentage of unprotected acts during the period of 1999 to 2006. However, this decline in condom use cannot completely explain the rise in notifications. Treatment during primary infection has decreased in each state during the studied time period. Since viral loads are very high in primary infection [36-41], the trends away from treatment during primary infection account for some of the rise in HIV notifications but are also unable to account for the magnitude of the observed rise. Indeed, the combination of changes in all variables could not account for the large rise in HIV notifications.

Testing rates in each state have recently increased modestly in all states. Our simulations suggested that the increased testing rates in New South Wales actually had a negative effect (-0.31%) on the number of HIV notifications (Table 2). In contrast, in Victoria and Queensland the increases in testing had a small positive effect on HIV notifications, of 0.17% and 1.73% respectively. Our model suggested that increasing testing can be beneficial in reducing the incidence of HIV. MSM diagnosed with HIV are likely to take behavioural measures to reduce their risk of transmission to other people [18, 21-22, 24, 42-46], and if they receive treatment then their infectiousness will decrease substantially (especially if their infection is detected early). We have modelled a variety of testing levels and presented a 'maximum' achievable impact of increasing testing rates (to 90% of MSM each year). Whilst on its own such a high level of testing cannot turn the trends in HIV notifications in all states, our results suggest that testing is highly important and should be promoted further.

One factor that we have not attempted to model separately by state is serosorting, whereby MSM engage in UAI only with men of the same serostatus as themselves. If successful, serosorting would

reduce the risk of HIV transmission despite apparent increases in rates of UAI. There are some data that suggest that serosorting may have been more successful in New South Wales than in Victoria or Queensland [47]. It is possible that this has contributed to differences in trends in HIV notifications by state, and currently this has not been captured in the models. If serosorting was more successful in New South Wales than the other states, then it is likely that less dramatic differences in trends in rates of STIs would be required to reproduce the observed trends in HIV notifications by state. However, we have considered differences between states in the trends in disclosure of serostatus in established sexual partnerships. It is much more likely that negotiated protection, based on serostatus, within partnerships will occur than the establishment of partnerships on the basis of serostatus (personal communication, G. Prestage, National Centre in HIV Epidemiology and Clinical Research, pers. comm). It is also known that serosorting is more common among HIV-infected MSM than HIV-negative [15]. Thus, including serosorting is not likely to alter the incidence of new HIV infections. Of course, the impact of any serosorting among HIV-negative men is only as reliable as the frequency of HIV-testing and degree of monogamy.

We have shown that the prevalence of other STIs is a more important factor underlying the recent increase in HIV notifications than perhaps previously thought. Other STIs may have had the greatest direct impact on the recent increase in HIV trajectories in Australia. It should be noted that our model did not link STI prevalence with condom use. In our model these factors have been decoupled, such that any changes in condom use and the prevalence of STIs are independent. This is a limitation in our model. Future work will extend this analysis to model interacting infections and allow investigation of the indirect effects of condoms on reducing HIV by reducing the incidence (and thus prevalence) of other STIs. Other possible explanations for the observed increases in STI notifications could be due to

an increase in testing for STIs which may be capturing previously undiagnosed cases or changes in mixing patterns for acquiring new sexual partners (e.g. meeting potential sexual partners online). However, our model indicates that the decrease in condom use alone (i.e., its direct effect in reducing HIV transmission) is not enough to account for the increases in HIV notifications. Our projections show that targeting STIs in the community will be the most effective way to alter the epidemic trajectories. Condom use is also very important: our projections show that if condom use increased even moderately, then declines in new HIV infections would be observed. Of course, increasing condom use will also reduce the transmission of many other STIs. We also suggest that increasing testing rates and subsequent early treatment of individuals diagnosed in primary infection will have secondary benefits beyond the newly-infected individuals in averting significant numbers of onward transmissions.

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Chapter 3: Importance of promoting HIV testing for preventing secondary transmissions: modelling the Australian HIV epidemic among men who have sex with men

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Author Contributions

DPW conceived the analyses, conducted literature surveys, supervised the technical project, and wrote the manuscript. AH carried out all analyses and produced results and figures. DGR was involved in conceptualization, literature surveys, and manuscript editing. MGL was involved in conceptualization, facilitating steering of the project and the reference group, and manuscript editing. DPW, AH, and DGR developed the model framework.

Abstract

Background: We address the research questions: (i) what proportion of new HIV infections is transmitted from people who are (a) undiagnosed, (b) in primary HIV infection (PHI), (c) on antiretroviral therapy?; and (ii) what is the expected epidemiological impact of (a) increasing the proportion of newly acquired HIV infections receiving early treatment, and (b) increasing HIV testing rates?

Methods: We used a mathematical model to simulate HIV transmission in the population of men who have sex with men (MSM) in Australia. We calibrated the model using established biological and clinical data and a wide range of Australian MSM epidemiological and behavioural data sources.

Results: We estimate that ~19% of all new HIV infections are transmitted from the ~3% of Australian HIV-infected MSM who are in PHI; ~31% of new HIV infections are estimated to be transmitted from the ~9% of MSM with undiagnosed HIV. We estimate that the average number of infections caused per HIV-infected MSM through the duration of PHI is ~0.14–0.28. We also found that increasing testing coverage can lead to a reduction in new infections, falling from ~1600 per year with 0% coverage, to ~400 with 100% coverage.

Conclusions: The epidemiological impact of increasing treatment in PHI would be modest due to insufficient detection of newly-infected individuals. In contrast, increases in HIV testing rates could have substantial epidemiological consequences. The benefit of testing will also increase over time. Promoting increases in the coverage and frequency of testing for HIV could be a highly-effective public health intervention, but the population-level impact of interventions based on promoting early treatment of patients diagnosed in PHI is likely to be small. Treating PHI requires further evaluation of its long-term effects on HIV-infected individuals.

Introduction

The total number of HIV notifications in Australia has steadily increased in recent years to ~1000 per year, after a nadir of 720 HIV diagnoses in 1999. The majority of the rise in diagnosed HIV infections in Australia has occurred in men who have sex with men (MSM). Similar trends have also been observed in the USA, UK, the Netherlands, and other developed countries [1-6]. Understanding the preventative benefit of changes in implementation of current biomedical and behavioural interventions is important for planning public health campaigns to mitigate the current rises in HIV. One of the cornerstones of effective prevention programs is the promotion of HIV testing. Therefore, we investigate the relationship between expected HIV incidence and diagnoses and the proportion of MSM who are tested for HIV each year. We also investigate the population-level effectiveness of increasing the proportion of newly diagnosed people who receive early antiretroviral therapy to reduce their infectiousness.

Newly infected people enter the stage of primary HIV infection (PHI). In this stage viral loads are higher than at any other time during the course of infection. Consequently, people in PHI have the greatest infectiousness per sexual encounter [7-8]. Newly-infected people are generally unaware of their new serostatus and their potential to cause secondary HIV transmissions. However, PHI typically lasts for only 3–6 months [9-11], after which viral levels stabilise to considerably lower levels for the long chronic/asymptomatic stage of infection. Because of its short duration, the importance of PHI in contributing to secondary HIV transmissions relative to the longer chronic and AIDS stages of HIV infection is unclear. It is also unclear how reliably one can determine the presence of a PHI case and the duration of time since seroconversion. The short duration of PHI also makes it difficult to capture cases in this stage of infection.

Approximately 5 years ago, if a person in Australia was diagnosed in PHI s/he would have a large likelihood of commencing combination antiretroviral therapy (cART) at diagnosis. The trend has moved away from this, towards delaying therapy, but the best clinical practice is still being debated [7, 12]. Effective suppression of HIV using cART has remarkably altered the clinical outcomes of HIV-infected individuals [13]. cART first became widely available in Australia during 1996 and was rapidly and widely taken up among HIV-infected patients [14], leading to rapid improvements in morbidity and mortality. Despite the trend away from early treatment, the proportion of diagnosed HIV-infected MSM in Australia that are treated is high (70–90% are on cART) [14-16]. By decreasing HIV viral load in treated individuals [17-19], it is thought that cART also reduces infectiousness of treated individuals, but empirical studies to confirm this are yet to be completed. Treating patients who are diagnosed in PHI might have public health benefits for reducing HIV transmission.

Detecting newly infected people in PHI for initiating treatment can only occur if there are high rates of testing for HIV (in terms of coverage, i.e. the proportion of people who are tested, and the frequency of testing, i.e. number of times people are tested per year). High testing rates can also have additional epidemiological benefits. One benefit is that individuals who are diagnosed as HIV-positive typically change their behaviour in order to reduce onward transmission to others. Although some individuals might increase sexual activity and/or the acquisition of new sexual partners, most individuals diagnosed with HIV significantly decrease sexual partner acquisition by as much as 50% on average [20-28]. In Australian MSM, if a regular partnership is known to be serodiscordant, condoms are used ~75–80% of the time compared with less than 10% of the time in relationships thought to be seroconcordant [29]. In

casual partnerships, serological disclosure is not as common as in regular relationships, but condoms are used in ~60–70% of all casual sexual encounters [30]; presumably if the casual partnership was known to be serodiscordant then the proportion of acts in condoms are used would increase considerably or alternatively the partnership may not form at all. Knowledge of true serostatus is very important. Therefore, increasing the proportion of men who test for HIV each year could have large preventative benefits, from changing behaviour to reducing infectiousness, if the diagnosis leads to treatment.

In the present study we attempt to address the following research questions: (i) what proportion of new HIV infections in Australia is transmitted from people who are (a) undiagnosed, (b) in PHI, (c) on antiretroviral therapy?; and (ii) what is the expected epidemiological impact of (a) increasing of the proportion of those diagnosed in PHI that commence early treatment, and (b) increasing the proportion of MSM tested for HIV each year? To answer these questions we use a mathematical model to simulate HIV transmission in the population of MSM in Australia. We calibrate the model using established biological and clinical data from the published literature and a wide range of Australian MSM epidemiological and behavioural data sources (Table 1).

Methods

We use a previously published mathematical model [31-32] to address the research questions. Our dynamic transmission model simulates the HIV epidemic among the population of MSM in Australia. The model tracks the incidence of new HIV infections and the numbers of HIV-infected MSM as they progress in disease from PHI, to chronic infection, to the AIDS stage disease. The 'force of infection' [33] depends on the number of people in each HIV-infected stage, the average number of casual and regular partnerships per MSM, the average number of penile–anal acts per partnership, the proportion of these

acts in which condoms are used, and the efficacy of condoms. We also include the proportion of sexual partnerships in which HIV serostatus is disclosed and the effect of disclosure on condom usage. The model distinguishes undiagnosed HIV-infected MSM from those who become diagnosed through testing. In the model, MSM who are diagnosed with HIV might change their behaviour and could commence antiretroviral therapies, and MSM in AIDS stage have reduced sexual activity. For those on cART, a proportion is assumed to have undetectable viral load and thus, they are less likely to transmit infection. Although this is dependent on the level of adherence to therapy, we do not model adherence and its impact on suppression. Rather, we directly use data from the Australian HIV Observational Database [34] on the proportion of people on cART who attain viral suppression. The flows in the number of people between these compartments are presented schematically in Fig. 1 and are determined by biological, behavioural, clinical, and epidemiological parameters (Table 1).

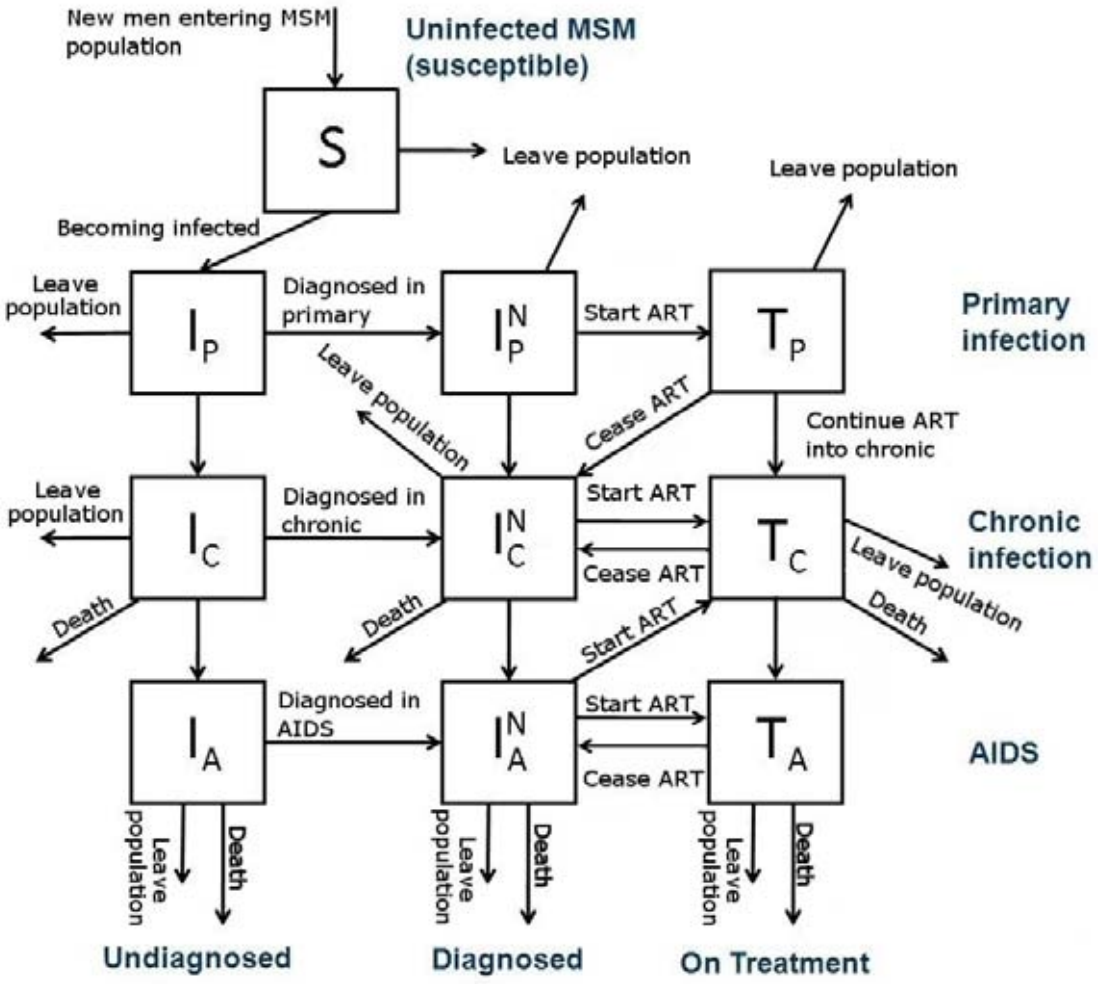

Figure 1: Schematic diagram of our compartmental model structure. Uninfected MSM enter the model as susceptible (S). Upon infection, they move from the susceptible group into undiagnosed primary infection (I_P). From here a certain proportion will get tested and will then move into the diagnosed arm (to I_P^N , I_C^N , or I_A^N depending on disease stage). Those who are not diagnosed will continue to progress through the different disease stages (I_C , or I_A). Once they eventually become diagnosed, a proportion will begin treatment (T_P , T_C , or T_A ; the proportion varies depending on the stage of infection). People can leave each group by 'ageing' out of the population or AIDS-related death once in AIDS stage (or at lower rates in chronic stage).

Description		Value	Reference
Average number of sexual partnerships per year (undiagnosed MSM)		a^*, [21, 34, 52]	
Multiplying factor for the reduction in number of sexual partners for men in AIDS stage disease		0.1 – 0.4	
Percentage of sexual partnerships in which penile-anal intercourse occurs		10-40%	[21]
Multiplying factor for the change in number of sexual partners post diagnoses of HIV infection (this reflects a possible range from 50% decrease to 10% increase)		0.4 – 1.1	[20-28]
Proportion of partnerships in which serostatus is disclosed (in negotiating condom usage)	Regular	0.8-0.9	[29-30, 53-54]
	Casual	b^*	
Proportion of acts in which condoms are used		c^*, [29-30]	
Efficacy of condom protection per act		0.85-0.9	[55-59]
Baseline viral load during chronic infection		$10^4 – 10^5$ copies/ml	[10, 60-63]
Average viral load at primary infection stage		$10^{6.5} – 10^8$ copies/ml	[10, 60-61, 63-64]
Average viral load at AIDS		$10^{5.5} – 10^{6.5}$ copies/ml	[61, 65-66]
Average viral load in effectively treated individual		10 – 100 copies/ml	[67-69]
Proportion of individuals on antiretroviral therapy in which viral load is suppressed		d^*, [20, 34, 70-71]	
Probability of HIV transmission per act from an individual in chronic stage of infection		0.0015–0.0025	[72-77]
Probability of HIV transmission per act from an individual in primary or AIDS stage of infection		e, [8]	
Probability of HIV transmission per act from a treated individual		e, [8, 78]	

Proportion of HIV-negative MSM who have other STIs	0.05-0.15	f , [79-80]
The multiplicative increase in transmission probability due to the presence of other STIs	2 – 5	g ,[81-87]
Average number of anal intercourse acts per regular partner per week	1.6 – 2.4	[88]
Average number of anal intercourse acts per casual partner (over duration of casual relationship)	1 – 2	[54, 88]
Proportion of MSM that test for HIV infection each year	h^* , [30]	
Average time from the beginning of AIDS before individual is likely to be diagnosed with infection	2–4 months	
Average time for untreated individuals to progress from primary infection to chronic infection	3–9 months	[9-11]
Average time for individuals to progress from chronic infection to AIDS	8 – 12 years	[60, 65, 89-92]
Proportion of people diagnosed in primary infection that will commence treatment	i	
Average time to cease treatment for individuals with primary infection	6 – 12 months	i
Proportion of people who started ART in primary infection and continue ART after finishing dosing schedule	65-75%	i
Proportion of people in chronic infection that will commence treatment	65-75%	[16, 29-30, 34]
Proportion of people with AIDS that commence treatment that experience treatment failure	0 – 0.1	
Average time before individuals with AIDS commence therapy	1–3 months	
Average time before diagnosed individuals in chronic infection commence therapy	2–10 years	
Average time to cease treatment for individuals with chronic infection	6 – 12 years	[34]

Average time to cease treatment for individuals with AIDS		8 – 14 years	[34]
Average time for individuals to 'retire' out of sexually active population (no longer obtaining new partners)		30-35 years	j ,[91]
Proportion of untreated MSM in chronic infection who die each year		1-2%	[93-97]
Proportion of treated MSM in chronic infection who die each year		1-2%	[93-97]
Average time until death from the onset of AIDS for untreated individuals		0.5-1.5 years	[97-100]
Average time until AIDS-related death for individuals in AIDS stage but on ART (with treatment failure)		0.5-5 years	[91, 97, 99, 101-107]
Average time of disease progression for treated individual with chronic infection to progress to AIDS		$1/\omega_C < 1/\tau_C < 20$	
Number of new susceptible individuals entering the MSM population per year (this is approximately 3-3.5% of men)	Nationally	2000-2500	k
	NSW/ACT	35-40%	
	VIC	22-27%	
	QLD	17-22%	

Table 1: Model parameter definitions, ranges, and references. For all time-dependent parameters the value used in our mathematical model is the linear interpolation of the weighted average across each Australian state, as weighted by the population size. See Appendix for Chapter 3 for explanation of how values were obtained for parameters associated with reference (a)–(k); ART, antiretroviral therapy; MSM, men who have sex with men; STI, sexually transmissible infection

For each model parameter we explored a range of input values to account for the intrinsic heterogeneity and for the uncertainty in the parameter. We sampled over the entire parameter space and conducted detailed uncertainty and sensitivity analyses from 10 000 simulations using the SaSAT software package (NCHECR, University of New South Wales, Sydney, Australia) [35]. Results presented in the present paper are based on median outcome variables obtained from running the 10 000 simulations. In each stage of infection we model different viral load levels, which influence differential transmission probabilities [8, 32]. Treated MSM have substantially lower viral loads, which also

significantly slows disease progression rates; we also account for the effectiveness of cART in achieving viral suppression. We also include HIV-related death rates. The dynamic transmission model is mathematically represented by 10 ordinary differential equations, one equation for each compartment/state (uninfected MSM and HIV-infected MSM in either primary, chronic, or AIDS stage, and for each of the three HIV-infected groups we distinguish between undiagnosed, diagnosed and untreated, or on treatment). See Fig. 1 for a schematic diagram of the model, and Hoare *et al.*[32] and Table 1 for detailed mathematical description of the model and data sources.

The model was calibrated in a similar fashion to the model presented in Chapter 2. The model was matched to the observed number of notifications in each state in 1999. Using the rate of diagnosis in primary infection as the calibrating parameter, each simulation was set to match the reported number of HIV diagnoses in 1999.

Results

Our simulations yielded 12 000–18 000 MSM living with HIV in Australia in 1999, the starting point of our simulations. This is consistent with other independent estimates of prevalence of ~5% in Australian MSM [36-37]. Of the HIV-infected MSM, we estimated the percentage in each disease stage as well as the percentage undiagnosed, diagnosed and untreated, and treated (Table 2). We also estimated the proportion of all new infections that are transmitted from MSM in each of these compartments (Table 2). Our simulations suggest that although ~9% of HIV-infected MSM are undiagnosed, they are responsible for ~31% of the new HIV infections, and although only ~3% of MSM are in primary infection, they are responsible for ~19% of all new HIV infections. It is not surprising that treated individuals contribute lower proportions of new infections because viral load is suppressed in a large number of treated patients. Thus, we compared untreated MSM who are undiagnosed with those who are

diagnosed but untreated; we found that although there are almost three times as many diagnosed but untreated MSM as undiagnosed MSM, the undiagnosed HIV-infected MSM contributed greater numbers of new infections (Table 2).

Disease Stage	Undiagnosed	Diagnosed	Treated
	Percentage of HIV-infected MSM in each compartment		
Primary	1.9% (1.2 – 2.7%)	0.46% (0.23 – 0.84%)	0.53% (0.28 – 0.81%)
Chronic	6.8% (4.2 – 9.3%)	29.0% (24.9 – 34.8%)	58.1% (52.6 – 63.1%)
AIDS	0.12% (0.07–0.17%)	0.44% (0.35 – 0.57%)	3.6% (2.6 – 5.5%)
	Percentage of new HIV infections attributable to MSM in each		
Primary	16.2% (9.9 – 22.7%)	1.48% (0.67 – 2.81%)	0.46% (0.22 – 0.79%)
Chronic	13.5% (8.5 – 18.2%)	16.0% (12.8 – 20.0%)	48.5% (39.8 – 57.5%)
AIDS	0.14% (0.09 – 0.23%)	0.18% (0.13 – 0.26%)	0.8% (0.5 – 1.2%)

Table 2: Estimated percentage of HIV-infected MSM in each model compartment in 1999 (stage of disease and diagnosis/treatment status) and the estimated percentage of new HIV infections attributable to HIV-infected MSM in each model compartment. We present the median results (and interquartile range) from our 10,000 simulations.

A type of reproductive ratio [38] per compartment can be obtained by scaling the number of infections caused by people in each compartment by the number of people in each compartment. We calculated two reproductive ratios: the average number of new HIV infections caused per MSM per year while (i) in primary infection, and (ii) undiagnosed. These ratios were calculated to be 0.54 (median, interquartile range (IQR) (0.44–0.64)) and 0.31 (median, IQR (0.28–0.35)), respectively; note that we standardised these ratios to the rate per year for comparative purposes. Since PHI lasts for ~3–6 months, we estimate that the average number of infections caused per HIV-infected MSM through the duration of PHI is ~0.14–0.28. This is consistent with independent estimates [39]. Sensitivity analyses of these ratios to the model input parameters [31, 35] revealed that the viral load in PHI, the duration of PHI, and the frequency of sexual acts were the most important parameters in determining the number of HIV transmissions from MSM in PHI and undiagnosed MSM The average number of infections caused per

MSM while undiagnosed *v.* the duration of PHI is shown in Fig. 2. The strong positive association suggests that targeting undiagnosed HIV-infected MSM for testing and treatment, particularly during PHI, could be an effective public health prevention strategy.

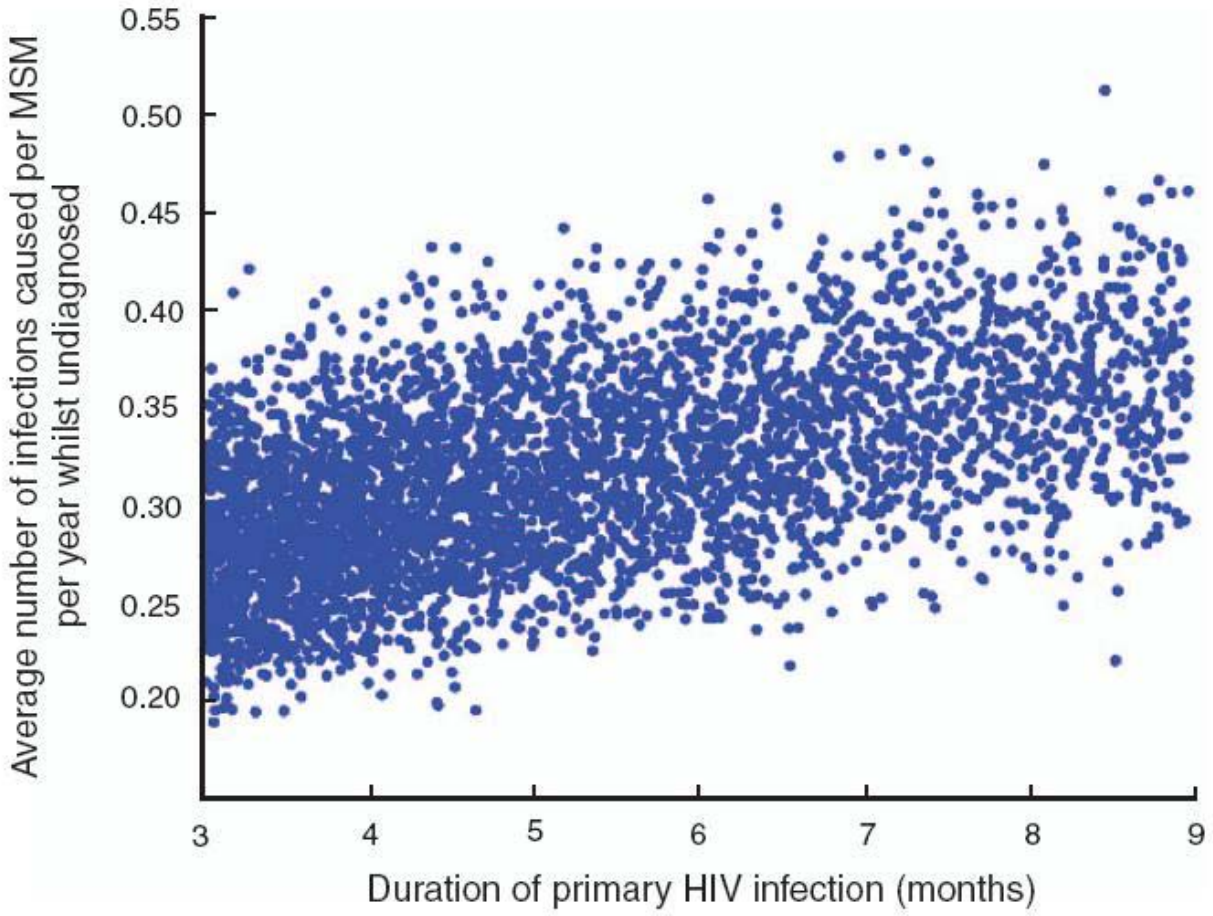

Figure 2: Scatter plot of the association between the average numbers of infections caused per MSM whilst undiagnosed and the duration of primary infection.

We used our model to estimate the potential impact of changes in the proportion of diagnosed PHI cases who initiate cART, assuming the annual proportion of men who are tested for HIV remains at current levels (~50–60%)[30]. We found that the epidemiological impact of increasing treatment in diagnosed PHI would be low (Fig. 3a). Indeed, if no diagnosed PHI cases received cART, ~611 HIV infections are estimated in Australian MSM per year (after 10 years) compared with ~580 infections if all

diagnosed cases of PHI initiated cART (Fig. 3a); that is, ~5% reduction in incidence. The number of notifications observed (as opposed to total incident infections) would also not change substantially with increases in the proportion of PHI cases that receive treatment (Fig. 3a). The minimal epidemiological impact resulting from treatment of MSM diagnosed in PHI is due to insufficient timely detection of newly-infected individuals following seroconversion. Based on our model results we predict that even with relatively high proportions of men tested for HIV each year, as observed in the Australian MSM community, treating a large proportion of PHI cases will not have a substantial public health benefit.

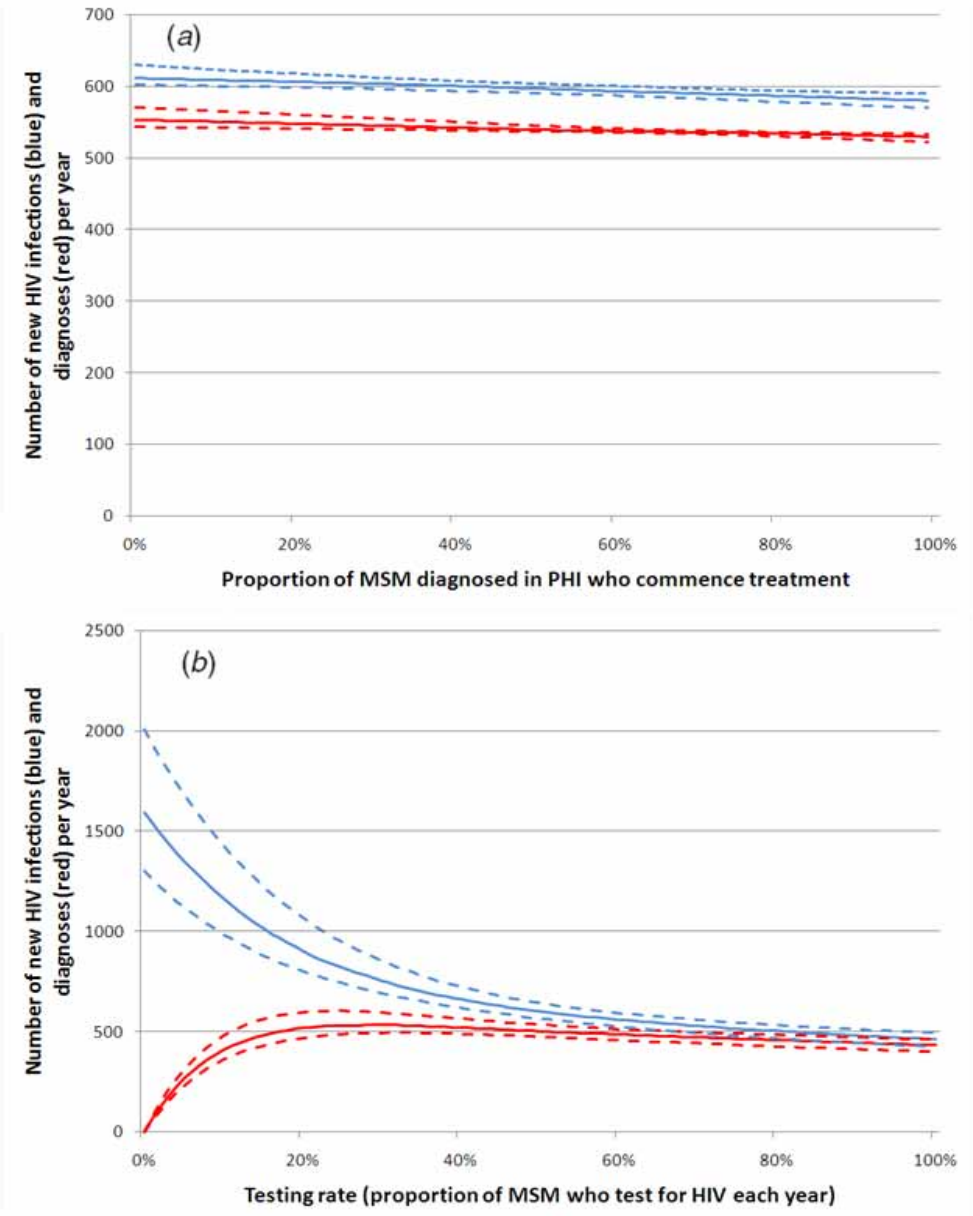

Figure 3: Relationship between the number of HIV infections (blue) and HIV notifications (red) for changes in **(a)** the proportion of PHI cases who initiate treatment, **(b)** the proportion of MSM who are tested for HIV each year. Here, all model parameters are set to their median values except for the PHI treatment coverage (for **(a)**) and the proportion of MSM who are tested for HIV each year (for **(b)**). Dashed lines show the inter-quartile range.

In contrast, we found that increases in the proportion of men who are tested for HIV each year could have substantial epidemiological consequences. We investigated the impact of changes in testing coverage on the number of HIV infections and notifications. HIV-infected MSM who become aware of

their serostatus generally reduce the acquisition of new sexual partners. They might also have the opportunity to receive cART. We found that the behavioural consequences of HIV diagnosis (and clinical consequences to a smaller degree) greatly influence HIV epidemiology. If the coverage of HIV testing was to decrease (from the current level whereby 50–60% of Australian MSM test each year) then large increases in HIV incidence could be expected. If there was no testing for HIV then the number of HIV infections per year could approximately treble (to ~1600 per year, after 10 years) (Fig. 3b). Of course, if testing was low then the number of notifications would also be low (Fig. 3b). There is a testing coverage threshold of ~30%, above which the observed HIV notifications start to decrease in alignment with the decline in HIV incidence (Fig. 3b). For high testing coverage, the gradient of the curves for HIV infections/diagnoses *v.* the testing coverage is approximately linear (Fig. 3b). Thus, we estimate that for every 10% incremental increase in the MSM population that is tested annually for HIV, there will be a decrease of ~13 HIV notifications observed each year and a decrease of ~22–27 HIV infections each year. But such reductions will not be observed immediately (results are shown after 10 years). We present surface plots to indicate the number of HIV infections (Fig. 4a) and HIV notifications (Fig. 4b) expected per year *v.* the testing coverage and number of years post introduction of the intervention. The infections *v.* testing coverage profile changes over time and the cumulative benefit of an intervention based on increased testing will increase with time. Clearly, also increasing the frequency of testing (to multiple times per year, especially for MSM at higher risk of HIV acquisition) will further increase the epidemiological benefits of campaigns for HIV testing. Testing more frequently than yearly could also be very important for detecting people in PHI, given the relatively short duration of acute infection. However, our simulations revealed that 100% coverage, at a frequency of once per year, would result in close to the maximum reduction in incidence that is possible due to testing; that is, higher frequencies would not result in a significant further decrease in the total expected number of new HIV infections.

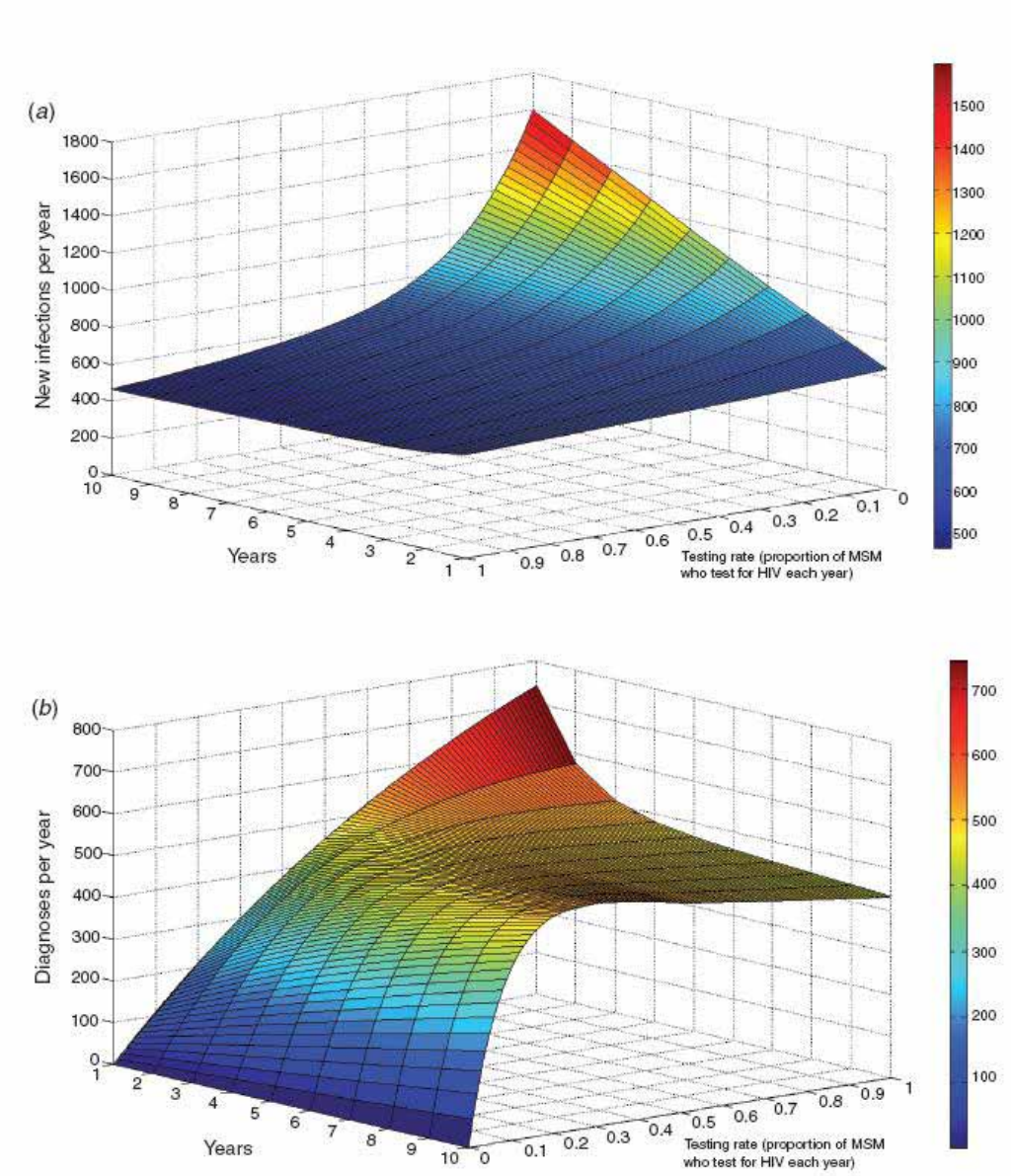

Figure 4: Surface plots fitted through model-generated data indicating the expected number of **(a)** HIV infections over time versus the proportion of MSM who test for HIV each year and the PHI treatment coverage, **(b)** HIV notifications over time versus the proportion of MSM who test for HIV each year and the PHI treatment coverage. Here, all model parameters are set to their median values except for the proportion of MSM who are tested for HIV each year.

Discussion

Our study confirms the disproportionate nature of HIV transmission [38-45] between different stages of disease and by diagnosis status for the MSM population in Australia. We have estimated that ~3% and ~9% of HIV-infected MSM in Australia are in PHI or are undiagnosed, respectively, but they are

responsible for ~19% and 31% of the new HIV infections, respectively. These ratios will differ between locations depending on behaviour and clinical practice specific to each setting. However, the qualitative conclusions of our analyses are generally applicable to other locations. We have shown that the coverage of testing for HIV can have substantial epidemiological impacts. In locations where HIV testing rates are low, even small changes in the coverage and frequency of testing, if accompanied with changes in behaviour similar to those which we have assumed, might have very significant reductions in incidence. The relative benefit of increased testing decreases with higher testing coverage. However, even if testing rates are relatively high, further increases in the coverage and frequency of testing for HIV might still result in noticeable reductions in HIV incidence. An implication of this is that if the rate of testing for HIV is relaxed then there is the danger of large consequent increases in HIV incidence. Promoting increases in the coverage and frequency of testing for HIV has benefits at numerous levels: for the HIV-infected patient, for the partners of HIV-infected individuals, and at the population-level. Testing for HIV informs individuals of their actual serostatus and is likely to lead to a decrease in risky behaviour and subsequent reduction in the risk of onward HIV transmission to partners of HIV-infected individuals. Our model suggests that promoting testing can be a highly-effective public health intervention.

In contrast to the large potential impact of increases in testing, our model suggests that the population-level impact of interventions based on promoting early treatment of patients diagnosed in PHI is likely to be modest at best. If testing rates were much higher, such that the majority of newly-infected individuals were diagnosed and received treatment, then the population-level benefit of early treatment would be greater. As we have shown, this cannot be achieved on a large scale just by increasing the coverage of HIV testing. To identify large numbers of PHI cases, much more frequent testing than yearly

would be required. For individuals who are diagnosed in PHI and are in serodiscordant partnerships, treatment during PHI could reduce the chance of onward transmissions and thus have preventative benefits for sexual partners [40]. However, the primary purpose of cART must be to benefit the patient infected with HIV. The evidence supporting benefits for HIV-infected patients who receive early cART is currently not substantial [7, 12]. Thus, caution must be exercised when considering promoting treatment of PHI for the purposes of public health interventions to reduce population-level incidence. Treating PHI could be considered for reducing the risk of HIV transmission in serodiscordant partnerships, but further evaluation of its long-term effects on HIV-infected individuals is required.

The objective of early treatment is to preserve immune function and enhance viral control in order to attenuate long-term clinical outcomes. The first randomised controlled trial (RCT) of treatment in PHI demonstrated beneficial clinical outcomes for patients receiving monotherapy with zidovudine for 6 months [41]. Subsequently, there have been various observational studies investigating different therapies in PHI [42]. However, currently there are no data addressing the impact of cART in PHI on long-term clinical outcomes. Results from observational studies [43-49] highlight the need for RCTs to be conducted. But most treatment guidelines do not recommend cART for treating PHI due to the lack of RCT evidence, along with drug toxicity, the risk of selecting for drug-resistant strains of HIV, and financial implications [50].

We have shown that treating PHI cannot be highly effective in reducing incidence when rates of testing for HIV are low-to-moderate. We have also shown that increasing average coverage levels of HIV testing can have large public health benefits. Benefits of undiagnosed HIV-infected individuals becoming aware

of their serostatus include the tendency for sexual behaviour to decrease and treatment also becomes an option. Both of these lower the risk of HIV transmission. Our results are highly dependent on behaviour change post-diagnosis. Many behavioural studies provide evidence that risky sexual behaviour decreases after HIV diagnosis [20-28]. However, some individuals diagnosed with HIV might increase transmission risk events, because they are no longer susceptible. Therefore, we investigated a range for the average change in behaviour, from a 10% increase to a 50% decrease; this is in agreement with behavioural studies that have investigated this issue [20-28]. If these trends for reducing risk are reversed or are different in other settings, such that diagnosed HIV-infected individuals increase behaviour that leads to the transmission of HIV, then our conclusions on the benefits of testing would then not hold. A limitation of our model is that we only considered the annual coverage of HIV testing and not the frequency of testing and its correlation with risk behaviour. To investigate this would require a more detailed model than the one developed for this analysis and would be of interest for future research.

The feasibility of increasing HIV testing rates differs between settings. In Australia, unlike some other regions, the health care system and infrastructure is well equipped to conduct screening for HIV. But greater efforts might be required to reach individuals who are not regularly tested for HIV, and this might include extending hours of operation of sexual health clinics or providing alternative testing facilities. The proportion of Australian MSM who are tested for HIV at least once per year is already relatively high. This proportion has been slowly increasing and its increase should be promoted further. Furthermore, persons who have higher HIV risk exposure tend to test more frequently [51] but there may be a saturation level to the frequency of testing that is attainable.

Increasing HIV diagnoses requires educating susceptible populations to seek HIV testing on the basis of indicators such as a known exposure to HIV or early recognition of symptoms. This could be complemented by population-level interventions to reduce factors that potentiate the transmission of HIV, including promoting condom use, strategic positioning, and testing and treatment of other sexually transmissible infections. This is especially important as most forms of HIV counselling have little effect on the behaviour of HIV-negative people. But as we have demonstrated, the potential impact of promoting HIV testing could be substantial in reducing secondary transmissions from HIV-positive individuals.

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Chapter 4: Frequent testing of highly sexually active gay men is required to control syphilis

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Author Contributions

RTG supervised the technical components of the analysis, developed the model, wrote code, conducted literature surveys, and wrote the manuscript. AH assisted with model development and coding, produced results and assisted with analyses, and contributed to writing of the manuscript. GPP, BD and JMK provided expert advice, model parameters, and manuscript editing. DPW supervised the project, conducted literature surveys, assisted with analyses and manuscript editing.

Abstract

Background: The incidence of syphilis infections has been substantially increasing in gay men in the developed world.

Methods: We developed an individual-based mathematical model describing syphilis transmission within a gay male population: we used the model to simulate the expected relative impact of numerous screening and treatment interventions, targeting different at-risk groups with various coverage and frequency rates and follow-up schedules.

Results: The model predicts that increasing the proportion of gay men tested each year would have a relatively modest impact on syphilis incidence. However, increasing the frequency of testing can have a large impact, with the prevalence of syphilis reduced substantially if individuals are tested every three months. Targeting frequent screening at gay men who have large numbers of partners or who engage in group sex is a more efficient way of reducing syphilis epidemics. Contact tracing the regular partners of infected individuals is the most efficient intervention and can have a significant epidemiological impact with relatively high coverage rates.

Conclusions: Increasing the frequency of testing and treatment are required to mitigate syphilis epidemics. Notifying and testing partners of infected men should occur where possible but the high rates required to reverse epidemic trends are likely to be infeasible. Contact tracing should be a secondary priority that is coupled with increases in the frequency of testing in the population. Encouraging testing among men not previously tested for syphilis is also recommended.

Introduction

Syphilis has re-emerged in numerous industrialized countries [1-5], particularly among gay men [6-9]. These epidemics are concerning since untreated cases may progress to tertiary syphilis [10-11] and the presence of syphilis lesions facilitate HIV transmission [12]. Coinciding with the rise in syphilis, HIV incidence has also been increasing among gay men [12-14]. Both infections often co-exist because both HIV and syphilis are transmitted sexually, however, oral sex is relatively safe with respect to HIV transmission but it is an efficient transmission mode for syphilis. Designing effective interventions to reduce the incidence of syphilis is currently important for many public health systems. One important control measure is routine screening [9]. Here, we evaluated different screening and treatment interventions using a mathematical model.

Mathematical models provide useful insights into the complex dynamics of disease transmission [15] and have been applied to syphilis epidemics in recent decades [16-20]. This study advances prior models by developing an individual-based computer simulation model to forecast the potential impact of screening interventions, informed by biological, clinical, and sexual behavior data of a population of gay men. Using this model the coverage and frequency of testing required to mitigate epidemics among gay men was determined.

Methods

We developed an individual-based transmission model that simulates the formation and breakup of sexual partnerships and tracks the transmission of syphilis within a virtual population of sexually active gay men. The assumptions/parameters of the model (appropriate for the context of Victoria, Australia)

are listed in Table 1 and a detailed description of the model is presented in the Supplementary Material. The model simulates a dynamic sexual partnership network that is updated daily with partnerships formed randomly (with uniform probability) between available men. This availability is determined by each person's sexual activity specified by the average number of sexual partnerships they have per year. Gay men can participate in casual partnerships (lasting up to one day), form long-term partnerships, and/or engage in group sex. A person's sexual activity and sexual behavior within a partnership are determined probabilistically (see Appendix for Chapter 4) such that our model simulates a realistic and heterogeneous sexual network. Sexual behavior simulated by this model is based on detailed behavioral research from a number of studies (see Table 1). Men in these studies were recruited entirely through gay community sites, and, for the most part, described themselves as being gay-identified with strong social connections to other gay men. For this reason, we have described them as 'gay' to avoid any confusion with broader samples of men who have sex with men that might include men with little or no connection to gay communities.

Parameter		Value
Demographic and Epidemiologic Parameters		
Population size		30,000 [a]
Prevalence of HIV in gay men		10% [a]
Percentage of HIV-positive gay men on ART		60% [a]
Distribution of the number of casual partners of HIV-negative gay men per year (proportion of men in each category) [b]	1-3	26%
	4-10	21%
	11-20	16%
	21-100	30%
	100-120	7%
Distribution of the number of casual partners of HIV positive gay men per year (proportion of men in each category) [c]	1-3	29%
	4-10	24%
	11-20	8.5%
	21-100	29%
	100-120	9.5%
Number of casual partners per year for 'low activity' gay men		1-10 [d]
Proportion of HIV-negative men who engage in group sex		17% [21] [e]
Proportion of HIV-positive men who engage in group sex		30% [21] [e]
Syphilis Biological Parameters		
Overall duration of infectious syphilis		1-2 years [f]

Average duration of incubation period		3-4 weeks [22] [f]
Duration of primary stage		45-60 days [23] [f]
Duration of secondary stage		100-140 days [11] [f]
Transmission probability per act in incubating, primary and secondary stages	Penile-anal	1.4% [g]
	Penile-oral	1.0% [g]
Transmission probability per act in early latent stage	Penile-anal	0.7% [g]
	Penile-oral	0.5% [g]
Percentage of syphilis cases that recur after infectious syphilis		25% [24]
Average duration of remission		6 months [11]
Average duration of relapse		90 days [11]
Average duration of latency before establishing tertiary disease		15 years [11]
Average duration of protective immunity post-treatment of late infection		5 years [18, 25] [h]
Sexual Behavior Parameters		
Percentage of gay men in a regular sexual partnership		50% [21]
Average duration of regular partnerships		4 years [25]
Average number of acts with regular partner per week	penile-oral	2
	penile-anal	2
Average number of acts per casual partner/encounter	penile-oral	1 [21]
	penile-anal	0.7 [21]
Proportion of partnerships in which HIV serostatus	Casual/Group	35% [21, 25]

is disclosed	Regular	85% [21, 26-27]
Proportion of sexual acts in which condoms are used for partnerships that are:	HIV discordant	90%
	HIV concordant	10%
	HIV status not disclosed	40%
Group sex parameters		
Average number of group sex events per year for men who engage in group sex		3.5 [25]
Average number of men in each group sex event		Median 4.4 [i]
Average number of sexual partners in group sex event per person		Min: 1, Max: 10
Clinical Parameters		
Efficacy of condoms in protecting against syphilis transmission	penile-anal	90% [28]
	penile-oral	90% (assumption)
Percentage of gay men who test for syphilis each year in the absence of a specific intervention (frequency one test per year except for gay men on ART who test on average three times per year)	Highly active	55% [21] [j]
	Engage in group sex	65% [21] [j]
	On ART	70% [21] [j]
	Everyone else	55% [21] [j]
Percentage of the gay population that never test for syphilis		15% [25] [k]
Sensitivity of syphilis test for detecting current infection		95% [29-30]
a: The population of gay men in Victoria is estimated to be ~30,000. In Australian gay populations the prevalence of HIV is ~ 10% [31]. Approximately 60% of HIV-infected gay men		

in Australia are on antiretroviral therapy [21].

b: Distribution obtained from the 'Health In Men' (HIM) study [26].

c: Distribution obtained from the 'Positive Health' (PH) study [26].

d: The population is categorized into 3 sexual activity groups. Low activity, high activity, and those who engage in group sex. Low activity people are those who have less than 10 casual partners per year and do not engage in group sex.

e: Recent studies of group sex among gay men in Australia suggest that most gay men have engaged in group sex at some time [32] with 47% of HIV-negative gay men and 64% of HIV-positive gay men engaging in group sex in the previous six months [21]. However, a large proportion of gay men only engage in group sex once off or very infrequently. The values here are estimates for the proportion of gay men who engage in group sex regularly every year. We assume that only high activity gay men engage in group sex, however, for a person who engages in group sex, their total number of casual partnerships also includes their group sex partnerships. In our model the proportions of high activity men who engage in group sex is calibrated so that the overall proportion is equal to the values in the table.

f: A primary stage of disease generally appears within 2-6 weeks of infection and manifests as a lesion, ulcer (or chancre) that appears at the site of inoculation. It is able to survive in a wide variety of tissues. The *Treponema pallidum* bacterium disseminates via the blood-stream and may result in secondary syphilis. As *T. pallidum* is present in mucosal or cutaneous lesions, infected adults are more likely to pass the infection on during the primary and secondary stages. Primary, secondary, and early latent syphilis are collectively called 'infectious syphilis' (Fig. 1a). Late latent and tertiary syphilis is generally regarded as no longer infectious for sexual partners. The duration in each stage of infectious syphilis for our model is sampled independently within the specified range for each infected person and the duration of the early latent stage for each individual is given by the difference between the overall infectiousness duration and sum of the time spent in the other stages.

g: Although various studies have provided estimates [33-34], there are very little unbiased data on the transmissibility of syphilis. Transmission risk has been inferred through studies

that trace sexual partners [11, 23, 35] and some prospective studies involving prophylactic treatment have been used to estimate transmission probabilities [36-37]. A review carried out by Garnett et al. [18] suggested that an appropriate transmission probability per partner is ~60% per year for heterosexual couples. Assuming 50-100 acts per partnership per year and the relationship $\beta_p = 1-(1-\beta_a)^n$

[38] where *n* is the number of sexual acts in the partnership, β_p is the per-partnership probability and β_a is the per-act probability, suggests that the per act transmission probability is 1-2%. Sexual transmission of syphilis is likely to be higher in male-to-male penile-anal transmission than heterosexual penile-vaginal intercourse. We assume that penile-oral sex has a lower transmission probability per act than penile-anal sex. The relative infectiousness of primary versus secondary syphilis is also unknown: Garnett et al. [18] assumed that the primary stage was more infectious than secondary but Pourbohloul et al. [20] assumed the converse. There are biological reasons to suggest that either assumption is plausible. In the absence of reliable data we assume uniform infectiousness over the duration of incubation, primary and secondary infectious syphilis stages. The probability of transmission during the early latent stage is assumed to be half the probability in the primary and secondary stages.

h: Relatively little is understood regarding immunity to syphilis. It is generally believed that immunity to syphilis does not follow natural infection [39-40]. But it is also thought that individuals previously infected are less likely to develop a chancre at the site of inoculation [39]. It has also been established that some immunity to syphilis (and clinical manifestations) could be attributed to local innate and adaptive cellular immunity and some to the humoral immune response to a lesser extent [41]. Completely protective immunity has been shown in a rabbit study [42] but not in humans. A controversial study in humans [39] demonstrated that individuals previously treated for syphilis and challenged intradermally with *T. pallidum* were less likely to develop a typical chancre at the site of inoculation, but were still thought to become infected. Based on the available evidence we conclude that the assumptions of Garnett et al. [18] are reasonable and we similarly assume that individuals treated in early infection obtain no protective immunity but individuals who clear infection in later stages

have immunity for up to 5 years.

i: Among Australian gay men who engaged in group sex during the previous six months, 32.8% indicated that their last group sex event was a threesome, and 28.8% indicated that it involved more than 5 other men [25, 43]. Based on this data we fit a generalized Pareto distribution for the group size.

j: The current background testing rates show the proportion of gay men in each population category that tested on average once per year. Men on ART are tested more frequently per year; we assume on average that 70% of men on ART are tested each year with an average frequency of 3 times per year.

k: We assume that there is a proportion of gay men who never test for syphilis.

Table 1: Model parameters and values for model calibration (baseline scenario)

The assumed disease progression of a syphilis-infected individual is described in the Appendix for Chapter 4 and is shown in Figure A1a. Individuals are designated to be infectious if they are in the exposed, primary, secondary, early latent or recurrent infectious stages of syphilis with the transmission probability per sexual act depending on the infection stage (see Table 1). Individuals treated in the early stages are assumed to be immediately susceptible to re-infection, while those treated in the later stages of syphilis are immune to re-infection for an average of 5 years [18, 25]. Prior to the introduction of interventions 55-70% of the population is tested for syphilis at least once every year [21] depending on their sexual activity and HIV status. We also include a proportion of the population who never get tested for syphilis [25, 44].

The model was implemented using Matlab® with each simulation tracking the dynamic sexual network, syphilis transmission, and disease progression of syphilis-infected individuals. Syphilis transmission was tracked over the years 1998 to 2007. The model was specifically calibrated to match the estimated

infections syphilis diagnoses among gay men in Victoria, Australia. The median trajectory of 50 model simulations, using realistic parameter values (Table 1), accurately reflected surveillance data for Victoria (Fig. A1b in the Appendix for Chapter 4). The 10 simulations that best fit the epidemic data were selected (using a Pearson chi-squared test) to forecast epidemic trajectories over the next 10 years under various interventions. Although the model used Australian behavioral data and was calibrated to reflect the epidemic in the state of Victoria, the relative impact of each intervention should be generally applicable to other settings.

Calibration of the model was preformed manually, by making minor changes to the transmission probability and the duration of each stage of infection. The parameters were kept constant throughout the 50 model simulations, with the simulations being used to account for the random variation inherent in an individual based model.

To compare different interventions, the median prevalence and syphilis diagnoses (taken as the number of treatments) per year were recorded. The following interventions were simulated:

(i) no change in screening;

(ii) increase coverage to screen all men previously tested (85% of the population) once per year; or screen all men once per year (including men not previously tested);

(iii) maintain the current testing coverage but increase the frequency to 2 or 4 times per year (with the testing frequency of HIV-positive individuals on antiretroviral therapy (ART) increased from 3 to 6 times per year in both cases); and

(iv) contact tracing and testing 50% and 75% of regular partners over the previous three months with 5% and 10% of casual partners over the previous month. The ideal scenario where all partners over these

time periods are tested was also investigated. It is important to note that 'contact tracing' is synonymous with 'partner notification' in some settings. 'Contact tracing' usually refers to that carried out by the Health Department's Disease Intervention Specialists to notify and test partners while 'partner notification' is when the patient informs their sexual partners of the infection and advises the partner to seek testing. The coverage rates for our simulations are the actual levels of partner testing that is achieved independent of the means by which the partners are reached. For the remainder of this paper we use the term contact tracing to describe this type of intervention.

These scenarios were independently applied to: HIV-positive gay men on ART; highly sexually active gay men; and gay men who engage in group sex; with the remaining population screened at baseline levels. The number of tests carried out and the number of infections averted (compared to the baseline case) was also recorded to measure the efficiency of each intervention scenario.

Results

Baseline Scenario

Our model projected future epidemic trajectories under conditions that all parameters and screening rates remain unchanged. The median prevalence and number of diagnoses for these simulations was used as a baseline from which the relative impact of different screening interventions could be measured.

Increasing testing coverage

Increasing the testing coverage (from 55-70% per year) to screening all gay men previously tested (85% of the population) results in a relative decrease in the peak prevalence and number of diagnoses of

~38% and ~25% (to ~6% and ~1011 cases), respectively (Fig. 1a,b). However, there is an increase in diagnoses above the baseline case immediately after this intervention is introduced (Fig. 1b), reflecting the increased proportion of syphilis infections discovered. Increasing the testing coverage to all gay men, including men not previously tested, results in an expected reduction in prevalence and diagnoses (with prevalence of ~1.6% and 504 diagnosed cases after 10 years). However, the rate of decrease in diagnoses in this case is similar to the other coverage scenario after a large initial spike due to the group of men not previously tested being a pool for late stage (non-infectious) syphilis. It is unlikely that 100% screening coverage will be achieved. Hence, increasing the coverage within the gay male population will likely have a relatively small impact on syphilis epidemics.

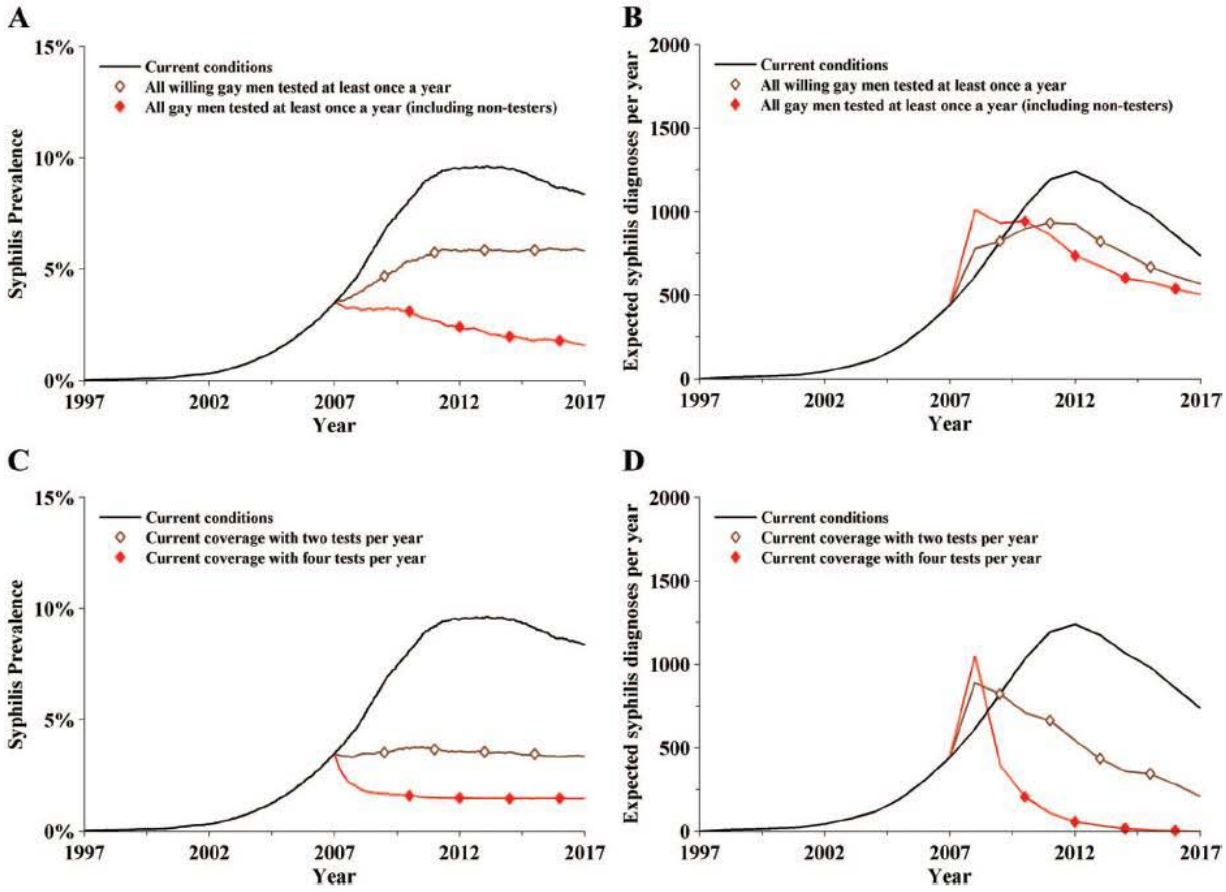

Figure 1: The impact of increasing testing coverage to 100% over 10 years on **(a)** syphilis prevalence, and **(b)** annual syphilis diagnoses. The impact of increasing testing frequency over 10 years on **(c)** syphilis prevalence and **(d)** annual syphilis diagnoses. The median prevalence for the 10 baseline simulations under current conditions are shown in black.

Increasing testing frequency

Increasing the frequency of testing can have a large impact on syphilis epidemics (Figs. 1c,d). Maintaining current coverage levels but increasing the frequency of testing to 2 times per year for HIV-negative gay men and HIV-positive gay men not receiving ART and to 6 times per year for HIV-positive men on ART results in a large relative decrease in the peak prevalence of ~ 61% (to ~3.8%) (Fig. 1c). However, when the testing frequency for gay men not on ART is increased to 4 times per year the syphilis prevalence immediately declines and slowly decays to a prevalence of ~1.47% by 2017 (Fig. 1c); that is, a relative decrease (from peak) of ~84%. For these interventions, the expected number of

syphilis diagnoses immediately increases to a sharp peak during the first year after initiating the intervention before decreasing (Fig. 1d). When testing is carried out every three months, the number of diagnoses decays rapidly to approximately zero after 10 years. Thus, increasing the frequency of syphilis testing could substantially mitigate an epidemic. However, the prevalence of syphilis in the population rapidly decreases to ~1.5% and then only very slowly decreases from this value despite diagnoses dropping to zero. Remaining prevalence is predominantly due to men who have never tested for syphilis progressing to late-stage (non-infectious) syphilis. This further emphasizes the importance of encouraging all men to get tested for syphilis.

Contact tracing

Tracing and testing a proportion of diagnosed individual's partners, and treating infected cases can be expected to reduce the level of syphilis prevalence (Fig. 2a). Treating 50% of regular sexual partners (from the previous three months) and 5% of casual partners (from the previous month) of diagnosed syphilis cases leads to a relative decrease in peak prevalence of ~29% (from ~9.6% to ~6.8%). Increasing the proportion of regular partners treated to 75% reduces the peak prevalence further, to ~6%. However, doubling the proportion of casual partnerships treated to 10% has only a minimal additional effect (Fig. 2a). In the unrealistic scenario of 100% of all sexual partners being traced and treated, the syphilis prevalence would immediately flatten out to a peak level of ~3.7% (~60% relative decrease) and then decrease slightly over 10 years to ~2.7%. These reductions are not sufficient to reverse trends in syphilis epidemics, even at unrealistically high rates of effective contact tracing. While overall contact tracing does have a measurable impact on the future of the epidemic, the difficulties in contacting partners may make this strategy difficult to implement.

Synchronized testing and Follow-up screening

We also investigated screening strategies where current testing rates are maintained but all syphilis testing is synchronized to occur during a one month period and screening strategies that follow up men who have previously been treated for syphilis. However, we determined that these interventions had minimal impact on syphilis epidemics (results not shown).

Targeting specific sub-populations

Increased syphilis testing in specific at-risk sub-populations that may be reached by public health services and community-based campaigns was also investigated. We simulated increased syphilis testing in gay men who engage in group sex, men who have greater than 10 partners per year, and HIV-infected men who are on ART. We found that if all men who engage in group sex are tested 2 or 4 times per year then the peak syphilis prevalence can be reduced by ~27% and ~50% (to ~7.0% and ~4.8%), respectively (Fig. 2b). Although this targeted strategy has some impact, the effect may be relatively small since it is estimated that only 17% of HIV-negative gay men and 30% of HIV-positive gay men regularly engage in group sex (Table 1).

Targeting men who have more than 10 partners per year is predicted to have a substantial impact on syphilis epidemics. Testing highly-active gay men and men who engage in group sex an average of two times per year has a larger effect on prevalence than only testing gay men who engage in group sex on a 3-monthly basis. Testing highly sexually active gay men and men who engage in group sex every 3 months has almost the same impact on syphilis epidemics as testing the entire population every 3 months (with HIV-positive men on ART tested 6 times per year) with a similar immediate decay in prevalence and only a slightly higher prevalence (~1.51% versus ~1.47%) by 2017 (Fig. 1c and 2b). This

suggests that men who have less than 10 partners per year do not contribute significantly to syphilis epidemics and targeting men with more partners is most efficient.

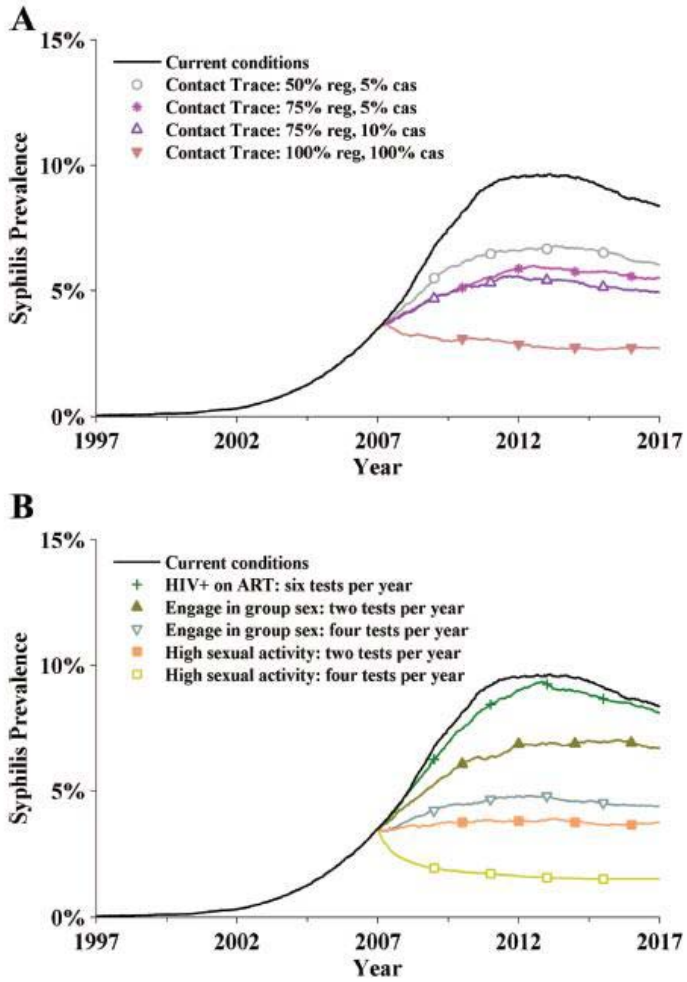

Figure 2: Change in syphilis prevalence due to **(a)** contact tracing and treatment for a proportion of regular partners in the previous 3 months and a proportion of casual partners in the previous month. **(b)** Syphilis prevalence for the entire gay male population after increasing the testing frequency in particular population groups. The median prevalence for the 10 baseline simulations under current conditions are shown in black.

Efficiency of interventions

The efficiency of each intervention was measured by calculating the number of infections averted compared to the baseline case versus the total number of tests performed for the intervention over 10 years (Table 2). We found that for interventions not involving contact tracing there is relatively linear

relationship between the number of infections averted and the number of additional tests carried out. This relationship breaks down when the average testing rate is 4 tests/year for each individual not on ART and 6 tests/year for men on ART. Almost twice as many tests are performed over 10 years (~550,183 versus ~277,070) with almost no increase in the number of infections averted (from ~9929 to ~9970). Therefore, increasing the testing rate in gay men with few partners is highly inefficient and gives little additional public health benefit. In contrast, contact tracing and testing the partners of an infected individual is highly efficient (Table 2) despite having less effect on the epidemic (Fig. 2a).

Intervention	Infections Averted (Over 10 yr)	Additional Tests (Over 10 yr)	NNT
Coverage of all men willing to test	2820	92,323	32.7
Coverage of all men	4498	145,437	32.3
Current coverage with 4 tests per year	9971	550,183	55.2
HIV-infected on ART: 6 tests per year	545	37,542	68.2
Engage in group sex: 2 tests per year	2244	38,076	16.9
Engage in group sex: 4 tests per year	5364	114,833	21.4
High sexual activity: 2 tests per year	5922	92,269	15.6
High sexual activity: 4 tests per year	9929	277,070	27.9
Contact trace: 75% reg, 5% cas	4030	5,237	1.3
Contact trace: 75% reg, 10% cas	4540	6,480	1.4
Contact trace: 100% reg, 100% cas	8133	16,983	2.1

Table 2: Efficacy of interventions in terms of the number of additional people needed to be tested (NNT) to avert one infection.

Discussion

Using a simulation model that incorporates detailed sexual-activity and testing data, realistic biological properties and heterogeneous sub-populations, we have shown that syphilis epidemics can occur in highly tested populations of gay men. Our model was used to predict the epidemiological outcomes of changes in testing strategies. Our results suggest that increasing the coverage of syphilis testing within the population of men who are already willing to get tested has moderate impact; coverage is already relatively high and only moderate improvements in coverage can be achieved. However, encouraging syphilis testing among men who have not previously been tested can have a large impact on syphilis epidemics. This is particularly important as this sub-population of men is at high risk of becoming infected and progressing to tertiary syphilis.

What is required is greater frequency of testing; if testing occurred every 3 months, on average, then syphilis incidence could be reduced substantially. However, targeting men who have low numbers of partners (<10 per year) is ineffective. Increasing testing rates of HIV-positive men on ART is also ineffective since they are a relatively small sub-population and they already have relatively high testing rates (an average of 3 tests per year). However, epidemiological data suggests that a disproportionate number of syphilis diagnoses are in HIV-positive men [45-46], therefore targeting this population may have significant benefits not detected by our model. It is a limitation of our model that HIV infection remains static and is has no links to syphilis infection; this is explored further in Chapter 5.

According to our model the key sub-populations that should be targeted for increased syphilis screening are gay men who engage in group sex and those with large numbers of partners (>10 per year). Testing

'higher activity' men every 3 months on average should reverse current trends in syphilis incidence and is an efficient intervention strategy.

We also explored the likely impact of tracing partners of cases that are treated for syphilis. We found that this would be a very effective and efficient strategy and should be carried out wherever possible. However, contact tracing will only have a substantial effect on a syphilis epidemic if a very large proportion of regular and casual partners are notified and tested. The intensive labor required to carry out contact tracing is unlikely to achieve the very high rates required to reverse syphilis epidemics. Therefore, we recommend that contact tracing should be a secondary objective for controlling syphilis epidemics among gay men. Contact tracing should be a supporting priority that is coupled with the primary priority of increasing the frequency of testing in the population. Although this analysis is limited to gay men our conclusions may be valid in some heterosexual settings, such as those in which large proportions of sexual partners are unlikely to be accessed. While partner notification and contact tracing are very important, increasing population-level testing frequencies is recommended as the most effective way to reduce the incidence and prevalence of syphilis.

The model estimates the syphilis prevalence at around 5% in 2007. This is substantially less than the prevalence levels suggested in Chapter 2. The model in Chapter 2 was not built to model STI prevalence in an accurate manner, for example it did not explicitly model new STI infections within the population. The findings of this model suggest that incidence of new infections may be a better measure of the patterns of spread of STIs (such as syphilis) than prevalence estimates which are not routinely collected in Australia.

Our results were obtained by calibrating our model to gay men in Victoria, Australia. These results are likely to be applicable to other populations worldwide. While quantitative results will vary between settings due to differences in sexual mixing behavior, accessibility to health services, different epidemic stages, and other social variables our qualitative findings should be generalizable to most settings. The need to substantially increase the frequency of syphilis testing (particularly among 'high-activity' subpopulations) and to promote contact tracing to reduce syphilis epidemics can be considered in any jurisdiction as interventions most likely to be effective and efficient.

Our model, although informed by the best data available to us, has a number of limitations. It held all parameters constant and thus did not capture changes in behavior over the last 10 years. Numerous biological and clinical aspects of syphilis infection are unknown. For example, it is difficult to model the infectiousness of individuals in the primary and secondary stages of syphilis: infected individuals could be highly infectious over a shorter time period. The degree of immunity following treatment at different stages is also uncertain. For these factors we reviewed the available literature and made the best assumptions possible (Table 1). Furthermore, we also neglected age- or group-specific assortative sexual mixing patterns. However, we believe that our model well characterizes syphilis epidemics (see Fig. S1b) and has been useful in evaluating potential interventions, gaining insight into those that are not likely to succeed, and determining which strategies should be adopted as goals.

The feasibility of increasing screening should be evaluated in each setting. Serologic screening is sensitive and inexpensive with infectious syphilis easily and cheaply treated using intramuscular

penicillin G. The cost-effectiveness of syphilis testing depends on the efficiency of the screening strategy. We have provided estimates of the number needed to test in order to avert an infection. While these numbers will differ between locations and settings our estimates can be used as a guide in the decision-making of public health policies and campaigns. Of course, ease of access to testing facilities as well as the likely behavior and attitudes of people to whom strategies are targeted should be considered. There is likely to be a maximum frequency of screening and some people will not be screened regardless of the extent of educational messages. However, if interventions successfully scale-up the frequency of syphilis testing then it is possible to reverse epidemiological trends of this important condition.

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Chapter 5: Could implementation of Australia's National Gay Men's Syphilis Action Plan have an indirect effect on the HIV epidemic?

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Author Contributions

AH conceived of the study, developed the model, produced results, conducted the analysis, and wrote the manuscript. RTG assisted with model development and manuscript editing. DPW supervised the project and contributed to writing of the manuscript.

Abstract

Objectives: The number of incident infections of syphilis and HIV have increased over the past decade across Australia, particularly among gay men. In other industrialised settings syphilis epidemics have also resurged coincidentally with increases in HIV diagnoses. Sexually transmissible infections are a biologically plausible cofactor for increasing HIV transmission. We pose the question: could strategies purely targeting syphilis also have an indirect impact on HIV incidence?

Methods: We developed an agent-based computer model that simulates the transmission and disease progression of HIV and syphilis among a population of sexually-active gay men, calibrated to reflect the epidemics in Victoria, Australia. The model was informed by detailed behavioural data from a variety of sources. The model was used to investigate the potential epidemiological impact of a variety of public health interventions.

Results: Assuming that syphilis could act as a biological cofactor for HIV transmission, from no effect to increasing risk 5-fold, our model indicates that if Australia's syphilis action plan is effectively implemented then the number of HIV infections could decrease by up to 48% over the next decade in the absence of any specific HIV interventions.

Conclusion: It is plausible that effective implementation of interventions targeting syphilis epidemics can have an indirect effect to mitigate the spread of HIV. The synergistic and interactive associations of all sexually transmissible infections should be considered in the design, implementation and evaluation of public health strategies and programs.

Introduction

During the last 10 years there has been a resurgence in syphilis among men who have sex with men (MSM) in numerous countries, including Australia [1-4]. Over the same period there has also been an increase in the number of HIV diagnoses, reversing previously decreasing trends [5-8]. If surveillance mechanisms reflect true increases then the coincidences in time and trends of these infections could be due to changes in the same underlying behavioural factors, synergistic biological factors, or both. A likely explanation for the observed increases of both infections in Australia is an increase in unprotected anal intercourse among MSM [9-10]. However, there is also evidence that the presence of sexually transmitted infections (STIs) can increase the transmission and acquisition of HIV; numerous studies have demonstrated a statistically significant increase in the relative risk of HIV transmission when another STI is present after adjusting for possible confounders, including level of risk behaviour [11-17]. This association is also highly biologically plausible, particularly for STIs that cause genital ulcers or lesions (such as syphilis) [18-22]. Consequently, some of the recent rise in HIV infections could be due to biological factors related to the presence of syphilis. It is thus logical to consider the indirect effect of interventions aimed at syphilis on HIV incidence. Despite this, numerous randomised controlled trials have found no difference in HIV incidence among groups that were treated for STIs compared with control groups [23-26]; however, there are some explanations for these outcomes consistent with real biological increases in HIV risk per exposure in the presence of STIs (e.g. [27-28]). Therefore, we consider whether public health strategies specifically targeting syphilis might also reduce new HIV infections.

At the end of 2008 the Blood Borne Virus and STIs Subcommittee of the Australian Population Health Development Principal Committee instigated the development of the National Gay Men's Syphilis Action Plan (NGMSAP). The development of the plan involved the determination of variables and targets to

underpin the shared goal of reducing the incidence of syphilis among gay men in Australia. Detailed mathematical modelling research was carried out to investigate the expected epidemiological impact of a large number of potential interventions and this was complemented by social research on the acceptability of interventions among gay men as ascertained in focus group sessions [29]. The recommendations of this research [29] has led to the commencement of implementing targeted strategies for reducing the spread of syphilis across Australia. Implementation will be on-going with progress monitored through behavioural and syphilis epidemiological indicators over the next few years. Specifically, the highest priorities of the NGMSAP are to:

1. Encourage gay men to test for syphilis as it pertains to their level of risk. Screening for syphilis is recommended to accompany routine HIV management and testing. Gay men who have more than 20 partners per 6 months are recommended to test for syphilis at least twice per year.
2. Increase the rate of partner notification and testing of sexual partners of men diagnosed with syphilis. To accompany this strategy education campaigns should occur to decrease stigma.

These specific strategies have no direct effect on HIV prevention and control. But if primary and secondary syphilis infections increase the risk of HIV transmission then controlling syphilis epidemics could have an indirect effect of reducing HIV incidence.

In this study we investigate the possible interactions between syphilis and HIV transmission through the development of a mathematical model calibrated to the population of MSM in Victoria, Australia. We use the model to explore the expected impact on HIV incidence if the NGMSAP was implemented effectively without any other direct HIV prevention interventions.

Methods

The mathematical transmission model used in this study is an extension to a previously published syphilis model [29-30]. In brief, it is an individual-based computer model that simulates a population of 30,000 MSM, similar to the size of the MSM population in Victoria, Australia [31]. The model contains two major components: 1) sexual partnership dynamics, and 2) transmission and disease progression for both syphilis and HIV. Table 1 contains a list of all parameter values and assumptions used in the model.

Partnership formation

We model three types of sexual partnerships: regular partnerships, casual partnerships, and group sex encounters. The frequency of acquiring new sexual partnerships for any individual in the model is informed by the distribution of reported partners from behavioural studies among relevant populations. Indeed, all relevant behavioural characteristics of the individuals are informed from several sources, including the Melbourne Gay Community Periodic Surveys, Three or More Study, and Health in Men study [9-10, 32-33] (see Table 1). We assign each simulated person to be of a sexual activity class of low, high, or group: low sexual activity is defined as having less than 10 partners per year and high activity defined as 10 or more partners per year. Individuals who are highly sexually active have more casual partners and may participate in group sex events. Casual and group sex partnerships are assumed to be one-off encounters. Regular partnerships have an average duration of 4 years with a 95% range of 36 days to 14.7 years (see Table 1).

Parameter		Value
Demographic and Epidemiologic Parameters		
Population size		30,000 [31]
Age of entering population		15-25 years
Age of leaving the population		65-85 years
Sexual Behaviour Parameters		
Distribution of the number of casual partners of HIV-negative gay men per year (proportion of men in each category) [32]	1-3	26%
	4-10	21%
	11-20	16%
	21-100	30%
	100-120	7%
Number of casual partners per year for 'low activity' gay men		1-10
Proportion of HIV-negative men who engage in group sex		17% [9]
Syphilis Biological Parameters		
Overall duration of infectious syphilis		1-2 years
Duration of incubation period		3-4 weeks [35]
Duration of syphilis primary stage		45-60 days [36]
Duration of syphilis secondary stage		100-140 days [37]
Transmission probability per act in incubating, primary and secondary stages [36-45]	Penile-anal	1.4%
	Penile-oral	1%
Transmission probability per act in early latent stage [36-45]	Penile-anal	0.7%
	Penile-oral	0.5%
Per act multiplicative increase in transmission probability of syphilis to HIV infected men		1.5-2.5
Percentage of syphilis cases that recur after infectious syphilis		25% [46]
Average duration of remission		6 months [37]

Average duration of relapse		90 days [37]
Average duration of latency before establishing tertiary disease		15 years [37]
Average duration of protective immunity post-treatment of late infection		5 years [33, 39]
HIV Biological Parameters		
Duration of Primary HIV stage		70-110 days
Duration of Chronic HIV stage		3000-5000 days
Length of time with AIDS before death		100-365 days
HIV transmission probability per act in primary stage		1.5-3%
HIV transmission probability per act in chronic stage		0.15-0.25%
HIV transmission probability per act in AIDS stage		1.5-3%
HIV transmission probability per act for men on ART		0.0015-0.005%
Per act multiplicative increase in transmission probability of HIV due to a syphilis infection in either partner		1-5
Sexual Behaviour Parameters		
Percentage of gay men in a regular sexual partnership		50% [9]
Average duration of regular partnerships		4 years [33]
Average number of acts with regular partner per week	penile-oral	2 *
	penile-anal	2 *
Average number of acts per casual partner/encounter	penile-oral	1 [9]
	penile-anal	0.7 [9]
Proportion of partnerships in which HIV serostatus is disclosed	Casual/Group	35% [9, 33]
	Regular	85% [32, 47-48]
Proportion of sexual acts in which condoms are used for partnerships that are (the HIV discordant value decreased from 80% to 69% from 1999 to 2009 [9]):	HIV discordant	90%
	HIV concordant	10%
	HIV status not disclosed	40%

Proportion of HIV infected men who disclose their infection status that serosort for other HIV infected partners		10% *
Group sex parameters		
Average number of group sex events per year for men who engage in group sex		3.5 [33]
Average number of men in each group sex event		Median 4.4 [33, 49]
Average number of sexual partners in group sex event per person		Min: 1, Max: 10
Clinical Parameters		
Efficacy of condoms in protecting against syphilis transmission	penile-anal	90% [50]
	penile-oral	90% *
Percentage of gay men who test for syphilis each year in the absence of a specific intervention (frequency one test per year except for gay men on ART who test on average two times per year)	Highly active	55% [9]
	Engage in group sex	65% [9]
	On ART	70% [9]
	Everyone else	55% [9]
Percentage of the gay population that never test for syphilis		15% [33]
Sensitivity of syphilis test for detecting current infection		95% [51-52]
Proportion of HIV infected men in primary stage who go onto treatment each year		11% *
Proportion of HIV infected men in chronic stage who go onto treatment each year		11% *
Proportion of men with AIDS who go onto treatment each year		95% *
Sensitivity of HIV test for detecting current infection		90-100% *
Percentage of high sexual activity men that get tested for HIV at least once per year		50% *
Percentage of men who engage in group sex that get tested for HIV at least once per year		75% *
The HIV testing rate for low sexual activity men was calibrated so that HIV prevalence was 10% in the population and notifications matched surveillance data. * Assumption based on discussions with expert stakeholders.		

Table 1: Model parameters and values for calibration (baseline scenario)

Transmission and disease progression

We incorporated both syphilis and HIV transmission into the model. The natural history of each infection is associated with different disease stages requiring different assumptions. Figure 1a shows the disease progression for syphilis. Each stage is associated with different durations and properties (see Table 1). Individuals are able to transmit syphilis, with varying transmission probabilities, depending on whether they are in primary, secondary, early latent, or recurrent stages of disease but not late stages of disease (see Table 1). Figure 1b shows the HIV disease progression included in the model. Upon infection, individuals are undiagnosed and in 'Primary' stage of *Treponema pallidum* infection. At any stage they may be tested and become diagnosed, and there is a probability of initiating treatment. The different stages of HIV infection have distinct transmission probabilities associated with them (see Table 1).

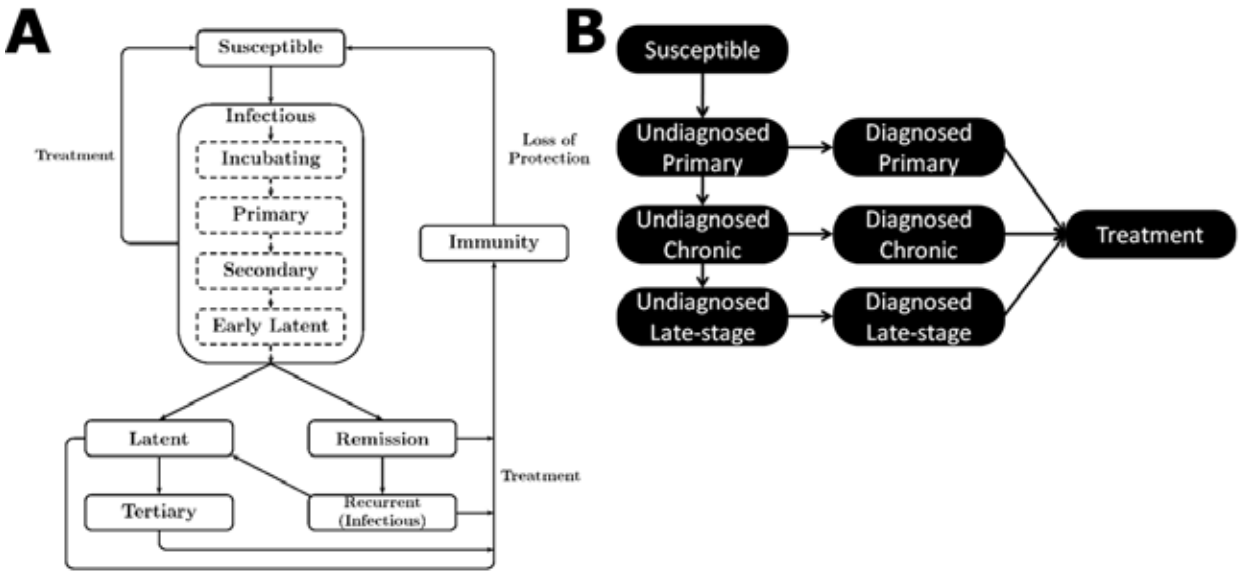

Figure 1: a) Schematic diagrams of the natural disease progression for (a) syphilis and (b) HIV, used in the model.

To model the interaction between syphilis and HIV we assumed that if syphilis was present in either the HIV-infected or non-HIV-infected partner then the probability of HIV transmission between partners is increased by a multiplicative factor, sampled from a uniform distribution between 1 and 5 [11-17], that is, a number between 1 and 5 is selected as the cofactor for each exposure event.

Calibration

The model was calibrated to match the number of syphilis and HIV diagnoses over the period of 1999 to 2008 in Victoria, Australia (Figure 2). Fifty model simulations were performed and the 10 simulations that fitted both HIV and syphilis diagnoses best were selected for projections using a Chi-squared test.

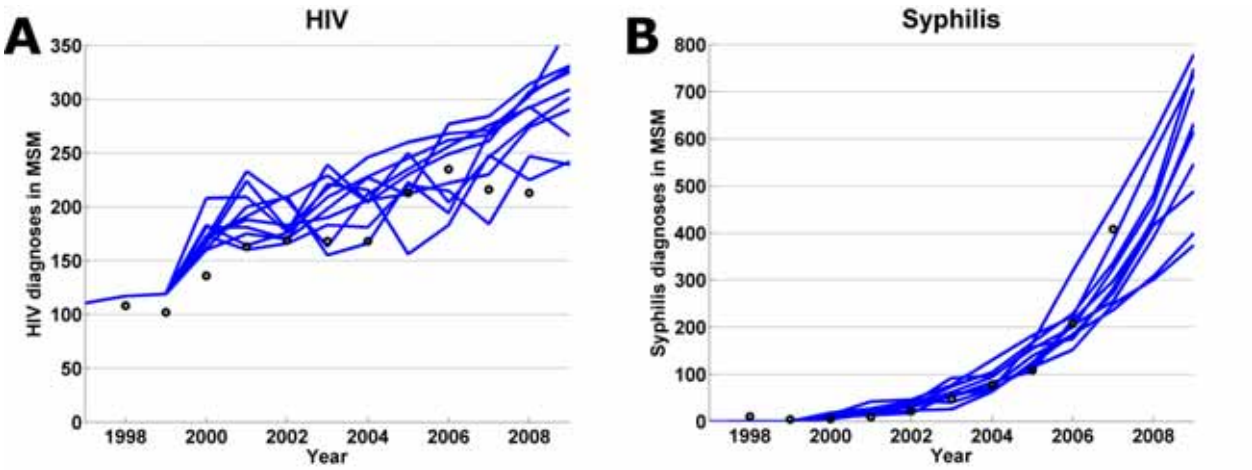

Figure 2: Comparison of the 10 best fitting curves (blue), against the data on the observed incidence (black circles) for a) HIV, and b) syphilis, with the multiplicative cofactor varying between 1 and 5.

Intervention strategies

In this study, we modelled five types of possible syphilis interventions that were priority recommendations from the NGMSAP [29]. The simulated interventions started from the beginning of 2010 and are applied for the next 10 years. The first priority set of recommendations of the NGMSAP consisted of including testing for syphilis with: (i) regular HIV testing for men who have not previously been diagnosed with HIV; (ii) HIV management (such as at routine clinical appointments for viral load

monitoring and receiving antiretroviral prescriptions) for men who have been diagnosed with HIV. Additionally, gay men with more than 20 partners per six months would be targeted such that 90% of them would receive two syphilis tests per year. The second priority set of recommendations of the NGMSAP consisted of implementing notification and testing of sexual partners of men diagnosed with syphilis. We simulated an intervention that resulted in syphilis tests for 75% of regular partners in the past three months and 10% of casual partners in the past month. Partners found to be positive for syphilis would also have their other partners notified where appropriate. Each of these intervention components were simulated separately and together.

Detailed description of the development, constructs, population distributions and other assumptions of the mathematical model can be found in the NGMSAP report [29].

Results

The expected impacts of NGMSAP interventions on the number of HIV and syphilis diagnoses in Victoria, Australia over the next 10 years are shown in Figures 3a and 3b respectively. The black curve represents the median of 10 simulations of the baseline scenario in which no HIV or syphilis interventions are implemented. According to our model, if syphilis testing is implemented routinely with tests for HIV and with management of HIV-infected cases then the total number of syphilis cases could be reduced by ~75% (red curve in Figure 3b). Although this does not directly affect HIV epidemics, the reduction in syphilis is likely to result in a decrease in the annual number of HIV cases by ~34% from the number projected in 2019 (red curve in Figure 3a).

If gay men who have more than 20 partners per six months receive syphilis tests twice per year then the syphilis epidemic could potentially be largely mitigated; our model estimates that the number of syphilis diagnoses would be reduced by ~99% after 10 years (blue curve in Figure 3b). This reduction in syphilis is likely to result in a decrease in the number of annual HIV cases by ~46% by 2019 (blue curve in Figure 3a).

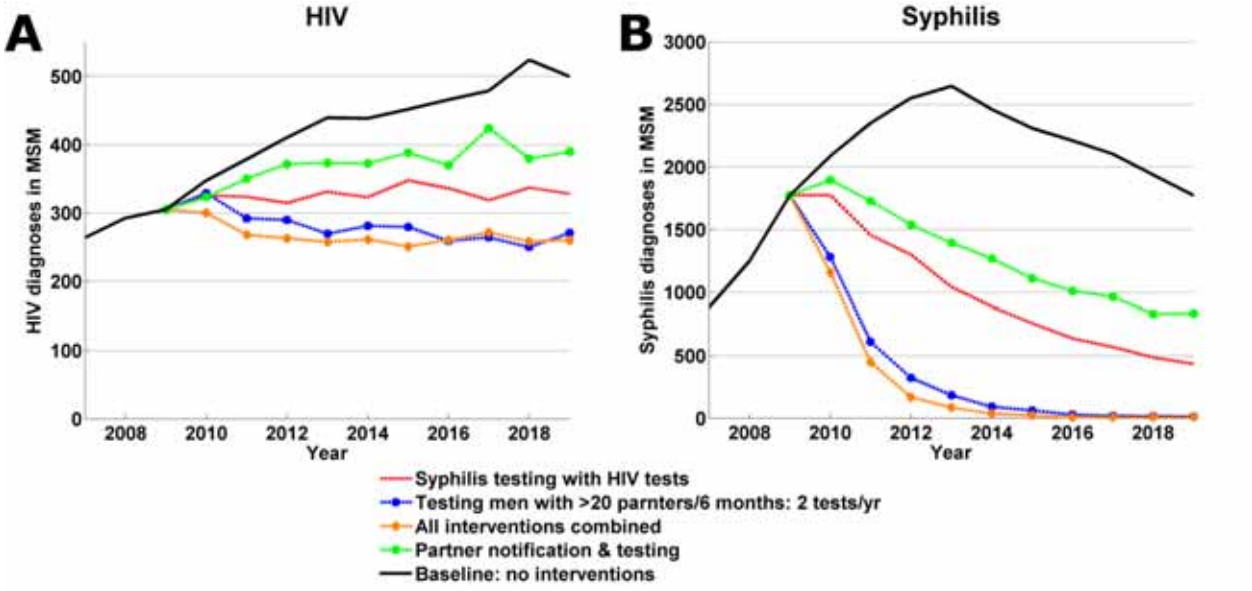

Figure 3: Model-simulated results of the impact on a) HIV and b) syphilis epidemics in Victoria, Australia from implementation of the NGMSAP interventions. Curves shown are median of 10 simulations of the baseline no-intervention case (black), implementing syphilis testing with HIV tests (red dashed line), testing men with more than 20 partners per six months for syphilis twice per year (blue dashed square line), partner notification and testing (green dashed circles line), all interventions combined (orange dashed diamonds line).

Our model suggests that if the coverage and frequency of syphilis testing remains unchanged but 75% of regular sexual partners and 10% of casual partners of gay men diagnosed with syphilis are tested then the number of syphilis cases could reduce by ~53% (green curve in Figure 3b). Although this is not sufficient to completely suppress *Treponema pallidum* transmission it is likely to control syphilis in an efficient manner. This reduction in syphilis is likely to result in a decrease in the annual number of HIV cases by ~22% by 2019 (green curve in Figure 3a).

If all of these strategies are effectively implemented then our model predicts that over the next 10 years, provided other sexual risk behaviours do not substantially change, it is possible to substantially reduce the number of syphilis cases. By 2019, diagnoses of syphilis will have dropped by over 99% compared with the baseline scenario of no interventions (orange curve in Figure 3b). Under these circumstances, the model predicts that ~48% of HIV infections would be averted in 2019 (orange curve in Figure 3a).

Discussion

In Chapter 2, it was shown that an increase in STIs was required to match the modelled HIV epidemic to data. With no change in STIs, the HIV epidemic diminished. This is consistent with the results shown in this chapter, where we introduced some intervention strategies that were explored in Chapter 4. These strategies resulted in significant declines in syphilis incidence, which in turn led to a flattening in HIV incidence (Figure 3). This consistency between the chapters, despite being vastly different types of models, does show that STIs can play an important role in the HIV epidemic. However, it should be noted that both models do share similar sets of parameters.

Our results found that the implementation of the NGMSAP priority interventions for the mitigation of the syphilis epidemic in Australia may have an additional noticeable benefit in reducing HIV incidence. However, even if syphilis is almost eradicated with the most effective combination of interventions there is not likely to be the same reversal in HIV trends. Such effective control of syphilis could control HIV to relatively stable levels (as opposed to the significantly increasing trend observed in recent years) (Figure 3a). At best, our modelling estimated that the annual number of HIV infections over the next 10 years could be reduced by up to 48% if syphilis is effectively controlled even in the absence of any HIV-specific prevention programs.

These results are subject to the assumption that syphilis acts as a biological cofactor for increasing the risk of HIV transmission. Our model considered a range from no effect on transmission up to a maximum of increasing transmission by 5-fold. The size of this multiplicative factor could influence our results. There is strong statistical evidence that both ulcerative and non-ulcerative STIs can increase the probability of HIV transmission [11-17]. Several studies (in heterosexuals) estimate the relative risks of HIV infection due to infection with other STIs in the range 2-24, but largely clustering between 2 and 5. However, the fact that randomised controlled trials conducted to date have not shown a reduction in HIV incidence by treating STIs is somewhat perplexing [23-26]. It is possible that the statistical associations between acquiring HIV and the presence of STIs have not appropriately considered all confounding factors such that there is not a real increase in transmission risk. It is also possible that the biological cofactor of other STIs for increasing HIV risk is real and could not be adequately captured by the trials previously conducted due to various factors including re-infections and that numerous STIs (such as HSV-2, which has been targeted in the trials) are important factors during specific periodic episodes (such as the occasional times in which they lead to increased viral shedding). Further understanding of the association between HIV and other STIs is required.

Of course, HIV and other STIs such as syphilis are transmitted by similar exposure routes, namely, sexual exposure. In the Australian context the majority of HIV and syphilis infections occur among gay men due to unprotected anal intercourse. Interventions that target sexual behaviour (condom usage and rates of partner acquisition) are likely to result in reductions in both syphilis and HIV. In this study we did not explore such interventions. Risk reduction strategies like increased condom use or reduction in sexual

partners can have a greater impact on broader HIV/STI control. For example, such strategies will have a two-fold benefit of 1) directly reducing HIV and syphilis transmission, and 2) reducing HIV transmissions through the decline of syphilis [34]. In the fight to prevent and control the spread of all sexually transmissible infections it is logical to ensure that not only are behavioural, social and clinical campaigns conducted in a complementary manner but that epidemiological monitoring and evaluation also considers these infections together.

Acknowledgements

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Chapter 6: Hidden drug resistant HIV to emerge in the era of universal treatment access in Southeast Asia

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Author Contributions

AH led the analysis, conducted literature surveys, developed the model, produced all results, and wrote the manuscript. SJK, KR, JA, MGL, DAC, and PP provided expert advice for model parameters and manuscript editing. DPW supervised the project, assisted with model development, literature surveys and manuscript editing.

Abstract:

Background: Universal access to first-line antiretroviral therapy (ART) for HIV infection is becoming more of a reality in most low and middle income countries in Asia. However, second-line therapies are relatively scarce.

Methods and Findings: We developed a mathematical model of an HIV epidemic in a Southeast Asian setting and used it to forecast the impact of treatment plans, without second-line options, on the potential degree of acquisition and transmission of drug resistant HIV strains. We show that after 10 years of universal treatment access, up to 20% of treatment-naïve individuals with HIV may have drug-resistant strains but it depends on the relative fitness of viral strains.

Conclusions: If viral load testing of people on ART is carried out on a yearly basis and virological failure leads to effective second-line therapy, then transmitted drug resistance could be reduced by 80%. Greater efforts are required for minimizing first-line failure, to detect virological failure earlier, and to procure access to second-line therapies.

Introduction

HIV/AIDS arose in Asia in the early-to-mid 1980s. By the 1990s HIV epidemics had established in numerous countries; among the worst affected were Thailand and Cambodia with HIV prevalence levels of 1-2%. Currently Thailand, Cambodia, and Myanmar have been experiencing declines in HIV prevalence [1-2], however, countries such as Vietnam, Indonesia, Pakistan and China have observed growth in their epidemics [3].

Effective antiretroviral therapy (ART) is currently being scaled up in most countries in the region. In principle, anyone who is treatment eligible, according to country-specific guidelines but generally similar to the WHO treatment guidelines for resource limited settings [4], can receive ART to slow disease progression [5]. But with greater treatment coverage there is concern about the development of drug resistance, especially in countries where second-line therapy is not widely available, such as Myanmar, and Nepal [6]. The transmission of drug-resistant strains can potentially lead to ineffective treatment for individuals [7] and reduce their treatment options.

Transmitted drug resistance is a problem around the world, including the Southeast Asia region. Documented rates of transmitted drug resistance include 4% in 2003-2004 in Japan [8] and increases in Taiwan from 6.6% in 1999-2003 to 12.7% in 2003-2006 [9] and Thailand from <1% in 2003 to 5.2% in 2006 [10]. The vast majority of patients (~80%) in Asia start treatment on AZT/d4T plus 3TC plus EFZ/NVP [11]. This regimen is likely to be the standard for the foreseeable future (perhaps with tenofovir replacing AZT/d4T). If mutations that confer resistance to this standard regimen become widespread, ART rollout strategies could be compromised in a way that is not seen in developed countries with more treatment options.

The primary means to detect transmitted drug resistance is to perform blood tests on newly infected treatment-naïve individuals. Resistance strains can be divided up into two broad categories, namely, majority-resistant and minority-resistant variants. Majority resistant strains are detected through conventional nucleotide sequencing methods after polymerase chain reaction (PCR) amplification, however, these methods are not sensitive enough to detect minority-resistant strains that comprise less than ~25% of the viral population [12]. These minority-resistant variants can be detected using advanced real time PCR assays [13-14]. There is potential for these minority strains to go undetected in the population, leading to under-estimates of transmitted resistance levels.

We sought to estimate the potential levels of acquired and transmitted (majority and minority) drug resistant strains of HIV that could emerge in a typical Southeast Asian population. We do this through the development of a biologically realistic mathematical transmission model. We use the situation in Thailand as a representation for a general Asian epidemic and thus calibrated the model to reflect the epidemic in Thailand. Thailand is a leading example of treatment scale-up with the introduction of ART through the National Access to Antiretroviral Program for People who have AIDS by the Ministry of Public Health Access to Care program [15-16] and extended to the government's National AIDS Program by the National Health Security Office in 2004 [17]. Our mathematical model is parameterized using specific clinical, demographic, biological, and behavioral data in and around Bangkok, Thailand, before second-line therapy became available. Although second-line therapy is rolling out in Thailand, it is not available for many HIV-infected people in other countries. Our model extends previous mathematical models of HIV drug resistance applied to other settings (e.g. [18-21]) and models that incorporate at-risk groups for the Southeast Asian setting [22].

Methods

Our model describes the unique nature of Asian HIV epidemics whereby epidemics typically emerge and are initially driven by injecting drug use and sex work. Waves of infection occurred in these population groups, followed by infection among clients of sex workers and their regular sexual partners which led to generalized epidemics. In recent years HIV epidemics have emerged among men who have sex with men. This epidemic pattern has been observed in numerous Southeast Asian countries [23-24] and is captured by our model (see Figure S1). To reflect disease progression, we assumed that all HIV-infected people progress from primary/acute HIV infection, to chronic/asymptomatic infection, to a treatment-eligible stage, and then may receive treatment (Fig. 1). Each disease stage is associated with a different viral load and hence a different level of infectiousness [25-26]. Disease progression rates are assumed to be different in the presence of a majority-resistant strain due to lower viral fitness, but we assume minority-resistant strains have the same fitness as wild-type virus. We assume that reduced viral fitness of majority-resistant strains diminishes their replicative capacity and thus their ability to be transmitted. A multiplying factor was used to model a decrease in viral fitness between 5% and 50% [19-20].The Appendix for Chapter 6 contains more details about the implementation of this viral fitness factor. Once on treatment, we assume that patients will continue using their ART regimen, even if treatment failure occurs, as limited second or third line treatment options are available in many settings.

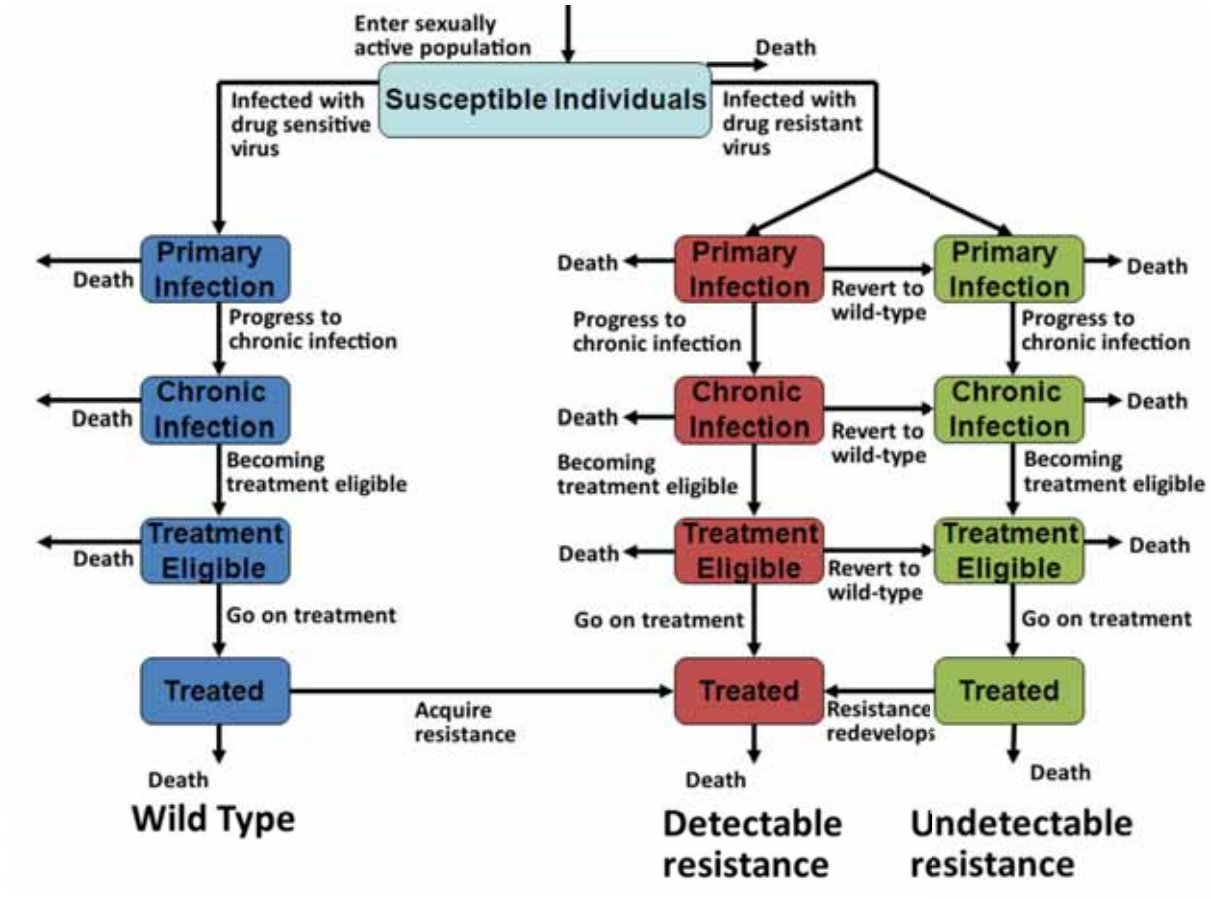

Figure 1: Schematic diagram of our mathematical model. The natural progression of HIV infection captured by our model, with disease progression illustrated vertically; the model is also divided into three arms: each arm governs a different type of virus (wild-type, majority-resistant variants, minority-resistant variants).

The level of adherence to ART is associated with clinical success [27-28] as systemic drug concentrations determine the degree of pressure to select for drug resistant strains [29-33]. Although there is variability in adherence between people, in our model we do not explicitly model adherence to ART but based on international clinical data [34-36] we assume that 3-5% of people on first-line ART select for drug resistant mutations each year and acquire drug-resistant strains. We track populations of people infected with either wild-type HIV or strains of drug-resistant HIV that are detectable or appear to have reverted to wild-type. Those people who have strains that appear to revert to wild-type have minority-resistant variants and it is assumed that majority-resistant variants will quickly emerge under pressure of ART. We use our model (and uncertainty and sensitivity analyses [37-38]) to estimate the future

trajectories of wild-type and drug-resistant HIV epidemics, determine the biological, clinical, and behavioral factors that are most important in giving rise to these evolving epidemics and how they might change with time in order to plan public health prevention and clinical practice strategies most appropriately. Some mathematical modeling has been carried out to forecast HIV epidemics in Southeast Asia [22], but no previous model has investigated the impact of drug resistance in this region.

The model was then used to assess the impact of regular viral load testing in a setting where second line treatment is available and commenced once virological failure is detected. We assumed that viral load tests could be performed at regular intervals on all those who are receiving treatment. We simulated different scenarios of frequency of viral load testing: once every 2 years, every year, twice yearly, or quarterly. We also assumed that a period of one week was required between the time of the test and receiving the test results and starting the patient on effective second-line treatment. Full technical detail of the model structure, assumptions and parameter values can be found in the supporting information.

Results

Emergence of Drug Resistance

After 10 years of universal ART without access to any second line therapies, moderately high levels of drug resistance can be expected in the HIV-infected population. People on ART will start to acquire drug resistant strains of virus. If second and subsequent lines of therapy are not widely available and failed regimens continue to be used then the emergent drug-resistant strains can be transmitted to susceptible individuals. Subsequently, the proportion of newly-infected treatment-naïve HIV cases that have drug-resistant strains could be substantial. Our model estimates that after 10 years of universal ART without monitoring of treatment failure and optimizing therapy ~24% of new infections could include drug-resistant mutations (Fig. 2a). Approximately one-third of cases in the primary/acute stage

of infection with drug-resistant mutations could have majority-resistant variants of HIV that are detectable and the remainder would have minority-resistant variants (Fig. 2a).

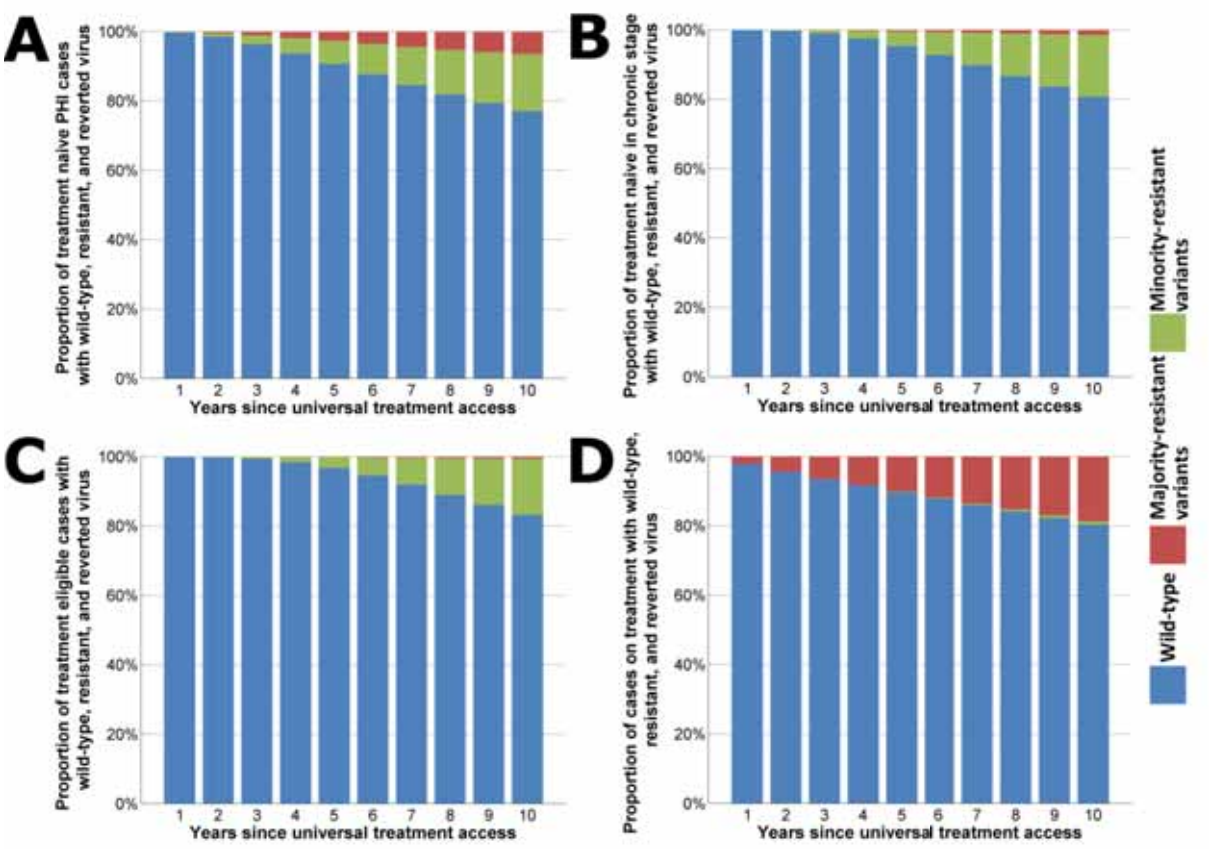

Figure 2: Stacked column charts indicating proportions of HIV viral types. Proportions of all HIV infections that are predominantly wild-type virus (blue), drug-resistant strains that are undetectable/minority-resistant variants (green), or drug-resistant strains that can be detected/majority-resistant variants (red) for HIV-infected cases in **(a)** primary infection, **(b)** chronic infection, **(c)** treatment-eligible stage, and **(d)** on treatment. Plots are over the time period since the introduction of universal access, and without any options for second-line therapy.

Most subjects infected with transmitted resistant virus appear to revert to wild type

In the absence of the pressure of ART, majority-resistant strains of HIV tend to revert to become minority-resistant variants that appear to be exclusively wild-type and not detected by standard sequencing methods. According to our model, after 10 years of universal access to ART without second-line options ~20% of treatment-naïve cases in asymptomatic stage would have some drug-resistant strains and ~17% of cases at treatment-eligible stage of infection would have some drug-resistant strains

(Fig. 2b, c). However, it is likely that the vast majority of these cases would have minority-resistant variants: only ~1% and <1% of the respective HIV cases would have detectable majority-resistant variants after 10 years (Fig. 2b,c). Thus, drug-resistant HIV could remain hidden and will only re-emerge when selective pressure of ART is applied. Of course, the rate of reversion could differ between different antiretroviral drug-based mutations. The re-emergence of drug-resistant strains could be quick once treatment is commenced by individuals. The vast majority (~95%) of individuals on ART who have drug-resistant strains would have majority-resistant variants (Fig. 2d). Based on our model we estimate that after 10 years of universal treatment access ~20% of all people that are on ART would have drug-resistant strains of HIV (Fig. 2d).

Factors determining the prevalence of drug resistance

Key factors giving rise to the prevalence of drug resistance differ between populations of treatment-naïve and treatment-experienced individuals. Multivariate sensitivity analyses revealed that the average time for resistant strains to appear to revert to wild-type virus and the relative fitness of drug-resistant strains were the most important parameters for determining the prevalence of majority-resistant variants in treatment-naïve cases (Fig. 3a). The relative fitness of viral strains with resistant mutations is a key determinant in the prevalence of transmitted drug resistance. The greater the fitness of these strains the larger the prevalence of 'hidden' resistance in the treatment-naïve population. Transmitted drug resistance increases with fitter drug-resistant strains and slower majority-to-minority variant reversion times. In contrast, the average time for drug-resistant strains to re-emerge upon pressure of ART (in individuals with minority-resistant variants; that is, to become majority-resistant variants upon applying pressure of ART) and the percentage of patients that acquire drug resistance per year (in individuals with wild-type) were found to be the most important factors in determining the proportion of treated individuals with majority-resistant variants (Fig. 3b-d). Interestingly, the relative importance

of these two factors changes over time. To illustrate this, in Figure 3b-d we present a series of contour plots of the prevalence of majority-resistant variants among the treated population after 1 year (Fig. 3b), 5 years (Fig. 3c), and 10 years (Fig. 3d) after commencing universal treatment access. We found that the number of people receiving treatment that have detectable drug resistance after one year of universal access to treatment is almost completely dependent on the percentage that acquire resistance per year, as indicated by the close to vertical lines in Figure 3b. After five years, the dependence has begun to shift such that the average time for resistance to reemerge begins to have an impact on the prevalence of drug-resistant HIV (Fig. 3c). After 10 years, the prevalence of detectable drug resistance is now more dependent on the average time for drug resistance to reemerge for transmitted drug-resistant strains than on the rate of acquired resistance (Fig. 3d). When projected even further, after 20 years the vast majority of drug-resistant cases are due to transmitted resistance (see Figure S2 in the supporting information). This suggests that the nature of the drug-resistant HIV epidemic could change considerably, initially being driven by acquired resistance and then evolve to be dominated by cases who have transmitted (but hidden) drug resistance.

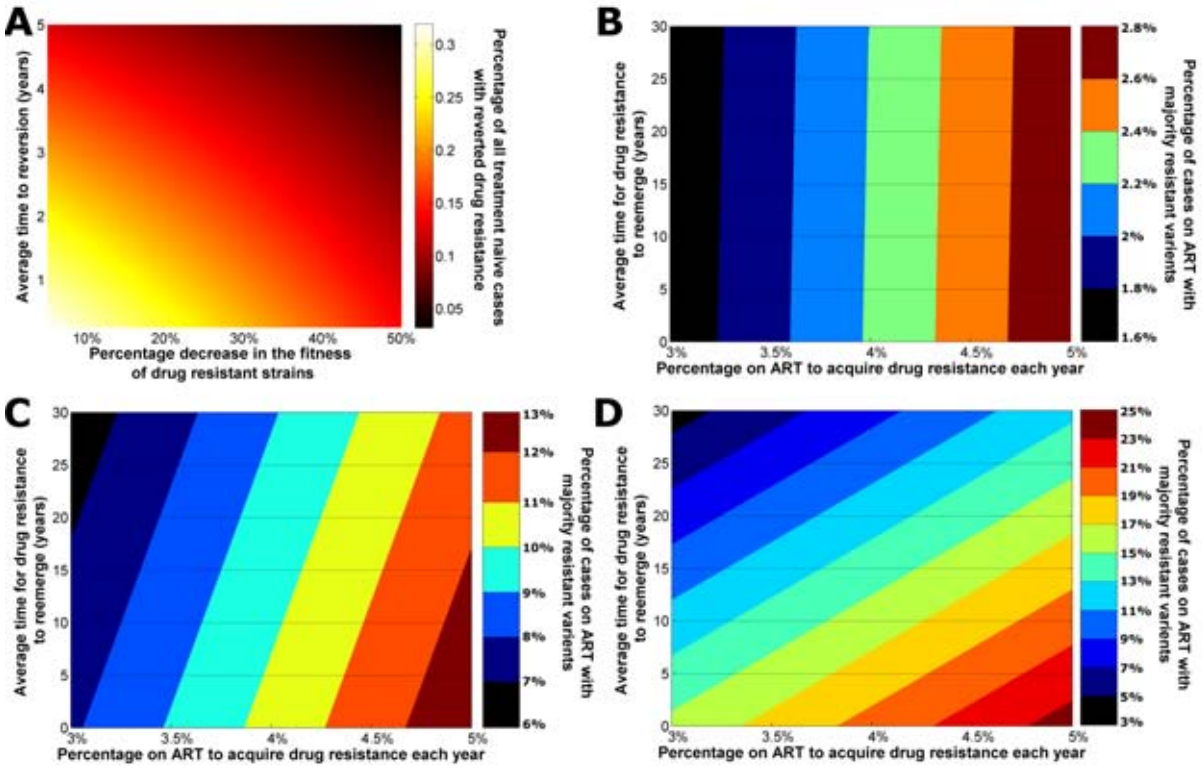

Figure 3: Series of response surfaces from sensitivity analyses. **(a)** A response surface plot of the proportion of treatment-naïve HIV-infected cases with minority-resistant variants versus viral fitness of drug-resistant strains and the average time for majority-resistant variants to revert to minority-resistant variants in the absence of ART. **(b)-(d)** Contour plots of the proportion of cases on ART that have majority-resistant variants (colored contours) versus the rate at which people infected with wild-type acquire drug resistant virus (x-axis) and the average time for majority-resistant variants to emerge for people infected with minority-resistant variants (y-axis) after **(b)** 1 year, **(c)** 5 years, and **(d)** 10 years of universal treatment access.

Reducing transmitted drug resistance through viral load testing

In many Southeast Asian countries, treatment failure is often realized due to clinical symptoms rather than the presence of mutations or virological or immunological failure. Frequent viral load testing is generally infeasible due to financial constraints. However, viral load testing for monitoring patients' responses to ART is available in some settings and it could be expected that it will become more common across the region in the future. Therefore, we used our model to estimate the expected proportion of newly acquired HIV infections to have drug-resistant strains versus the frequency of viral load testing of individuals on ART (assuming that treated cases that experience virological failure commence and are maintained on second and subsequent lines of therapy that successfully suppresses

viral load). In Figure 4 we present the expected levels of transmitted drug resistance versus the frequency of viral load testing. As the testing frequency is increased, a substantial reduction in the prevalence of transmitted drug resistance is observed. Providing a test every two years will reduce the prevalence by more than 50% compared to no viral load testing. With yearly testing, the proportion of all new infections with transmitted resistance drops below 5% (that is, an 80% relative reduction). According to our model, if viral load testing is further increased to every three months, transmitted drug resistance will make up only ~2.5% of all infections (reducing transmitted resistance by 90% compared to the situation where no testing is carried out).When compared to yearly testing, our model found that six and three monthly testing offered a relative reduction of 28% and 44% in transmitted drug resistance levels, respectively.

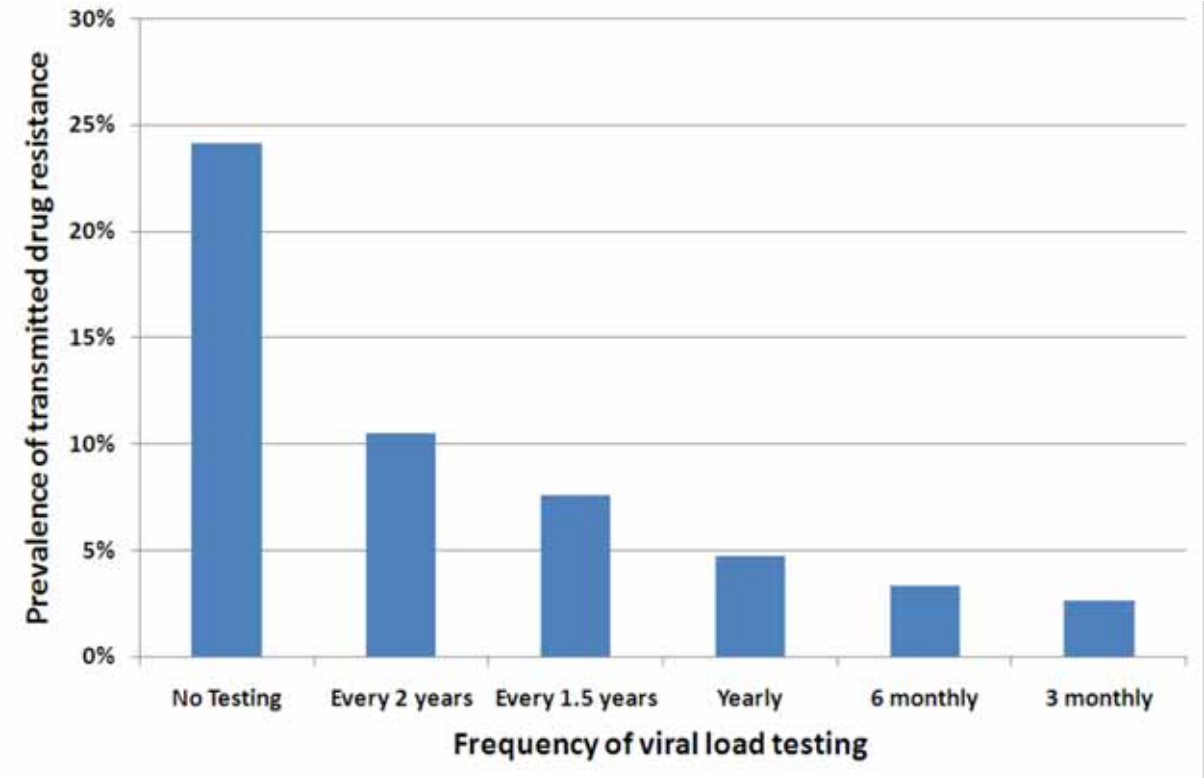

Figure 4: Prevalence of transmitted drug resistance after 10 years with various viral load testing frequencies. Testing scenarios include: no testing, once every two years, once every 1.5 years, yearly, twice yearly, and quarterly. Once tested, it is assumed that anyone failing treatment is taken off the failed regimen and given access to new treatment.

Discussion

Effective treatment with antiretroviral drugs reduces viral load which improves the health of treated individuals and also decreases infectiousness and the potential to transmit the virus to others [25-26, 39]. However, persons infected with drug-resistant HIV have reduced therapeutic options for their survival [40-41]. Antiretroviral resistance was detected against the first drug used against HIV, AZT, shortly after it was introduced [42]. Subsequently, resistance to every currently licensed antiretroviral drug has been observed. Drug-resistant strains of HIV that are acquired through use of ART can then be transmitted to susceptible people. The first report of observed transmission of drug-resistant HIV was in 1993 [43]. The transmission of drug resistance is becoming an increasing problem among many nations with long histories of ART. Data on rates of transmitted and acquired resistance in Southeast Asian countries is limited. In the few areas in which HIV transmitted resistance have been measured in Asia, already moderate levels (~4-5%) have been observed in some countries [44-46]. In other regions of the world, prevalence of drug resistant HIV among treatment-naïve persons has been estimated to be up to 25% [47]. It is important to implement strategies in Southeast Asian countries to avoid the high prevalence of transmitted drug resistance that has occurred elsewhere.

We demonstrated that if treatment options are limited for those who fail first-line therapy then the prevalence of acquired and transmitted drug resistant strains of HIV could be relatively large. The prevalence of transmitted drug resistance could be ~24% after ten years of universal treatment access if there is no viral load monitoring and access to second-line therapy. However, most (99%) of the drug resistance could remain 'hidden' as minority-resistant variants that are not detectable by standard sequencing methods. Majority-resistant variants are likely to emerge at significantly faster rates than expected once treatment is initiated [48]. While there is some uncertainty about whether minority-resistant strains have a substantial [13, 49] or limited [14] impact on the success of antiretroviral

therapy, the impact of majority-resistant strains on treatment is known to be significant. Majority-resistant strains may be more likely to survive in the presence of antiretroviral therapy than wild-type strains, however, they are likely to have reduced replicative capacity leading to lower viral loads in plasma and genital fluids and thus lower potential to be transmitted to other people. Our model demonstrated the importance of viral fitness whereby strains with higher fitness are more likely to lead to higher population levels of transmitted drug resistance (Figure 3a).

To reduce the prevalence of drug resistance among treatment-naïve individuals it is recommended that treated cases are regularly monitored and that second-line and subsequent lines of therapy are made available for those who have failed first-line regimens. We investigated the expected impact on transmitted drug resistance of different frequencies of viral load monitoring and access to second-line therapy when required. Even with a modest testing frequency of once every two years for patients on ART, the model demonstrates a large reduction in the amount of transmitted drug resistance would be achieved. Testing as frequently as quarterly could reduce the prevalence of transmitted drug resistance by ~90%. In Thailand, since 2008 second-line therapy with TDF/3TC/LPV/r has been widely available as well as once yearly viral load monitoring and genotyping (for those with viral load of more than 2000 copies per ml). However, there are limited treatment options in Thailand and patients with TDF resistance will have difficulties in finding effective second line treatment options. Wide availability of third line treatments for patients in this region will be unlikely in the near future. Therefore, it is highly important to minimise drug resistance. Based on our model, yearly testing can reduce transmitted drug resistance to below 5%. It is important for countries in Southeast Asia to procure access to second-line therapies and determine ways of implementing regular viral load monitoring. It will then be important to procure third-line and salvage therapies for patients in this region, however, this is unlikely to be feasible in the near future. Viral load testing is not widely available in many Asian countries and the

emergence of drug resistant HIV is not typically assessed during patient consultation [50-51]. Without viral load or genotypic monitoring, late detection of treatment failure may facilitate the acquisition of numerous additional resistance mutations [52]. Monitoring of patients' CD4 counts and viral load levels is being carried out in the Treat Asia HIV Observational Database (TAHOD) study [53]. TAHOD and other surveillance activities such as the Treat Asia Studies to Evaluate Resistance (TASER) study are important foundations for monitoring treatment success and detecting the development of resistance to antiretrovirals. In some countries governments pay for the first triple combination, but patients pay for other drugs if the first regimen fails. This barrier to accessing second-line therapy needs to be overcome else persistent use of sub-optimal or failed regimens will occur. Continued use of a failed regimen may select for increases in drug-resistant HIV strains that may then be transmitted to others.

Limited combinations of antiretrovirals are available for first-line treatment in most Southeast Asian countries. In Thailand, first-line therapy is based on NNRTIs and usually consists of a fixed dose combination of d4T/3TC/NVP, with a newer regimen of ZDV/3TC/NVP recently rolled out [54]. The prevalence of resistance in Thailand to NNRTI and NRTI based drug combinations can restrict second-line options in close to half of patients [55]. The World Health Organization has recently made recommendations against use of Triomune (d4T/3TC/NVP) in initiation of first line therapy [56-57]. New treatment guidelines for Thailand will also be released shortly [58]. These guidelines recommend AZT- and TDF- with EFV or NVP and 3TC as preferred first-line. There is a planned 2-year phase out of d4T for patients already receiving d4T. Similar clinical approaches may not be achievable in all resource-limited settings and the use of Triomune is likely to continue. Obtaining access to more first-line antiretroviral combinations will also assist with treatment options and could prolong the time until second-line therapies are required and reduce the risk of resistant strains being transmitted

While first-line therapy continues to scale-up around Southeast Asia it is important to plan for, and control, the emergence of drug-resistant HIV, particularly as most drug-resistant cases in the future could be 'hidden' as minority-resistant variants. Current surveillance programs, which are based around testing newly diagnosed subjects aged less than 25 years rather than genuinely acute infections, will not detect the scale of the problem. Hidden transmitted drug resistance has the potential to drive relatively high levels of drug resistance over the next 5-10 years unless treated cases are monitored regularly and initiate second-line therapies soon after the failure of first-line options. Data from TAHOD suggest that around half of patients beginning ART will require second-line therapies 3 years after beginning treatment [11]. Diagnosing newly acquired infections is important for understanding the true degree of transmitted drug resistance [10, 59] and should be prioritized as we approach the next phase of HIV epidemics in an era of universal treatment access.

While our model is specifically constructed and calibrated to reflect the unique epidemiology of HIV transmission in Southeast Asia, the conclusions drawn from our study can also be applied to other settings. Most countries in Southeast Asia still use d4T-based first-line therapy, which is similar to Sub-Saharan Africa. Access to antiretrovirals is similarly limited in both regions. Our results are generally applicable to non resource-rich settings in which suboptimal regimens are used and there are limited therapeutic options. Our conclusions concerning the dangers of continued use of failed treatment regimens and important value of regular viral load monitoring coupled with access to second-line therapies may assist countries in their scale-up of antiretroviral treatment.

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Conclusion

In Chapter 1, the Sampling and Sensitivity Analysis Tools (SaSAT) program was presented. Not only is the software presented, but also an overview of several powerful techniques for uncertainty and sensitivity analysis. This set of tools has been distributed to at least 200 research groups around the world, including academic and industry organisations. Notes of appreciation for developing this software have been received from numerous leading modelling research groups. The software has efficiently allowed modelling researchers to easily perform sensitivity and uncertainty analysis on their own mathematical models. This is important as the use of sensitivity analysis will lead to better analysis of model results, and can in turn lead to a better understanding of the relationship between input parameters and modelled outcomes. Regardless of the complexity of a model, uncertainty and sensitivity analysis should be considered an important part of the modelling process. For some types of models, such as individual based models, computational power may be an inhibiting factor to performing a full sensitivity analysis. In these types of models, the inherent stochasticity captures uncertainty in model outcomes. However, it is still difficult to assess how changes in input parameters affect model outcomes in such models. With SaSAT, we have provided all modellers with a powerful and easy-to-use set of tools that will further enhance the analysis of their research.

The work presented in Chapter 2 investigated the recent observed increases in HIV diagnoses in several States of Australia (New South Wales, Queensland, and Victoria) and aimed to posit an explanation for the differences in incidence in each of these States. A simple deterministic model was used in this investigation, and uncertainty and sensitivity analysis was also conducted. While it was noted that condom use had declined in recent years in each of the States, the model found that this alone was not

able to explain the observed trends. The results also suggested that the recent rises in HIV diagnoses can be explained by the observed increases in the notifications of other STIs. One of the limitations of the model was that it did not directly include other STIs specifically, and there was no modelled link between STI prevalence and condom use. This would form the foundation of future investigations. The model was also used to predict the impact of several scenarios. These results were also compiled into a large report [1] and distributed among various stakeholders including community groups and policy makers. It formed a key document that was used in 'Think Tank' exercises around Australia in 2007-2008 and is frequently cited in State-based strategies and plans for responding to HIV epidemics.

As one of the findings from Chapter 2, testing for HIV can have an important impact on the epidemic. This was examined more thoroughly in Chapter 3, where several scenarios of testing and treatment were evaluated. The model showed that increasing treatment for those diagnosed in primary HIV infection would have a modest epidemiological impact. However, it showed that large benefits can be gained from increasing HIV testing rates and coverage. The benefit of more regular testing helps inform individuals of their serostatus, and then they can alter their behaviour accordingly, for example serosorting (seeking partners of the same serostatus), or increased condom use. This helps to prevent secondary infections and can have a significant impact on the course of the HIV epidemic. Australia has one of the highest HIV testing rates in the world among populations most at risk of HIV infection. This chapter demonstrated how important this has been in the control of HIV. Interesting, since this chapter was published a World Health Organisation group published a mathematical model that suggested increases in HIV testing and treatment could have very large epidemiological benefits. This body of work has led to one of the current controversial but 'hot' topics in the international public health HIV field.

Another important finding from Chapter 2 was the potential impact of other STIs on the HIV epidemic. Syphilis was found to have been increasing in incidence in most States in Australia, with the largest increase in Victoria. Chapter 4 investigated the syphilis epidemic in Victoria, and evaluated a range of strategies to reduce annual incidence. This employed the use of a more complex individual-based model to help model specific intervention strategies, such as contact tracing, where the previous partners of a newly diagnosed patient are called in for testing. This type of model also enabled the investigation of targeting specific intervention strategies to different sections of the population. This model found that increases to the frequency of testing for syphilis are required to reduce the incidence of syphilis. More specifically, targeting men who have more than 10 partners per year, or who engage in group sex, can reverse the trend in *treponema pallidum* infection. The research conducted in this chapter was crucial in the development of Australia's National Gay Men's Syphilis Action Plan (NGMSAP) which has started programmatic implementation in 2010.

That work was extended to incorporate HIV into the model, and analysis of the link between HIV and syphilis was investigated in Chapter 5. This work investigated the potential impact that syphilis-focused interventions would likely have on HIV incidence, specifically the interventions outlined in the National Gay Men's Syphilis Action Plan (NGMSAP) [2]. This is based on the assumption that a person's infectivity or infectiousness is increased in the presence of syphilis. While designed to focus on reducing syphilis, the model showed that the priority interventions proposed by the NGMSAP will also likely provide some benefits in reducing HIV incidence. This is despite the fact that none of the interventions are intended to

have a direct HIV prevention role. However, none of the proposed interventions were able to substantially reverse increasing trends in HIV incidence.

Chapter 6 presented an investigation into the possibilities of drug resistant HIV viruses developing with the scale-up of antiretroviral therapy (ARVs) in resource-poor settings, and the transmission of these drug resistant strains. This study was applied to countries in the Southeast Asian region, such as Thailand, Cambodia, Myanmar, and Vietnam who have begun or are beginning to implement universal treatment access. However, the qualitative results are also more generally applicable to other low- and middle-income countries. The rollout of antiretroviral therapy will reverse the poor health of many people living with HIV and reduce HIV/AIDS related morbidities and mortality. However, if effective second-line drugs are not available and regular monitoring does not take place then people will continue to use sub-optimal drug regimens. It is then possible that drug resistant strains of HIV will emerge but they could be hidden by a dominant wild-type strain. However, both strains may be transmitted to others and the true prevalence of drug-resistant HIV may not be detected. The results of this modelling study show that high levels of transmitted drug resistant virus can be spread throughout the population; however, the majority of these resistant strains are likely to be hidden from usual PCR testing. To avoid the large amounts of transmitted resistance developing, the model evaluated the likely impact of performing regular viral load testing.

This thesis has investigated a number of areas using modelling. In Australia, the main findings of this investigation conclude that to control HIV and syphilis, testing should be encouraged and promoted. Rapid tests have been available for a number of years [3-4], and newer tests have made improvements

in accuracy [5-6] ; these can provide a supplement to regular checkups with a doctor. With increased testing, the modelling shows that significant reductions in HIV and syphilis are possible. In Southeast Asia, the main focus is on the rollout of antiretroviral therapy. We have showed that the antiretroviral rollout will reduce new infections of HIV, but may result in high levels of transmitted drug resistance. The model showed that the availability of second and third line therapy and the addition of yearly viral load testing can help reduce the possible emergence of epidemics of drug resistant HIV.

The field of mathematical epidemiology is continuing to grow at a fast pace. With access to high performance computing becoming cheaper, models are able to increase in complexity. These more complex models will be able include more biological and behavioural details. Individual-based models are ideally placed to investigate the influence of behaviour at the level of individuals or groups of individuals while considering the large heterogeneity in a population. With the increased importance of behavioural and biological data, another key area for potential growth is improved communications between modellers, social researchers, biologists, and policy makers. Strong collaboration between researchers and stakeholders will help ensure that results can be put into practice.

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Appendix for Chapter 2

Transmission model equations

The mathematical model for the dynamical transmission model is represented by ten ordinary differential equations. The mathematical description of our schematic model is described here. Individuals enter the susceptible MSM population (S) at a rate of π per year. These individuals enter into the 'pool' of male homosexual activity, choosing sexual partners from the population. On average they leave the population of those choosing new sexual partners after an average of $1/\mu$ years. Thus, out of each compartment we include an outflow at rate μ. The other means by which susceptible individuals can leave this compartment is by becoming HIV-infected. The rate of flow in the number of people who become infected - that is, the force of infection (λ) - is defined below. Then, the rate of change in the total number of susceptible men at time *t* is given by

$$\frac{dS}{dt} = \pi - \big(\mu + \lambda(t)\big)S(t).$$

Once an individual has become infected with HIV, he will initially enter the undiagnosed primary infection compartment (I_P). Thus, the number of MSM who leave the susceptible population per year, λS, becomes the source for the I_P compartment. There are three ways in which men can leave the undiagnosed primary HIV infection compartment: (i) become diagnosed as HIV positive at a health centre (at a rate γ_P), (ii) remain undiagnosed and progress in disease to chronic infection stage (at a rate ω_P), or (iii) leave the sexually active population (at rate μ). Accordingly, the rate of change in the total number of undiagnosed HIV-positive men in primary infection at time *t* is given by

$$\frac{dI_P}{dt} = \lambda(t)S(t) - I_P(t)\left(\mu + \gamma_P + \omega_P\right).$$

Similarly, the rate of change of the total number of undiagnosed HIV-positive men in chronic and AIDS stage infection at time *t* is given by

$$\frac{dI_C}{dt} = \omega_P I_P(t) - I_C(t)\left(\mu + \gamma_C + \omega_C + \delta_C\right)$$

and

$$\frac{dI_A}{dt} = \omega_C I_C(t) - I_A(t)\left(\mu + \gamma_A + \delta_A\right),$$

respectively, where the subscripts refer to the different disease stages and people in AIDS stage die of AIDS-related illnesses at a rate δ_A.

Rates of movement out of compartments of untreated HIV-infected and diagnosed men can be due to (i) disease progression (at rate ω), (ii) commencing antiretroviral therapy (at rate η), (iii) death (at rate δ), or (iv) leaving the sexually active population (at rate μ). Rates of movement into compartments of untreated HIV-infected and diagnosed men can be due to (i) newly diagnosed as HIV-infected (at rate γ) or (ii) previously treated men stopping antiretroviral therapy (at rate ν). Then, the rate of change in the total numbers of diagnosed but untreated HIV-positive men in primary, chronic, and AIDS stages of infection at time *t* are given by

$$\frac{dI_P^N}{dt} = \gamma_P I_P(t) - I_P^N(t)\left(\mu + \omega_P + \eta_P\right),$$

$$\frac{dI_C^N}{dt} = \gamma_C I_C(t) + \omega_P I_P^N(t) + \nu_C T_C(t) + \nu_P T_P(t) - I_C^N(t)\left(\mu + \omega_C + \eta_C + \delta_C\right),$$

and

$$\frac{dI_A^N}{dt} = \gamma_A I_A(t) + \nu_A T_A(t) + \omega_C I_C^N(t) - I_A^N(t)\left(\mu + \eta_A + \delta_A\right)$$

where the subscripts refer to the respective disease stages.

Individuals diagnosed with HIV have the option of initiating antiretroviral therapy (ART). Based on the proportion of HIV-infected MSM who are on ART or initiate ART each year we determine the rate of movement from untreated diagnosed compartments to treatment compartments (denoted by η). The rates of initiating therapy are different for each of the stages of disease. Individuals on therapy can cease therapy until a potentially later time (due to toxicities etc.), and we define the rate of ceasing treatment as ν (individuals treated in primary infection could initiate an early treatment schedule and upon ceasing ART would move into chronic infection (at rate ν_P)). Treatment will delay the progression of disease, but HIV-infected patients on ART can still progress in their disease (at rates τ) and if in AIDS-stage can still die of AIDS-related illnesses by at a slower rate to untreated people (due to ineffective treatment for various possible reasons including drug resistance). Then, the rate of change in the total numbers of treated HIV-positive men in primary, chronic, and AIDS stages of infection at time *t* are given by

$$\frac{dT_P}{dt} = \eta_P I_P^N(t) - T_P(t)\left(\mu + \nu_P + \tau_P\right)$$

$$\frac{dT_C}{dt} = \eta_C I_C^N(t) + \tau_P T_P(t) + (1 - p_A)\eta_A I_A^N(t) - T_C(t)\left(\mu + \nu_C + \tau_C + \delta_C^T\right),$$

and

$$\frac{dT_A}{dt} = p_A \eta_A I_A^N(t) + \tau_C T_C(t) - T_A(t)\left(\mu + \nu_A + \delta_T\right).$$

Table A.1 gives a full description of all of the parameters mentioned above, along with values that were used in the model.

Force of infection

The force of infection, λ, is the dynamic rate at which susceptible individuals become infected with HIV. This function contains many of the factors that contribute to HIV transmission. Typically λ is calculated as the average number of sexual partners each susceptible person has per year, multiplied by the probability that each new partner is HIV-positive, multiplied by the probability of HIV transmission occurring per partnership per year. Various factors contribute to each of these components.

Number of sexual partners

We distinguish between the numbers of casual sexual partners and the numbers of regular partners MSM are likely to have, on average, each year. We let c_{cas} represent the number of casual partners and c_{reg} represent the number of casual partners. We use behavioural data [1-3] on the proportion of men who have 0, 1, 2-10, 11-50, >50 partners to calculate a weighted average at each available time point, to obtain the following trends. We also make the assumption that 1 partner is regular and the remaining partners are casual partners.

Probability that new sexual partner is HIV-positive

If there was homogeneous non-differential mixing and no change in sexual behaviour between any categories of MSM in our model, then the probability that a new partner is HIV-positive is simply the ratio of the number of HIV-infected men to the total number of men in the population.

There is evidence of significant levels of serosorting in the MSM population in Australia. A proportion of uninfected men serosort in seeking of new partners $\left(p_{\text{serosort}}\right)$; but the new partner will be HIV-positive if undiagnosed with infection and thus unaware of his serostatus (that is, in the compartments I_P, I_C, or I_A). New partners for serosorting HIV-negative men will be chosen from the susceptible compartment or any of the undiagnosed HIV-positive compartments. However, men in AIDS stage disease are likely to have reduced numbers of partners due to their sickness. If healthy undiagnosed and susceptible men have c partners per year, then we model the number of partners per year that men with AIDS have as $\theta_{AIDS} \cdot c$, where θ_{AIDS} is a multiplying factor for the reduction in sexual activity due to the effect of illness. Thus, for men who serosort, the probability of a new partner being HIV-positive is

$$\frac{I_P + I_C + \theta_{AIDS} I_A}{S + I_P + I_C + \theta_{AIDS} I_A}.$$

The remaining proportion of men, who do not serosort, could choose partners from any compartment/serostatus. However, men who have been diagnosed with HIV may change their sexual behaviour; if undiagnosed and susceptible men have c partners per year then diagnosed men have $f \cdot c$ partners per year. Here, f refers to the multiplicative increase or decrease in sexual activity. We consider both possibilities since HIV-positive men may reduce risky sex to avoid infecting others or they may increase risky sex as they are no longer at risk of seroconverting. Thus, for men who do not serosort, the probability of a new partner being HIV-positive is

$$\frac{I_P + I_C + \theta_{AIDS} I_A + f\left(I_P^N + I_C^N + \theta_{AIDS} I_A^N + T_P + T_C + \theta_{AIDS} T_A\right)}{S + I_P + I_C + \theta_{AIDS} I_A + I_P^N + f\left(I_C^N + \theta_{AIDS} I_A^N + T_P + T_C + \theta_{AIDS} T_A\right)}.$$

The overall average probability of a new partner being HIV-positive is then given by

$$p_{\text{serosort}} \frac{I_P + I_C + \theta_{AIDS} I_A}{S + I_P + I_C + \theta_{AIDS} I_A} + \left(1 - p_{\text{serosort}}\right) \frac{I_P + I_C + \theta_{AIDS} I_A + f\left(I_P^N + I_C^N + \theta_{AIDS} I_A^N + T_P + T_C + \theta_{AIDS} T_A\right)}{S + I_P + I_C + \theta_{AIDS} I_A + f\left(I_P^N + I_C^N + \theta_{AIDS} I_A^N + T_P + T_C + \theta_{AIDS} T_A\right)}$$

Sexual partnerships are likely to be formed irrespective of HIV serology status. A proportion of men will disclose their HIV serostatus to their partner (which is generally reciprocated). We denote the proportion of men who disclose their serostatus to their partner as p_{disclose}. The decisions associated with disclosure and serosorting are shown in Figure A.1. If serostatus is disclosed and a partnership is serodiscordant then we assume that condoms are used in the majority of acts, but if the partnership is thought to be seroconcordant then we assume that condom use will be low [4]. The risk of transmission in the relationships thought to be seroconcordant is due to partners that are undiagnosed but HIV-infected. If serostatus is not disclosed, then we assume that there is average condom use (at the average level reported in survey studies) and that partners of any status/compartment can be chosen.

Serosorting for the formation of partnerships is rare; particularly among HIV-negative MSM (it is more common among HIV-positive MSM). Consequently, we simplify our model system and set $p_{\text{serosort}} = 0$, but still have the general structure in the model to allow for future studies involving non-zero serosorting. Negotiating condom use based on disclosure of serostatus is relatively common and an important aspect retained in our model.

Our model requires estimates of the proportion of partnerships in which serostatus is disclosed in order to negotiate condom usage, p_{disclose}. We use data on the percentage of men who reported UAI and always disclosed serostatus, and we included a +/- 5% uncertainty on the data in case this is a under representative sample.

Condom use

In regular relationships that are serodiscordant, we assume that average condom usage is high. Based on the Futures study [4], we assume condoms are used in 75-85% of anal intercourse acts between discordant MSM. However, in regular relationships that are seroconcordant we assume that average condom usage is relatively low; we assume condoms are used in 5-10% of acts [4]. In casual relationships, serological disclosure is not as common as in regular relationships, but if the MSM in a casual relationship determines the relationship is serodiscordant then we assume condoms are used in 95-100% of acts. We assume that condoms are used more frequently in casual partnerships than in regular partnerships; thus, if it is thought that a casual relationship is seroconcordant then $p_{\text{condom}}^{\text{reg}} < p_{\text{condom}}^{\text{cas}} < 10\%$.

Probability of HIV transmission per discordant partnership per year

We denote the probability of HIV-transmission from an infected male to an uninfected male during a single unprotected act of anal intercourse by β . However, if a condom is used as protection during intercourse then the probability of transmission is reduced. If ε is the efficacy of condoms then the transmission probability per protected act is $(1\text{-}\varepsilon)\beta$. We consider the average number of coital acts per partner per unit time (n) and the proportion of these acts in which condoms are used (p_{condom}) to calculate the probability of transmission of infection per partnership over time. If β_i is the probability of HIV-transmission during a single coital act in a discordant partnership with protection type i (condom or no protection), then the probability of remaining uninfected after the single act is $(1-\beta_i)$. Since each discordant coital act results in either transmission of infection or not (two possible outcomes), we have

a Bernoulli trial, assuming each act is independent and has equal transmission for each protection option.

Accordingly, the probability of remaining uninfected after all $n \cdot p_{\text{condom}}$ and $n\left(1-p_{\text{condom}}\right)$ discordant sex acts that involved protection or no protection is binomial: $\left(1-\left(1-\varepsilon\right)\beta\right)^{n \cdot p_{\text{condom}}}$ and $\left(1-\beta\right)^{n\left(1-p_{\text{condom}}\right)}$, respectively. Thus, together the probability of acquiring infection per discordant partner per year is given by

$$\hat{\beta} = 1-\left(1-\left(1-\varepsilon\right)\beta\right)^{n \cdot p_{\text{condom}}} \left(1-\beta\right)^{n\left(1-p_{\text{condom}}\right)}.$$

This expression is valid in the case of a standard transmission probability β. But the presence of other sexually transmitted infections, both ulcerative and non-ulcerative (but particularly ulcerative), can increase the transmission of HIV. Therefore, we consider the proportion of men who have other sexually transmitted infections $\left(p_{STI}\right)$ and the multiplicative increase in the transmission probability due to the presence of other infections $\left(b_{STI}\right)$. Accordingly, the probability of acquiring infection per discordant partner per year is adjusted to become

$$1-\left(1-\left(1-\varepsilon\right)\beta'\right)^{n \cdot p_{\text{condom}}} \left(1-\beta'\right)^{n\left(1-p_{\text{condom}}\right)},$$

where $\beta' = \left(1-p_{STI}\right)\beta + p_{STI} b_{STI} \beta$.

Combining factors for the resultant force of infection function

The force of infection is not as simple as multiplying each of the components together. This is because each compartment of HIV-infected person will have a different transmission probability. Average HIV viral load differs between disease stages and in individuals effectively treated with combination

antiretroviral therapy. To calculate the transmission probabilities for each of these compartments we employ the relation described by Quinn et al. [5], namely,

$$\hat{\beta} = 2.45^{\log_{10}\left(\frac{V}{W}\right)}\beta_C,$$

where V is the average viral load associated with a stage of infection, W is a baseline viral load taken at chronic infection, and β_C is the transmission probability for someone in chronic infection. That is, for each $\log_{10}$ increase in viral load there is a 2.45 times increase in the transmission probability.

Taken together, our expression for the force of infection is given by:

$$
\begin{aligned}
\lambda = c_{reg}\Bigg[& p^{\text{reg}}_{\text{serosort}} \frac{\hat{\beta}^{\text{reg}\,|\,\text{low condom}}_{P} I_P + \hat{\beta}^{\text{reg}\,|\,\text{low condom}}_{C} I_C + \hat{\beta}^{\text{reg}\,|\,\text{low condom}}_{A} \theta_{AIDS} I_A}{S + I_P + I_C + \theta_{AIDS} I_A} \\
& + \left(1 - p^{\text{reg}}_{\text{serosort}}\right) p^{\text{reg}}_{\text{disclose}} \frac{\hat{\beta}^{\text{reg}\,|\,\text{low condom}}_{P} I_P + \hat{\beta}^{\text{reg}\,|\,\text{low condom}}_{C} I_C + \hat{\beta}^{\text{reg}\,|\,\text{low condom}}_{A} \theta_{AIDS} I_A}{S + I_P + I_C + \theta_{AIDS} I_A + f\left(I^N_P + I^N_C + \theta_{AIDS} I^N_A + T_P + T_C + \theta_{AIDS} T_A\right)} \\
& + \left(1 - p^{\text{reg}}_{\text{serosort}}\right) p^{\text{reg}}_{\text{disclose}} \frac{f\left(\hat{\beta}^{\text{reg}\,|\,\text{high condom}}_{P} I^N_P + \hat{\beta}^{\text{reg}\,|\,\text{high condom}}_{C} I^N_C + \hat{\beta}^{\text{reg}\,|\,\text{high condom}}_{A} \theta_{AIDS} I^N_A + \hat{\beta}^{\text{reg}\,|\,\text{high condom}}_{T} \left(T_P + T_C + \theta_{AIDS} T_A\right)\right)}{S + I_P + I_C + \theta_{AIDS} I_A + f\left(I^N_P + I^N_C + \theta_{AIDS} I^N_A + T_P + T_C + \theta_{AIDS} T_A\right)} \\
& + \left(1 - p^{\text{reg}}_{\text{serosort}}\right)\left(1 - p^{\text{reg}}_{\text{disclose}}\right) \frac{\hat{\beta}^{\text{reg}\,|\,\text{ave condom}}_{P} I_P + \hat{\beta}^{\text{reg}\,|\,\text{ave condom}}_{C} I_C + \hat{\beta}^{\text{reg}\,|\,\text{ave condom}}_{A} \theta_{AIDS} I_A}{S + I_P + I_C + \theta_{AIDS} I_A + f\left(I^N_P + I^N_C + \theta_{AIDS} I^N_A + T_P + T_C + \theta_{AIDS} T_A\right)} \\
& + \left(1 - p^{\text{reg}}_{\text{serosort}}\right)\left(1 - p^{\text{reg}}_{\text{disclose}}\right) \frac{f\left(\hat{\beta}^{\text{reg}\,|\,\text{ave condom}}_{P} I^N_P + \hat{\beta}^{\text{reg}\,|\,\text{ave condom}}_{C} I^N_C + \hat{\beta}^{\text{reg}\,|\,\text{ave condom}}_{A} \theta_{AIDS} I^N_A + \hat{\beta}^{\text{reg}\,|\,\text{ave condom}}_{T} \left(T_P + T_C + \theta_{AIDS} T_A\right)\right)}{S + I_P + I_C + \theta_{AIDS} I_A + f\left(I^N_P + I^N_C + \theta_{AIDS} I^N_A + T_P + T_C + \theta_{AIDS} T_A\right)} \Bigg] \\
+ c_{cas}\Bigg[& p^{\text{cas}}_{\text{serosort}} \frac{\hat{\beta}^{\text{cas}\,|\,\text{low condom}}_{P} I_P + \hat{\beta}^{\text{cas}\,|\,\text{low condom}}_{C} I_C + \hat{\beta}^{\text{cas}\,|\,\text{low condom}}_{A} \theta_{AIDS} I_A}{S + I_P + I_C + \theta_{AIDS} I_A} \\
& + \left(1 - p^{\text{cas}}_{\text{serosort}}\right) p^{\text{cas}}_{\text{disclose}} \frac{\hat{\beta}^{\text{cas}\,|\,\text{low condom}}_{P} I_P + \hat{\beta}^{\text{cas}\,|\,\text{low condom}}_{C} I_C + \hat{\beta}^{\text{cas}\,|\,\text{low condom}}_{A} \theta_{AIDS} I_A}{S + I_P + I_C + \theta_{AIDS} I_A + f\left(I^N_P + I^N_C + \theta_{AIDS} I^N_A + T_P + T_C + \theta_{AIDS} T_A\right)} \\
& + \left(1 - p^{\text{cas}}_{\text{serosort}}\right) p^{\text{cas}}_{\text{disclose}} \frac{f\left(\hat{\beta}^{\text{cas}\,|\,\text{high condom}}_{P} I^N_P + \hat{\beta}^{\text{cas}\,|\,\text{high condom}}_{C} I^N_C + \hat{\beta}^{\text{cas}\,|\,\text{high condom}}_{A} \theta_{AIDS} I^N_A + \hat{\beta}^{\text{cas}\,|\,\text{high condom}}_{T} \left(T_P + T_C + \theta_{AIDS} T_A\right)\right)}{S + I_P + I_C + \theta_{AIDS} I_A + f\left(I^N_P + I^N_C + \theta_{AIDS} I^N_A + T_P + T_C + \theta_{AIDS} T_A\right)} \\
& + \left(1 - p^{\text{cas}}_{\text{serosort}}\right)\left(1 - p^{\text{cas}}_{\text{disclose}}\right) \frac{\hat{\beta}^{\text{cas}\,|\,\text{ave condom}}_{P} I_P + \hat{\beta}^{\text{cas}\,|\,\text{ave condom}}_{C} I_C + \hat{\beta}^{\text{cas}\,|\,\text{ave condom}}_{A} \theta_{AIDS} I_A}{S + I_P + I_C + \theta_{AIDS} I_A + f\left(I^N_P + I^N_C + \theta_{AIDS} I^N_A + T_P + T_C + \theta_{AIDS} T_A\right)} \\
& + \left(1 - p^{\text{cas}}_{\text{serosort}}\right)\left(1 - p^{\text{cas}}_{\text{disclose}}\right) \frac{f\left(\hat{\beta}^{\text{cas}\,|\,\text{ave condom}}_{P} I^N_P + \hat{\beta}^{\text{cas}\,|\,\text{ave condom}}_{C} I^N_C + \hat{\beta}^{\text{cas}\,|\,\text{ave condom}}_{A} \theta_{AIDS} I^N_A + \hat{\beta}^{\text{cas}\,|\,\text{ave condom}}_{T} \left(T_P + T_C + \theta_{AIDS} T_A\right)\right)}{S + I_P + I_C + \theta_{AIDS} I_A + f\left(I^N_P + I^N_C + \theta_{AIDS} I^N_A + T_P + T_C + \theta_{AIDS} T_A\right)} \Bigg]
\end{aligned}
$$

where the $\hat{\beta}$ parameters are each specified by the transmission probability per partnership per year as defined above and based on the various behavioural and biological parameters (including number of acts for each type of relationship, condom usage, and viral loads affecting the transmission probabilities).

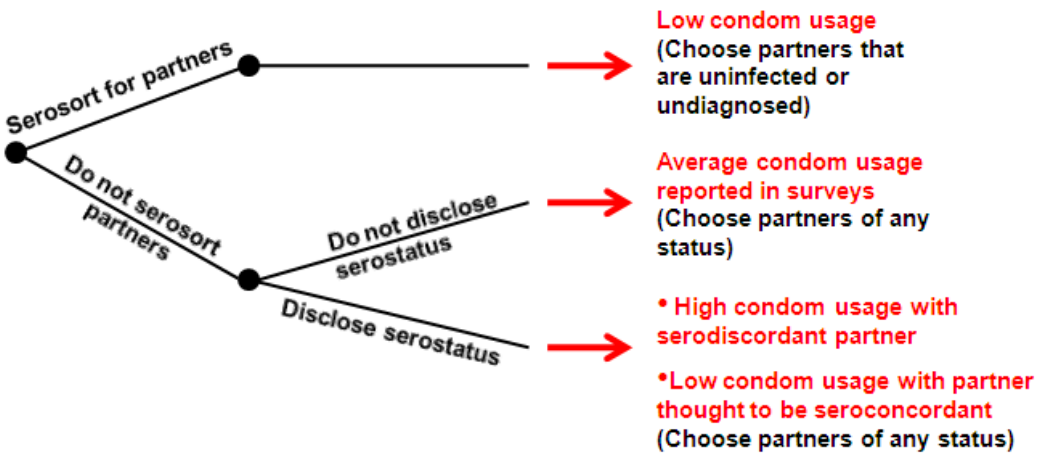

Figure A.1: Decision tree and assumed behaviour associated with serosorting and disclosing serostatus

Parameter	Description		Value	Ref
c	Average number of sexual partnerships per year (undiagnosed MSM)		* [1-3]	
θ_{AIDS}	Multiplying factor for the reduction in number of sexual partners for men in AIDS stage disease		0.1 – 0.4	
p_{anal}	Percentage of sexual partnerships in which penile-anal intercourse occurs		10-40%	[6]
f	Multiplying factor for the average change in number of sexual partners post diagnoses of HIV infection (this reflects a possible range from 50% decrease to 10% increase)		0.4 – 1.1	[6-14]
p_{disclose}	Proportion of partnerships in which serostatus is disclosed (in negotiating condom usage)	Regular	0.8-0.9	[1, 4, 15-16]
		Casual	*	
p_{condom}	Proportion of acts in which condoms are used		*[1, 4]	
ε	Efficacy of condom protection per act		0.85-0.9	[17-21]
W	Baseline viral load during chronic infection		$10^4 – 10^5$ copies/ml	[22-26]
V_{PI}	Average viral load at primary infection stage		$10^{6.5} – 10^8$ copies/ml	[22-24, 26-27]
V_A	Average viral load at AIDS		$10^{5.5} – 10^{6.5}$ copies/ml	[24, 28-29]
V_T	Average viral load in effectively treated individual		10 – 100 copies/ml	[30-32]
p_s	Proportion of individuals on antiretroviral therapy in which viral load is suppressed		* [1, 7, 33-34]	
β_C, β_C^N	Probability of HIV transmission per act from an individual in chronic stage of infection		0.0015–0.0025	[35-40]
β_P, β_P^N, β_A, β_A^N	Probability of HIV transmission per act from an individual in primary or AIDS stage of infection		[5]	

β_P^T, β_C^T, β_A^T	Probability of HIV transmission per act from a treated individual	[5, 41]	
p_{STI}	Proportion of HIV-negative MSM who have other STIs	0.05-0.15	[42-43]
b_{STI}	The multiplicative increase in transmission probability due to the presence of other STIs	2 – 5	[44-50]
n_{reg}	Average number of anal intercourse acts per regular partner per week	1.6 – 2.4	[51]
n_{cas}	Average number of anal intercourse acts per casual partner (over duration of casual relationship)	1 – 2	[16, 51]
p_{test}	Proportion of MSM who test for HIV infection each year	* [1]	
$1/\gamma_A$	Average time from the beginning of AIDS before individual is likely to be diagnosed with infection	2–4 months	
$1/\omega_P$	Average time for untreated individuals to progress from primary infection to chronic infection	3–9 months	[23, 52-53]
$1/\omega_C$	Average time for individuals to progress from chronic infection to AIDS	8 – 12 years	[22, 28, 54-57]
p_P	Proportion of people diagnosed in primary infection who will commence treatment	a	
$1/\nu_P$	Average time to cease treatment for individuals with primary infection	6 – 12 months	a
p_P^C	Proportion of people who started ART in primary infection and continue ART after finishing dosing schedule	65-75%	a
p_C	Proportion of people in chronic infection who will commence treatment	65-75%	[1, 4, 58]
p_A	Proportion of people with AIDS who commence treatment that experience treatment failure	0 – 0.1	
$1/\eta_A$	Average time before individuals with AIDS commence therapy	1–3 months	
$1/\eta_C$	Average time before diagnosed individuals in chronic	2–10 years	

	infection commence therapy			
$1/\nu_C$	Average time to cease treatment for individuals with chronic infection		6 – 12 years	[1]
$1/\nu_A$	Average time to cease treatment for individuals with AIDS		8 – 14 years	[1]
$1/\mu$	Average time for individuals to 'retire' out of sexually active population (no longer obtaining new partners)		30-35 years	[56]
δ_C	Proportion of untreated MSM in chronic infection who die each year		1-2%	[59-63]
δ_C^T	Proportion of treated MSM in chronic infection who die each year		1-2%	[59-63]
$1/\delta_A$	Average time until death from the onset of AIDS for untreated individuals		0.5-1.5 years	[63-66]
$1/\delta_T$	Average time until AIDS-related death for individuals in AIDS stage but on ART (with treatment failure)		0.5-5 years	[56, 63, 65, 67-73]
$1/\tau_C$	Average time of disease progression for treated individual with chronic infection to progress to AIDS		$1/\omega_C < 1/\tau_C < 20$	
π	Number of new susceptible individuals entering the MSM population per year (this is approximately 3-3.5% of men)	Nationally	2000-2500	b
		NSW	35-40%	
		VIC	22-27%	
		QLD	17-22%	

a : We evaluated available data from primary infection cohorts of the percentage of HIV-infected MSM who commenced ART within one year of HIV diagnosis, including patients recruited to the Acute Infection and Early Disease Research Program (CORE 01) protocol established by the National Institutes of Health, and the Primary HIV and Early Disease Research: Australian Cohort (PHAEDRA) established by the National Centre in HIV Epidemiology and Clinical Research. This data has large uncertainty (summarised in [58]), is limited in time and only includes NSW and VIC. Sample sizes are also not sufficient (as low as 4 in some years for VIC and 6 for NSW). Consequently, this has been used as a rough guide but we make assumptions in the trends in early treatment based on personal communication with clinicians (e.g. Prof. Tony Kelleher (NCHECR and Centre for Immunology at St Vincent's Hospital, t.kelleher@cfi.unsw.edu.au)). We estimate the basic anecdotal trends observed over the last few years

by the figure below. However, since there are no firm data for the trends, we include greater uncertainty bounds on this time-dependent parameter than on the others (we use a multiplicative uncertainty range on these trends of 0.6-1.2). We then assume that the initial dosing schedule for these patients who commence treatment in primary infection is 6-12 months, after which time 60-70% of these patients will continue ART and the remaining patients will discontinue therapy until a later time. b : This leads to approximately 150,000-175,000 MSM nationally. The proportion of new MSM in NSW, VIC, QLD each year as a subset of the total National number are indicated.
*: For each of these time-dependent parameters we include an uncertainty range of ±5%

Table A.1: Definitions, ranges, and references for input parameters used in our mathematical model

References:

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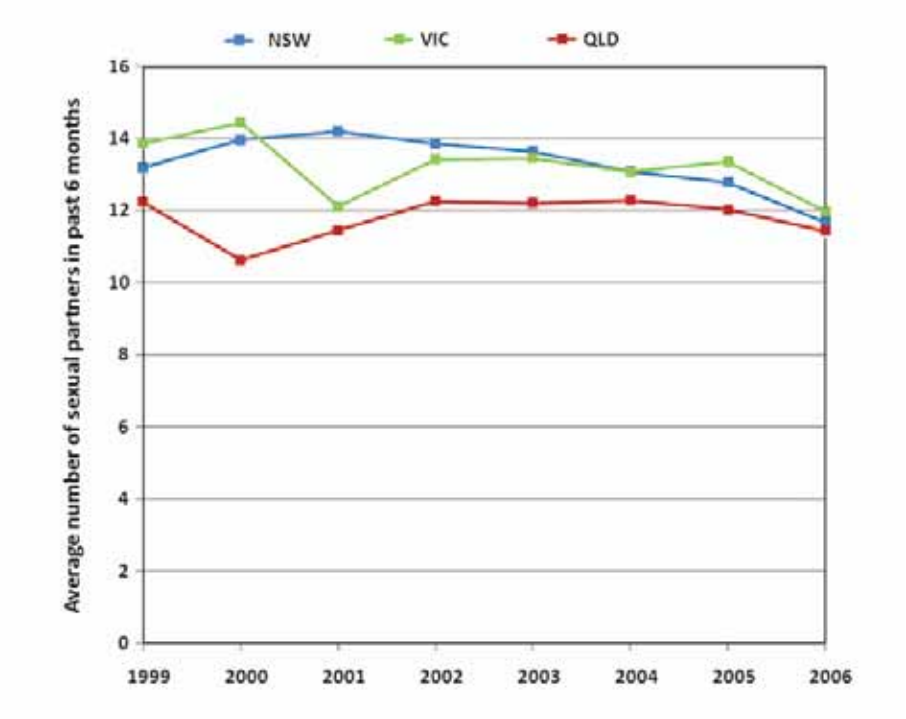
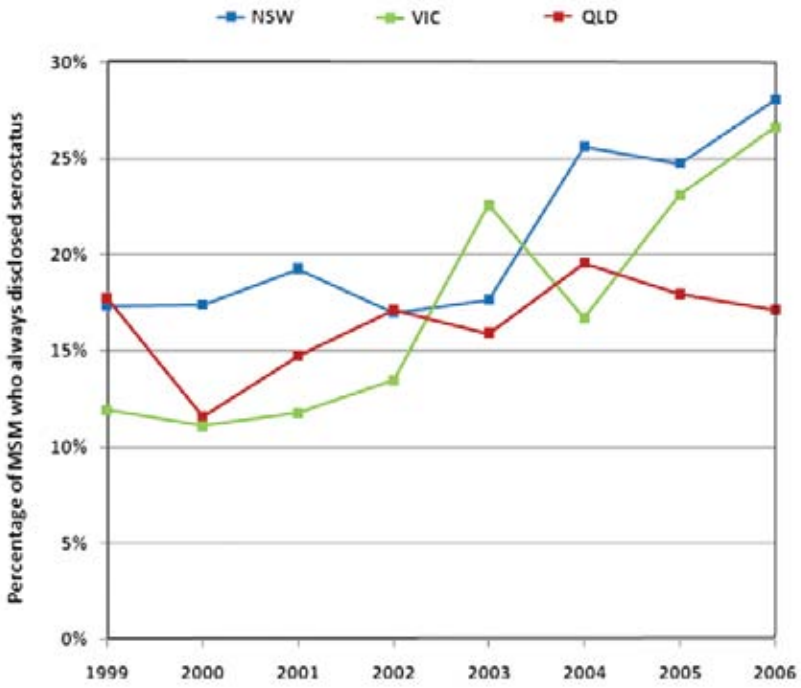
Appendix for Chapter 3

a: We use behavioural data on the proportion of men that have 0, 1, 2-10, 11-50, >50 partners to calculate a weighted average at each available time point, to obtain the following trends:

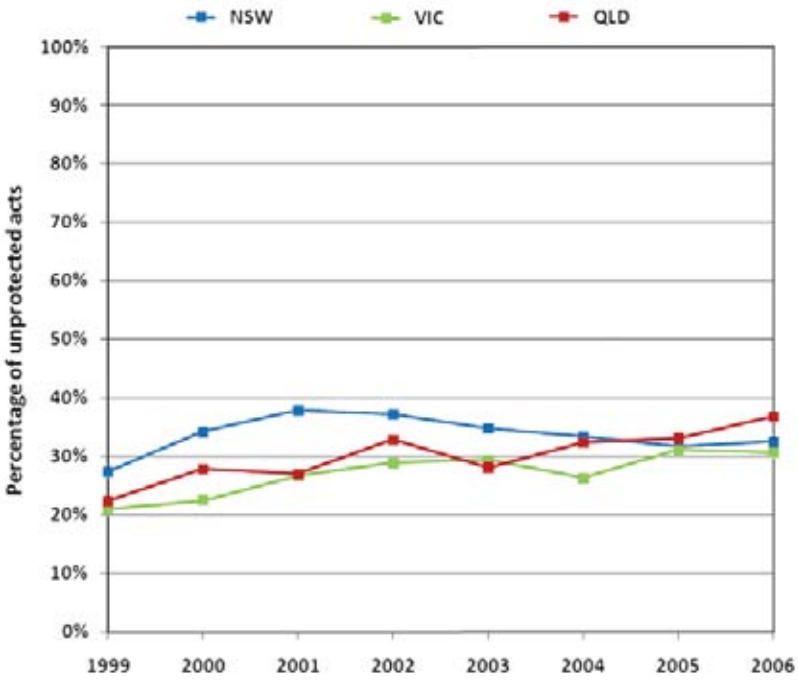


We assume that 1 partner is regular and the remaining partners are casual partners.

b: Serosorting and disclosure of serostatus are discussed in the Appendix methods section. Our model requires estimates of the proportion of partnerships in which serostatus is disclosed in order to negotiate condom usage. We use data on the percentage of men who reported UAIC and always disclosed serostatus:

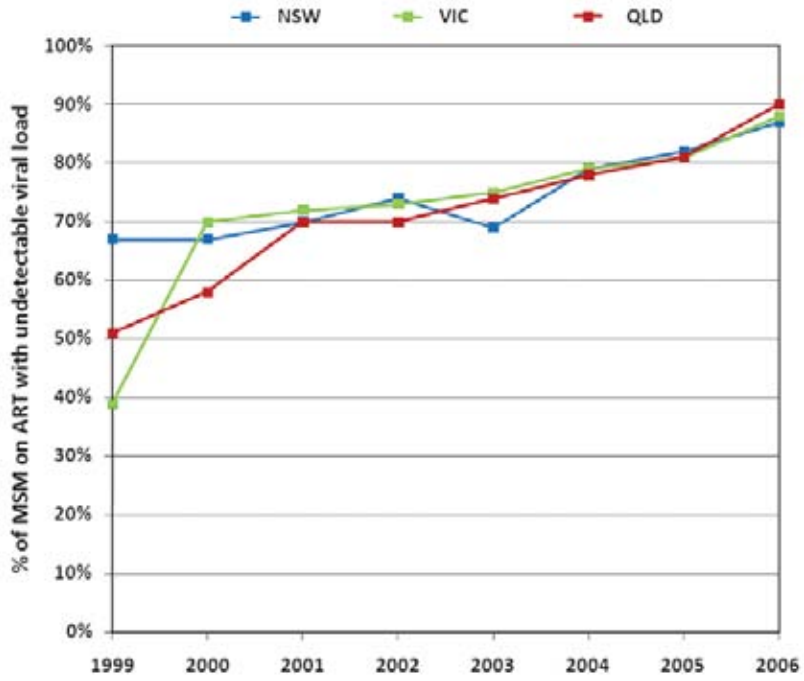


c: Condom usage will vary between types of relationships and the disclosure of HIV serostatus. For relationships in which serostatus is not ascertained we use the data from the State gay periodic surveys [1] to obtain the following trends over time:



In regular relationships that are serodiscordant we assume that average condom usage is high. Based on the Futures study [2] we assume condoms are used in 75-85% of anal intercourse acts between discordant MSM. However, in regular relationships that are seroconcordant we assume that average condom usage is relatively low; we assume condoms are used in 5-10% of acts [2]. In casual relationships, serological disclosure is not as common as in regular relationships, but if the MSM in a casual relationship determine the relationship is serodiscordant then we assume condoms are used in 95-100% of acts. We assume that condoms are used more frequently in casual partnerships than in regular partnerships.

d : There is evidence to suggest that the percentage of treated patients with undetectable virus has increased over time [3]. This could be due to numerous factors such as greater adherence or different drug regimes. We use data from the AHOD database [3]:



e: We use the established relationship from [4-6] to determine the change in transmission probability as viral load changes, namely, $2.45^{\log_{10}\left(\frac{V}{V_{CI}}\right)}\beta_C$ if the viral load (V) is greater than the baseline during chronic infection (V_{CI}), where β_C is the transmission probability associated with the baseline viral load, and $\beta_C \Big/ 2.45^{\log_{10}\left(\frac{V_{CI}}{V}\right)}$ if $V < V_{CI}$. Although this relationship was originally determined for heterosexual penile-vaginal intercourse, we use a greater baseline transmission probability for homosexual penile-anal intercourse, β_C, and assume that the same multiplicative increase in transmission holds with changes in viral load. This relationship was established based on empirical data in a cohort of African heterosexual couples. In the absence of information to the contrary, we assume that this relationship holds for penile-anal transmission and that it applies across the range of viral loads, including those that are below detectable levels, regardless of whether or not a person is under

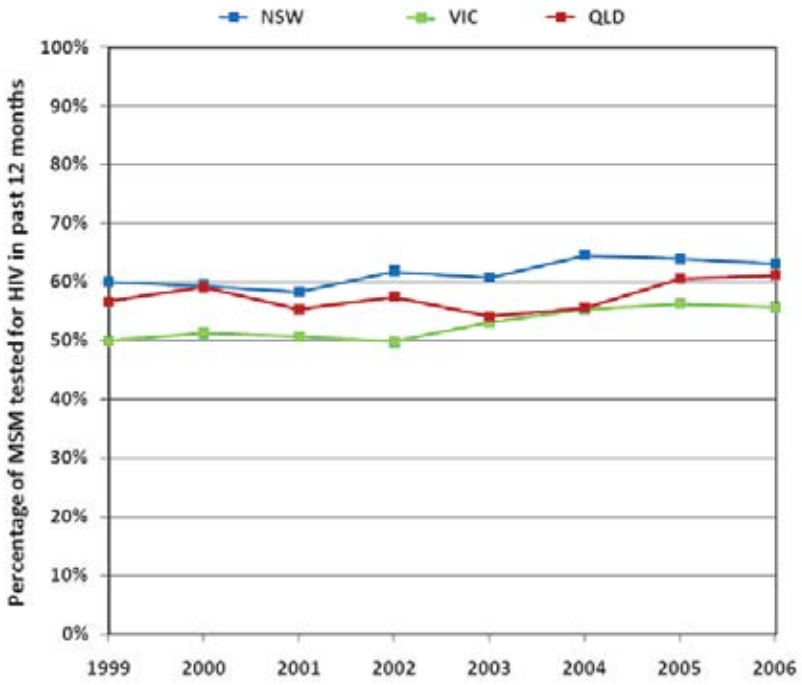
treatment with antiretroviral therapy. However, the baseline transmission probability differs between the different modes of transmission [5].

f : In order to model the impact of STIs on HIV transmission it is necessary to estimate the proportion of MSM with other STIs as well as trends over time and by State. This is problematic for a number of reasons. First, while there are indications that the prevalence of some STIs, notably syphilis, is increasing in MSM in Australia, most data is reported only as notifications, not as the proportion of tests that are positive. Furthermore, the National Centre for HIV Social Research reports significant increases in testing (10-20%) in the last few years. Second, much of the published data on STIs in MSM in Australia is from the HIM (Health In Men) study and the incidence of STIs has decreased in this Sydney-based HIV-negative cohort over the last few years. Third, there is little data on trends in STI incidence and prevalence in MSM for the other states. Fourth, the most prevalent STI associated with HIV transmission is HSV-2 with prevalence in the HIM cohort estimated at ~23% masking any trends that might be occurring with other STIs. Of course, HSV-2 is latent for significant proportions of the time in infected people and virus is shed periodically; thus, the effective prevalence of HSV-2 for which it increases HIV transmissibility is reduced. Given the uncertainty we assume that the average proportion of MSM with STIs (ulcerative or non-ulcerative, that contribute to increasing HIV transmissibility) is in the range 5 - 15% initially (that is, at 1999). To investigate National HIV trends we do not distinguish STI levels between States. Although there is currently no published data, the prevailing perception amongst epidemiologists and sexual health clinicians is that there has been a rise in the number of STIs in recent years. However, because the magnitude of increase is different between different STIs we do not use STI data. Our initial analyses are based on an initial uncertainty range of 5-15% but constant over time. We

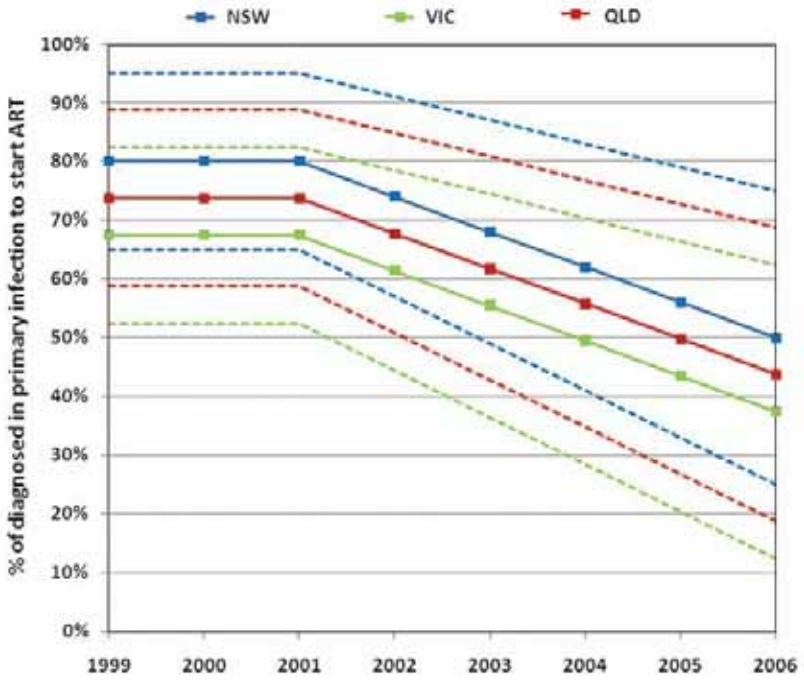
then investigate numerous rates of increase in the prevalence of other STIs to determine the influence of increasing STIs on the HIV epidemic.

g : There is strong evidence that both ulcerative and non-ulcerative STIs can increase the probability of HIV transmission by augmenting HIV infectiousness and susceptibility. Reciprocally, HIV infection can enhance the transmission of other STIs. This is a complex synergy and the results of several prospective studies estimate the relative risks of HIV infection due to infection with other STIS in the range 2 to 24, but largely clustering between 2 and 5. We therefore assume that the multiplicative increase in transmission probability due to concurrent infection with another STI is in the range 2 - 5.

h : Data from the Gay periodic surveys over time for the percentage of men who have sex with men who tested for HIV in the last 12 months is used as shown in the graph below:



i : We evaluated available data from primary infection cohorts of the percentage of HIV-infected MSM who commenced ART within one year of HIV diagnosis, including patients recruited to the Acute Infection and Early Disease Research Program (CORE 01) protocol established by the National Institute of Health, and the Primary HIV and Early Disease Research: Australian Cohort (PHAEDRA) established by the National Centre in HIV Epidemiology and Clinical Research. This data has large uncertainty (summarised in [7]), is limited in time and only includes NSW and VIC. Sample sizes are also not sufficient (as low as 4 in some years for VIC and 6 for NSW). Consequently, this has been used as a rough guide but we make assumptions in the trends in early treatment based on personal communication with clinicians (e.g. Prof. Tony Kelleher). We estimate the basic anecdotal trends observed over the last few years by the figure below. But since there is not firm data for the trends we include greater uncertainty bounds on this time-dependent parameter than on the others (we use a multiplicative uncertainty range on these trends of 0.6-1.2).



We then assume that the initial dosing schedule for these patients who commence treatment in primary infection is 6-12 months, after which time 60-70% of these patients will continue ART and the remaining patients will discontinue therapy until a later time.

j : We assume that individuals who have not been diagnosed with HIV infection, but are infected, will have the same lifetime duration (30-35 years) of sexual activity (in terms of choosing new partners) as those that are uninfected or at different disease stages. However, the number of partners chosen will differ between some disease stages.

k : This leads to approximately 150,000-175,000 MSM nationally. The proportion of new MSM in NSW/ACT, VIC, QLD each year as a subset of the total National number are indicated.

References

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Appendix for Chapter 4

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 $(1-\grave{o})\beta$.

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 $\left(1 - p_t^n\right)$ 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

$$p_t = 1-\left(1-p_t^s\right)\left(1-p_t^h\right)$$

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 $p_c = 0.8$, $f_t = 1$, $d_t = 31$, and $g_t = 151$. 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_t while g_t 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_t 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_t days, if they are tested within the following d_t days they are again reminded to return after g_t days. This pattern continues until they miss being tested during the d_t 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 $p_t = 1/14$. 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 notifications 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. 1b in main text). 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.

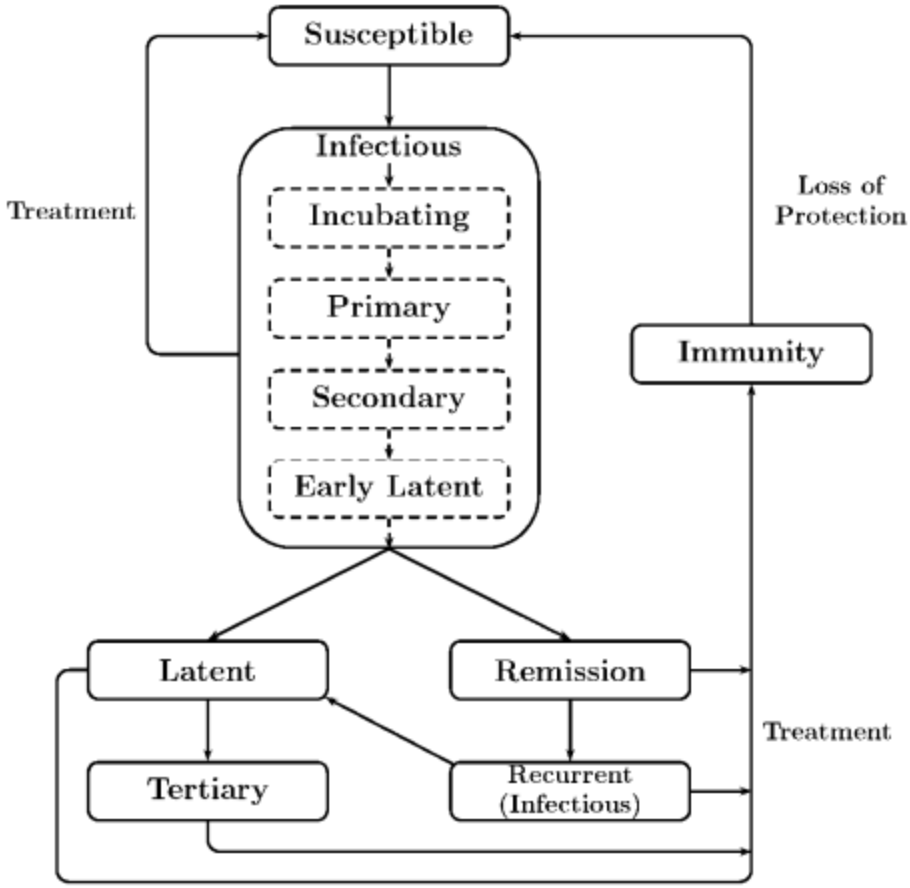

Figure A1a: Schematic diagram of the stages and disease progression of syphilis included in the model. Infectious syphilis includes the incubating, primary, secondary, early latent and recurrent stages.

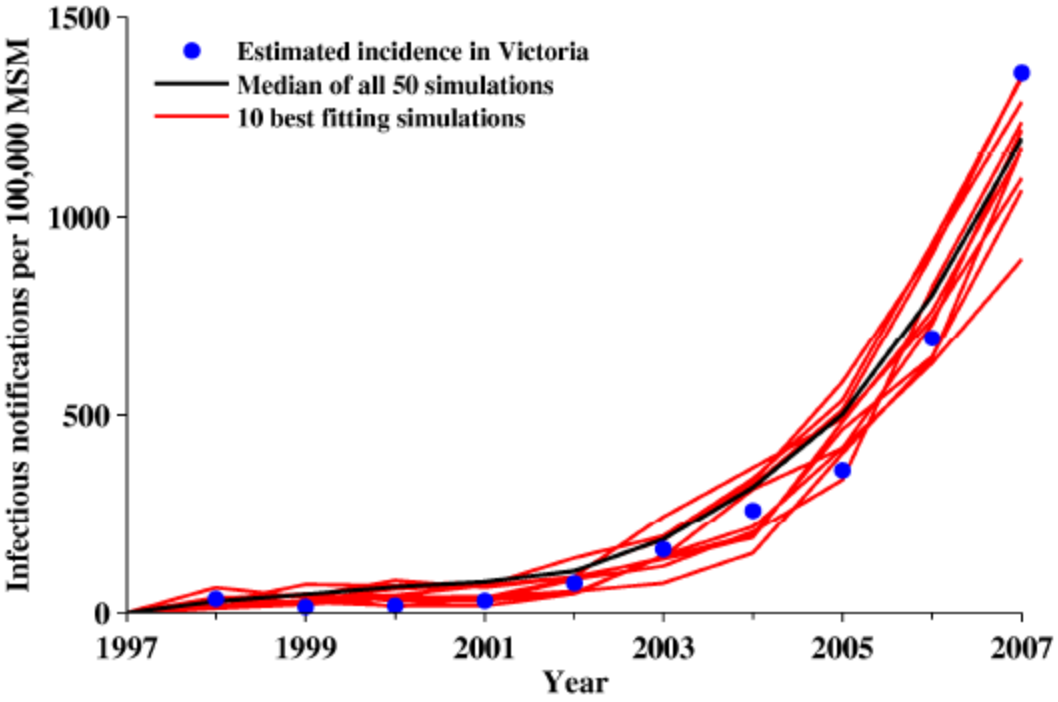

Figure A1b: The number of infectious syphilis diagnoses in the state of Victoria, Australia (blue discs, data) compared with 10 model-based simulations (red) and median (of 50) simulations (black) over the 10 year period from 1998 to 2007.

References

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3. Fogarty, A., et al., *The Health in Men and Positive Health cohorts: A comparison of trends in the health and sexual behaviour of HIV-negative and HIV-positive gay men, 2002–2005, National Centre in HIV Social Research Annual Report of Trends in Behaviour*. 2006, University of New South Wales: Sydney.
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Appendix for Chapter 6

Introduction:

The results presented in the main text are based on a mathematical model. Here we present a full description of the model and a listing of all parameters and assumptions used.

Model Equations

HIV disease and transmission dynamics are described with a system of 91 ordinary differential equations, one for each of the 13 structural compartments of our model (Fig. 1) multiplied by the seven population subgroups (Fig. S1). These equations are as follows, where subscripts *i*, and *j* are used to denote the population subgroups, Table S1 outlines all parameter values used in the model:

$$\frac{dS_i}{dt} = \pi_i - S_i\left[\mu + c_i^j\left(\Lambda_i^S + \Lambda_i^R\right)\right] \quad (1)$$

$$\frac{dPI_i^S}{dt} = S_i c_i^j \Lambda_i^S - PI_i^j\left(\gamma_S^{PI} + \mu + \delta_S^{PI}\right) \quad (2)$$

$$\frac{dPI_i^{DRD}}{dt} = S_i \psi c_i^j \Lambda_i^R - PI_i^{DRD}\left(\gamma_R^{PI} + \mu + \delta_R^{PI} + \phi\right) \quad (3)$$

$$\frac{dPI_i^{DRU}}{dt} = S_i\left(1-\psi\right)c_i{}^j\Lambda_i^R + \phi PI_i^{DRD} - PI_i^{DRU}\left(\gamma_S^{PI} + \mu + \delta_S^{PI}\right) \quad (4)$$

$$\frac{dCI_i^S}{dt} = \gamma_S^{PI} PI_i^S - CI_i^S\left(\gamma_S^{CI} + \mu + \delta_S^{CI}\right) \quad (5)$$

$$\frac{dCI_i^{DRD}}{dt} = \gamma_R^{PI} PI_i^{DRD} - CI_i^{DRD}\left(\gamma_R^{CI} + \mu + \delta_R^{CI} + \phi\right) \quad (6)$$

$$\frac{dCI_i^{DRU}}{dt} = \gamma_S^{PI} PI_i^{DRU} + \phi CI_i^{DRD} - CI\left(\gamma_S^{CI} + \mu + \delta_S^{CI}\right) \quad (7)$$

$$\frac{dTE_i^S}{dt} = \gamma_S^{CI} CI_i^S - TE_i^S \left(\tau_i + \mu + \delta_S^{TE}\right) \quad (8)$$

$$\frac{dTE_i^{DRD}}{dt} = \gamma_R^{CI} CI_i^{DRD} - TE_i^{DRD} \left(\tau_i + \mu + \delta_R^{TE} + \phi\right) \quad (9)$$

$$\frac{dTE_i^{DRU}}{dt} = \gamma_S^{CI} CI_i^{DRU} + \phi TE_i^{DRD} - TE_i^{DRU} \left(\tau_i + \mu + \delta_S^{TE}\right) \quad (10)$$

$$\frac{dT_i^S}{dt} = \tau_i TE_i^S - T_i^S \left(\eta + \mu + \delta_S^T\right) \quad (11)$$

$$\frac{dT_i^{DRU}}{dt} = \tau_i TE_i^{DRU} - T_i^{DRU} \left(\mu + \delta_S^T + \omega\right) \quad (12)$$

$$\frac{dT_i^R}{dt} = \eta T_i^S + \tau_i TE_i^{DRD} + \omega T_i^{DRU} - T_i^R \left(\mu + \delta_R^T\right). \quad (13)$$

Change in the number of uninfected (susceptible) individuals is governed by equation(1); the force of infection terms, Λ_i^S and Λ_i^R (described below) for seroconverting with wild-type or drug-resistant virus respectively. Once infected, individuals progress into primary HIV infection, governed by equations (2)-(4). A proportion ψ of individuals infected with a drug resistant strain will have minority-resistant variants at the time of infection.

Equations (5) - (7) describe the change in the number of individuals in the chronic infection stage of HIV. After the chronic stage, HIV-infected individuals become treatment-eligible (governed by equations (8)-(10)), at which point they may receive ART at rate τ_i; we assume that in the era of universal treatment access people will initiate ART within a period of 6 weeks to 1 year of becoming treatment-eligible (see Table S1), although IDUs may take longer to seek treatment because of legal and social barriers. Once on treatment (governed by equations (11)-(13)), we assume that patients will continue using their ART regime, even if treatment failure occurs.

We assume that individuals with majority-resistance strains can become minority-resistant at a rate ϕ. This represents wild-type strains becoming the dominant type of virus. We also assume that once on treatment, individuals with minority-resistant strains become majority-resistant under the selective pressure of ART at a rate of ω. Drug susceptible individuals can acquire resistance at a rate of η.

In all equations, we assume that individuals can leave the sexually active population at a rate μ. Infected individuals can also leave the population due to death caused by HIV. This is represented by δ. We assume different rates for each disease stage, and also differing rates for those infected with drug resistant virus.

Probability of Transmission

The transmission probability is based on a number of factors. Disease stage alters the transmission probability according to viral load using the relation [1]:

$$\beta_v = 2.45^{\log(v/w)}\beta_w, \tag{14}$$

where *w* is the baseline viral load (in our case chronic infection), β_w is the baseline transmission probability, and *v* is the new viral load. Condom use is also a factor affecting transmission. We incorporate condom use in the per partnership calculation based using a binomial calculation [2] in the following equations:

$$1-(1-\beta_v)^{n_i(1-\chi)}(1-(1-\grave{o})\beta_v)^{n_i\chi} \tag{15}$$

$$1-(1-\alpha_2\beta_v)^{n_i(1-\chi)}(1-(1-\grave{o})\alpha_2\beta_v)^{n_i\chi} \tag{16}$$

Here, n is the number of acts, χ is the proportion of acts using condoms, $\grave{o}$ is the efficacy of condoms, and α_2 is the multiplicative factor affecting drug resistant virus due to reduced fitness.

During treatment failure, it is assumed that the transmission probability reverts to that of chronic infection with resistant virus. It is assumed that treatment is continued preventing the virus reverting completely back to wild-type.

Force of Infection:

The force of infection is governs the rate of new infections based on the transmission probabilities, number of partners, and the number of infected. These are described in equations (17) and(18):

$$\Lambda_i^S = c_i^j \lambda_S \tag{17}$$

$$\Lambda_i^R = c_i^j (\lambda_{DRD} + \lambda_{DRU}) \tag{18}$$

Where c_i^j represents the average number of contacts between population group *i* and group *j*, and λ_S, λ_{DRD}, and λ_{DRU} are described as follows:

$$\lambda_S = \frac{\beta_v^{PS} N_i^{PS} + \beta_v^{CS} N_i^{CS} + \beta_v^{TES} N_i^{TES} + \beta_v^{TS} N_i^{TS}}{N_{tot}} \tag{19}$$

$$\lambda_{DRD} = \frac{\beta_v^{PDRD} N_i^{PDRD} + \beta_v^{CDRD} N_i^{CDRD} + \beta_v^{TEDRD} N_i^{TEDRD} + \beta_v^{TDRD} N_i^{TDRD}}{N_{tot}} \tag{20}$$

$$\lambda_{DRU} = \frac{\beta_v^{PDRU} N_i^{PDRU} + \beta_v^{CDRU} N_i^{CDRU} + \beta_v^{TEDRU} N_i^{TEDRU} + \beta_v^{TDRU} N_i^{TDRU}}{N_{tot}} \tag{21}$$

Here, β_v^S, β_v^{DRD}, and β_v^{DRU} refers to the transmission probability associated with drug susceptible, detectible drug resistant, and undetectable drug resistant strains. The additional notations *P, C, TE,* and *T* in front of the viral class groups denote the disease stages, primary, chronic, treatment eligible and treated respectively. The number of infected individuals is denoted by N_i^S, N_i^{DRD} and N_i^{DRU}, using the same convention as for the transmission probabilities. The total population is given by N^{tot}.

Sensitivity Analysis and Calibration:

We performed a full uncertainty and sensitivity analysis using SaSAT [3]. We generated 10,000 individual parameter sets via Latin hypercube sampling for the parameters described in Table 1. The model was implemented with Matlab® R2008b. Calibration was achieved by reaching a steady state level, obtained in the absence of treatment. Simulations leading to an overall HIV prevalence between 0.5% and 5% (and similar for individual population groups) were retained, leaving 2,318 parameter sets. The model was then run to simulate 10 years of the HIV epidemic with full access to ART for treatment-eligible individuals.

Parameter	Description		Value	Ref
$1/\gamma_s^{PI}$	Average progression time from primary to chronic infection for individuals infected with drug-sensitive HIV		2-6 months	[4-6]
$1/\gamma_R^{PI}$	Average progression time from primary to chronic infection for individuals infected with drug-resistant HIV		$\alpha_1 . 1/\gamma_s^{PI}$ (min 2 months)	[7]
$1/\gamma_S^{CI}$	Average progression time from chronic infection to "treatment-eligible" or AIDS for individuals infected with drug-sensitive HIV		8 – 10 years	[8-10]
α_1	Multiplier for relative increase in average time for individual infected with drug resistant virus to progress from chronic infection to treatment eligibility, considering reduced viral fitness.		0.75 – 1.5	†
$1/\gamma_R^{CI}$	Average progression time from chronic infection to "treatment-eligible" or AIDS for individuals infected with drug-resistant HIV		$\alpha_1 \times 1/\gamma_S^{CI}$	
IDU_0	Percentage of population who are injecting drug users (IDUs)	% Total Pop	0.05 –0.5%	[11-13]
		% of IDU that are Female	10 – 20 %	
SW_0	Percentage of sexually active women that are sex workers (SWs)		0.5-1%	[14-15]
MC_0	Percentage of men who are clients of SWs		5 – 10%	[16-18]
MSM_0	Percentage of men who are MSM		1-5 %	[18-23]
$1/\delta_S^{PI}$	Average rate of AIDS deaths for individuals in Primary Infection class		~0	‡

$1/\delta_S^{CI}$	Average rate of AIDS deaths for individuals Chronic Infection class	~0	‡
$1/\delta_S^{TE}$	Average time to death for untreated individuals with drug-sensitive virus in the AIDS/"treatment-eligible" stage of infection	2 – 4 years	[24-26]
p_s	Proportion of drug-sensitive treated individuals that achieve viral suppression	0.6 – 0.85	[27]
$1/\delta_R^{TE}$	Average time to death for untreated individuals with drug-resistant virus in the AIDS/"treatment-eligible" stage of infection	$\alpha_1 \times 1/\delta_S^{TE}$ years	
$1/\delta_S^{T}$	Average time to death for treated individuals with drug-sensitive virus in the AIDS/"treatment-eligible" stage of infection	$\frac{1}{\delta_S^{TE}} < \frac{1}{\delta_S^{T}} < 15$	[24, 28-29][a]
$1/\delta_R^{T}$	Average time to death for treated individuals with drug-resistant virus in the AIDS/"treatment-eligible" stage of infection	$\frac{1}{\delta_S^{TE}} < \frac{1}{\delta_R^{T}} < \frac{1}{\delta_S^{T}}$	[28, 30][b]
η	Percentage of individuals on ART to acquire resistance (have treatment failure) each year	3-5%	[31-32]
$1/\omega$	Average time for drug resistance to re-emerge upon treatment in individuals that have reservoirs of drug-resistant strains	3 months -$1/\eta$	[33-34][c]
$1/\phi$	Average time for virus "reversion" to wild type	0.25 – 5 years	[35-36]
ψ	Proportion of those infected with transmitted drug resistant virus in which resistant viral strain is detectable	0-100%	†
$1/\mu$	Average time for individuals to be in	30 – 35 years	[28, 37]

	sexually active population			
β_v	Probability of transmission via needle sharing per single event, if initial user is HIV-positive		0.005 – 0.01	[38-39]
α_2	Reduction in fitness of drug resistant HIV, decreasing transmission probability of drug-resistant strains		0.05 – 0.5	[27, 40-41]
w	Baseline viral load taken at chronic infection		$10^4 – 10^5$ copies/ml	[42-43]
v_{PI}	Average viral load at primary infection stage		$10^5 – 10^8$ copies/ml	[5, 42]
v_{CI}	Average viral load at chronic infection stage		$10^4 – 10^5$ copies/ml	[5, 8, 42-43]
v_{TE}	Average viral load at treatment eligible stage		$10^5 – 10^6$ copies/ml	[10, 42]
v_T	Average viral load at Treated stage		10 – 200 copies/ml	[44-46]
β_w^m	Baseline male-to-female transmission probability per act[d]		0.0001 – 0.002	[1, 47-52]
β_w^f	Baseline female-to-male transmission probability per act		0.0001 – 0.0015	[47, 49-53]
β_w^{msm}	Baseline male-to-male transmission probability per act		0.001 – 0.01	[49, 52, 54]
c_{MC}	Number of sexual partnerships per year of males (who are also clients of SWs)	with SW	2 – 5	[55-56]
		With General Females (GF)	0.5 – 1.5	
c_{mIDU}	Number of sexual partnerships per year of a male injecting drug user	with SW	2 – 5	[55-56]
		with GF	0.5 – 1.5	

c_{GM}	Number of partnerships per year of general males (who are not IDUs nor clients of SWs)	0.75 – 1.5	[56]
c_{MSM}	Number of partnerships per year of MSM	2 - 6	[57-60]
χ_{GF}	Proportion of acts in which condoms are used for non-SW females	0 – 20%	[56, 61-62]
χ_{SW}	Proportion of acts in which condoms are used by SWs	10 - 50%	[61, 63]
χ_{MSM}	Proportion of acts in which condoms are used by MSM	10 – 50%	[57, 64]
ε	Efficacy of condoms (per act)	80-95%	[54, 65-66]
n_{SW}^{MC}	Number of acts per partnership between SW and MC per year	1-6	[63]
n_{MC}^{GF}	Number of acts per partnership between GF and MC	100 – 150	[67-68]
n_{GM}^{GF}	Number of acts per partnership between GF and GM	100 – 150	[67-68]
n_{needle}^{IDU}	Number of times injected drugs per year	300 – 1000 per year	[69-71]
ζ	Percentage of IDUs that share needles	60 – 75%	[72]
θ_{needle}	Proportion of injections in which sharing IDUs share needles	0 – 1	†
θ_{IDU}	Reduction factor in the rate at which IDUs seek treatment, since they are not as likely as other groups.	0 - 1	† Clinical experience
$1/\tau_{FSW}$	Average time to receive treatment for SWs	6 weeks – 6 months	Estimate[e]

$1/\tau_{GF}$, $1/\tau_{GM}$, $1/\tau_{MC}$, $1/\tau_{MSM}$	Average time to receive treatment for the non-SWs and non-IDUs	6 weeks – 12 months	Estimate[f]
$1/\tau_{mIDU}$, $1/\tau_{fIDU}$	Average time to receive treatment for IDUs	$1/\theta_{IDU} \times 1/\tau_{GM}$	Estimate[g]

† Experimental Parameter

‡ We assume that HIV-infected individuals will not die from AIDS-related illnesses until they have progressed through primary and chronic infection, to the stage of infection of AIDS.

[a] The ranges is assumed for those who achieve viral suppression

[b] For this range, it is assumed that an individual with a drug resistant virus will survive longer that those without any treatment, but not as long as those with a drug susceptible virus

[c] Low range is based on time taken for resistance to re-emerge after structured treatment interruption, and high range based on time for resistance to normally develop

[d] Baseline taken at Chronic infection

[e] Estimate based on high organisation of this group, with several testing options and locations available

[f] Assumed that testing may not occur as regularly for these groups as with FSW

[g] We assume that IDUs are less likely to seek treatment immediately due to social and cultural factors

Table S1: List of model parameters and their values

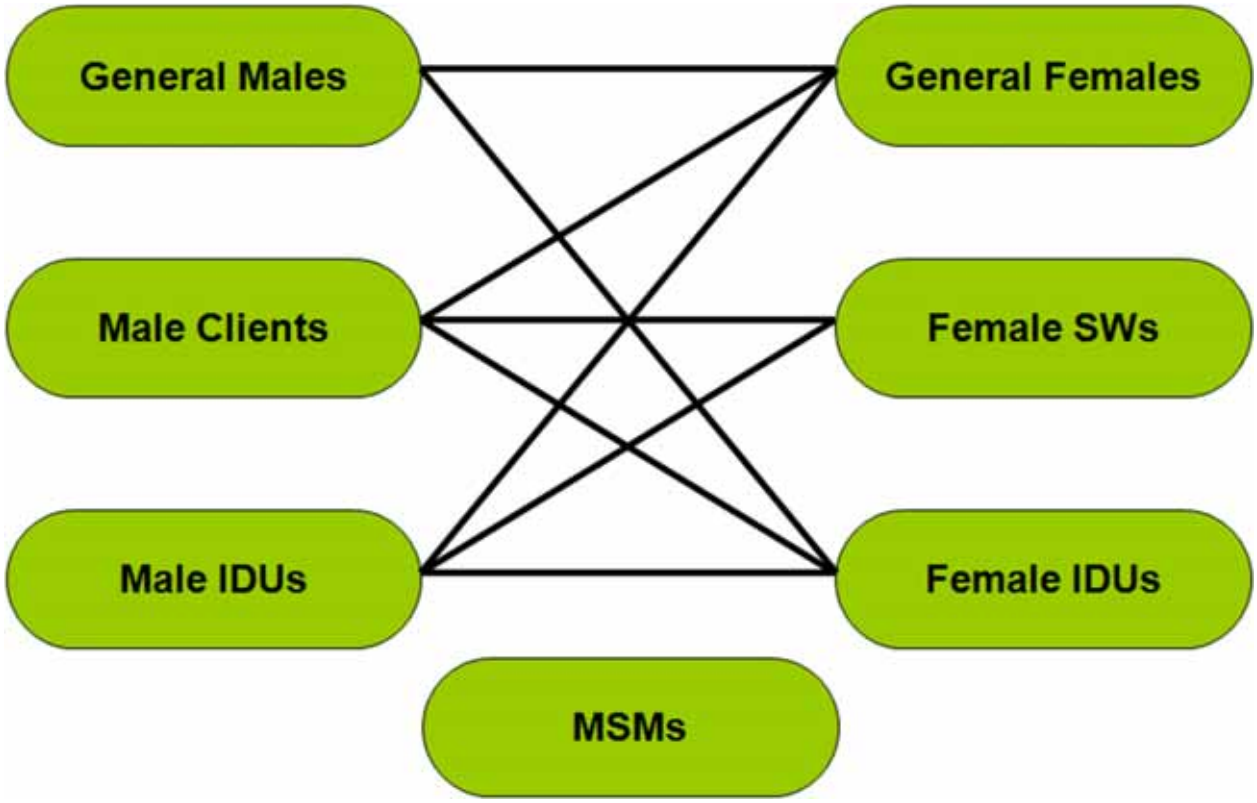

Figure S1: The seven population subgroups contained within the model. Lines between groups indicate interactions for sexual mixing.

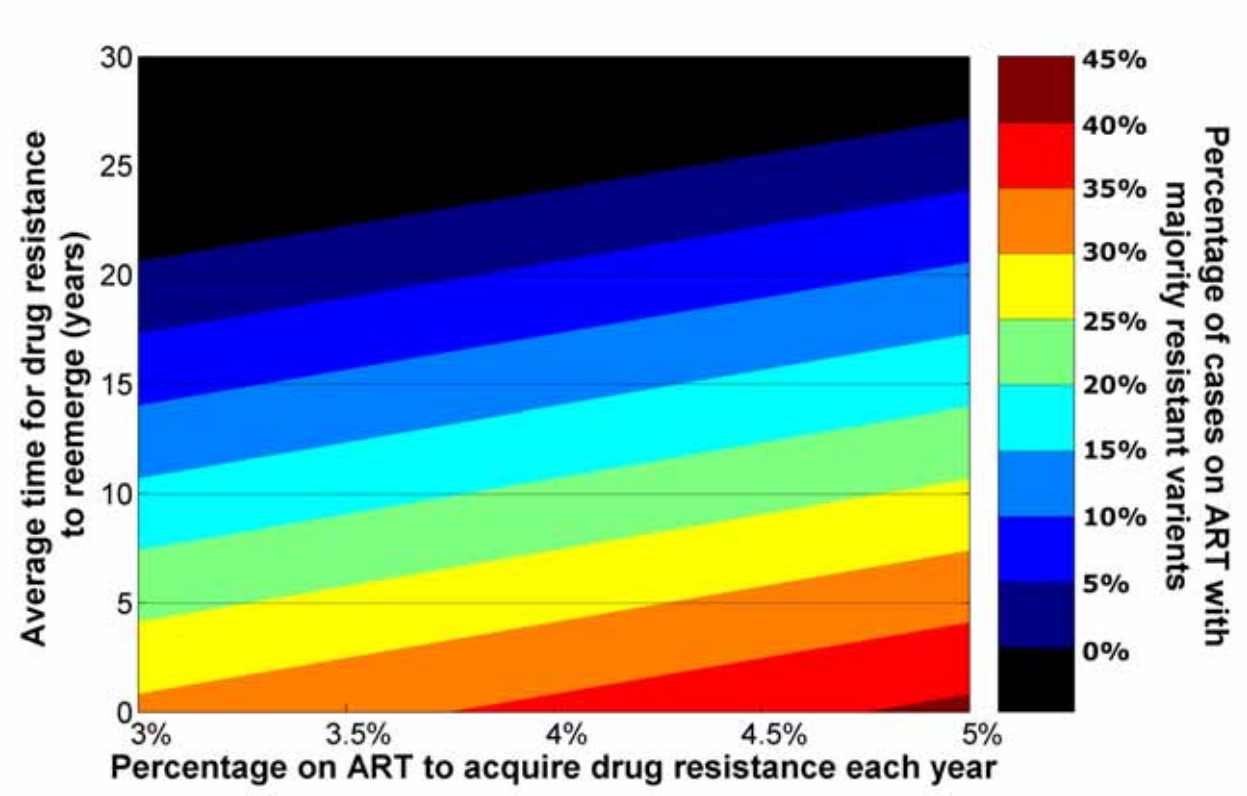

Figure S2: Response surface plot from sensitivity analysis. This plot shows the proportion of cases on ART that have majority-resistant variants (colored contours) versus the rate at which people infected with wild-type acquire drug resistant virus (x-axis) and the average time for majority-resistant variants to emerge for people infected with minority-resistant variants (y-axis) after 20 years of universal treatment access.

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