Challenges in epidemiological modelling: from socio-virulence dynamics to HIV interventions in MSM populations.

by

Joe Pharaon

A thesis
presented to the University of Waterloo
in fulfillment of the
thesis requirement for the degree of
Doctor of Philosophy
in
Applied Mathematics

Waterloo, Ontario, Canada, 2020

Examining Committee Membership

The following served on the Examining Committee for this thesis. The decision of the Examining Committee is by majority vote.

External Examiner: **Junling Ma**
Professor, Mathematics & Statistics, University of Victoria
Victoria, British Columbia

Supervisor: **Chris Bauch**
Professor, Applied Mathematics, University of Waterloo
Waterloo, Ontario

Internal Member: **Matthew Scott**
Associate Professor, Applied Mathematics, University of Waterloo
Waterloo, Ontario
Kevin G. Lamb
Professor, Applied Mathematics, University of Waterloo
Waterloo, Ontario

Internal-External Member: **Eihab Abdel-Rahman**
Professor, Systems Design Engineering, University of Waterloo
Waterloo, Ontario

Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Abstract

The spread of infectious diseases is one of the biggest challenges that public health faces nowadays. Their control is often not an easy task. Social behaviour plays an important role in disease prevention. However, the complex interplay between social behaviour and transmission dynamics is still not very well understood. This thesis tackles this topic by introducing a dynamic variable representing social behaviour that is coupled with epidemiological compartmental models. Under certain conditions, social behaviour can greatly impact the outcomes of an emerging virulent pathogen and thus it is necessary to explicitly model social behaviour for better understanding of transmission dynamics, and better and more accurate predictions.

The Human Immunodeficiency Virus (HIV) is a disease that attacks the immune system of its host. Since its emergence in the 1970s, it remains an epidemic that disproportionately affects gay and bisexual men who have sex with men (GbMSM). While diagnosis and treatment procedures kept improving, it still poses a public health concern. The introduction of Pre-Exposure Prophylaxis (PrEP) as a preventive drug in Canada in 2015 was a crucial step to help with decreasing HIV prevalence. PrEP however doesn't prevent the transmission of bacterial sexually transmitted infections (STIs). Previous studies have found a positive correlation between the increase in PrEP use and the decrease of condom usage. We investigated conditions under which the prevalence of bacterial STIs remains low under a PrEP regimen and we found that population level annual testing is essential for risk mitigation.

While PrEP has a great potential in reducing HIV prevalence, its impact might not be as strong as that created by frequent testing. In a final study, we examined different strategies, that are season specific and risk level specific, to derive an optimal strategy that aims to reduce HIV prevalence in Toronto by 2050. Given that higher risk sexual behaviour is more observed during the summer months, we concluded that testing the entire population twice during the summer is the most effective way to get a low HIV prevalence subject to plausible levels of testing and PrEP recruitment.

Acknowledgements

I would like to start by acknowledging the persistence and perseverance in me that led me to this moment. I think we don't appreciate ourselves enough and we can sometimes take our achievements lightly.

Reflecting on my journey, I would like to thank my advisor Chris Bauch for his patience, understanding and support. I would like to thank family members, specifically my mother Mirna and my cousin Cynthia, for their words of encouragement and love. I would like to thank my friends who have been a great support; especially Daniel, Judy, Margaret, and Ralph. I would like to thank all my students for they have kept challenging me and offering me new perspectives on how to be a better teacher and mentor.

A big thank you to my four legged friend, Kolyma. She has been my companion throughout my doctoral studies. She has been present during the darkest and brightest of times. She has taught me patience and unconditional love.

I would like to acknowledge the role that atheism has played in helping me grow and gain a more rational worldview, without dogmas and superstitions. Some of the people I look up to include, but are not limited to: the late Christopher Hitchens, Richard Dawkins, and Richard Carrier.

Finally, and for visibility purposes, I am a proud member of the LGBTQ community. The world keeps changing and while we still have work to do, I am grateful for how far we have come toward equality.

Dedication

To my canine best friend, Kolyma.

Table of Contents

List of Tables x

List of Figures xi

Abbreviations xvii

1 The Basics of Mathematical Epidemiology 1

1.1 A brief introduction to epidemiology 1

1.2 Analysis of an elementary model 3

1.3 A selection of other models and tools 9

1.4 Virulence of a pathogen 11

2 The Influence of Social Behaviour on Competition between Virulent Pathogen Strains 14

2.1 Publication record 14

2.2 Abstract 15

2.3 A background on social behaviour in the context of epidemiology 16

2.4 Coupling an epidemiological system with adaptive social behaviour 19

2.5 Invasion analysis of the uncoupled and coupled systems. 22
2.6 What do time series and parameter plane analysis tell us? 25
2.7 Human social behaviour can be critical in the mitigation of highly virulent strains 30

3 A brief history of the Human Immuno-deficiency Virus (HIV) and HIV in MSM populations 33

3.1 The origins of HIV 33
3.2 The biology and epidemiology of HIV 34
3.3 HIV in MSM communities 35
3.4 An early HIV model 36

4 The Impact of Pre-exposure Prophylaxis for Human Immunodeficiency Virus on Gonorrhea Prevalence 42

4.1 Publication record 42
4.2 Abstract 44
4.3 An overview of HIV in GbMSM communities 45
4.4 Constructing the model and its parametrization 47
4.5 Increasing PrEP recruitment rate increases Gonorrhea prevalence. 52
4.6 Sufficiently frequent STI testing controls Gonorrhea prevalence. 56
4.7 A 10–25 % decrease in risky behaviour on PrEP combined with increased testing frequency prevents gonorrhea prevalence from rising. 59
4.8 A deeper look with time series analysis. 61
4.9 Sensitivity Analysis 65
4.10 No drastic measures are needed to prevent a Gonorrhea outbreak 67

5 Toward a reduction in HIV prevalence in the Gay and Biseuxal Men who have Sex with Men (GbMSM) population of Toronto by 2050 **70**

5.1 Notification of submission 70

5.2 Abstract 71

5.3 HIV in numbers 72

5.4 A Stochastic framework to predict HIV prevalence 73

5.5 Optimal Strategy for HIV Reduction is Testing Everyone Twice during the Summer 81

5.6 Sensitivity Analysis 87

5.7 Recommendations to Public Health Units in Ontario about the Reduction of HIV Prevalence 89

6 Conclusions **91**

References **94**

APPENDICES **127**

A Appendices **128**

A.1 Sample MATLAB code for heat-maps in chapter 4 128

A.2 Transition rates for Chapter 5 130

A.3 Tables for Chapter 5 132

List of Tables

2.1 Baseline parameter values. Strain 1 is taken to be an avirulent resident strain, and strain 2 is taken to be a more virulent mutant strain. 21

4.1 Baseline parameter values. The assumed values of δ and μ are based on an average lifespan of 50 years. The parameters β_h and β_g and α_t were first calibrated neglecting all parameters and variables related to PrEP. Finally, α_p and ρ were calibrated. 50

5.1 Baseline parameter values. 79

List of Figures

1.1 SIR model with $\gamma = 0.1$ per day, $N = 10000$, $S(0) = 9980$, $I(0) = 20$. **(A)** The transmission rate is $\beta = 0.3$ per day giving a basic reproductive number $\mathcal{R}_0 = 3$. An epidemic occurs that peaks at about 3000 infections after about 40 days. **(B)** The transmission rate is $\beta = 0.08$ per day giving a basic reproductive number $\mathcal{R}_0 = 0.8$. There is no outbreak and the number of infected individuals decreases exponentially to 0. 5

1.2 SIR model with vital dynamics. $\gamma = 0.1$ per day, $N = 1000000$, $S(0) = 999000$, $I(0) = 1000$, $\delta = 1/(50 \times 365.25)$, $\beta = 0.2$ per day. The basic reproductive number $\mathcal{R}_0$ is approximately 2. **(A)** Short term dynamics: an epidemic occurs and the spike peaks at about 150000, roughly 15% of the total population and then the number of infected individuals decreases as they move to the R class. The number however does not decrease to 0. **(B)** Long term dynamics: the system exhibits oscillations on the long run where the number of infected individuals hovers around 300 (closer to the theoretical value). The period of the oscillations is roughly 8 years. 8

1.3 SIS model with vital dynamics. $\gamma = 0.1$ per day, $N = 10000$, $S(0) = 9800$, $I(0) = 200$, $\delta = \mu = 1/(50 \times 365.25)$. **(A)** $\beta = 0.12$ per day. The basic reproductive number is greater than 1 and this results in an endemic state with roughly 1666 cases (as predicted by the limiting value) present at all times. **(B)** $\beta = 0.08$ per day. The basic reproductive number is less than 1 and there is no outbreak. The number of infected individuals exponentially decreases to 0. 10

2.1 Numerical simulations for the $SI_1I_2R - x$ model at various values for the social and infection control parameters. **(a,b,c)** show baseline values where the mutant strain is perceived to be 10 times more severe ($\omega_2 = 10\omega_1 = 10^5$) and where efficacy of infection control against the resident strain is greater $\epsilon_1 = 0.7 > \epsilon_2 = 0.4$. The dynamics are shown at different timescales in **(a)**, **(b)** and **(c)**. **(d)** $\epsilon_1 = 0.4$. **(e,f)** $\omega_2 = 10^2$, $\epsilon_2 = 0.3$. **(g,h)** $\omega_1 = 10\omega_2 = 10^5$. **(i)** $\omega_1 = \omega_2 = 10^4$. $\epsilon_1 = 0.9$, $\epsilon_2 = 0.6$. All other parameters are held at their baseline values. Red line represents prevalence of protectors x. Blue line represents prevalence of the resident strain I_1. Black line represents prevalence of the more virulent mutant strain I_2. 26

2.2 Parameter plane analysis of the SI_1I_2R-x model. These dynamics are more complex than those exhibited by the SI_1I_2R model, which only predicts persistence of strain 1 for equivalent parameter values. The epidemiological parameters are at baseline values (Table 2.1). The social parameters are varied. **(a)** and **(d)** show no invasion of the mutant strain when $\epsilon_1 = 0.2$ and $\epsilon_2 = 0.1$ in the $\omega_1 - \omega_2$ parameter plane **(a)** and when $\omega_1 = \omega_2 = 10^2$ in the $\epsilon_1 - \epsilon_2$ parameter plane **(d)**. **(b)** and **(c)** represent similar qualitative results when for large $\epsilon_1 = 0.9$ we get invasion of the mutant strain in the black region and co-existence with the resident strain in the red region. The invasion region is bigger when 29

4.1 Diagram representing model structure. The eight compartments represent possible infection and treatment status for HIV and GC, while arrows represent transfers between those states. See main text and Table 4.1 for definitions of variables and parameters. 48

4.2 Gonorrhea prevalence heatmaps. Testing frequency for PrEP users (f_p) and gonorrhea transmission risk factor for PrEP users (α_p) are varied and all other parameters are held at baseline values. Different values of PrEP recruitment rate (ρ) are considered. **(a)** PrEP recruitment rate baseline value: $\rho = 2.375 \times 10^{-6}$. The white dot locates baseline values for α_p and f_p. **(b)** No PreP recruitment: $\rho = 0.0$. **(c)** PrEP recruitment rate 50% greater than baseline value: $\rho = 3.562 \times 10^{-6}$. **(d)** PrEP recruitment rate 5 times greater than baseline value: $\rho = 1.1875 \times 10^{-5}$. Black regions represent regions of lower gonorrhea prevalence. Yellow regions represent regions of higher gonorrhea prevalence. Note the difference in the ranges of the colour bars. 54

4.3 Gonorrhea prevalence heatmaps. PrEP recruitment rate (ρ) and gonorrhea transmission risk factor for PrEP users (α_p) are varied and all other parameters are held at baseline values. Different values of testing frequency for PrEP users (f_p) are considered. **(a)** Testing frequency once every three months (baseline value): $f_p = 1/90 \approx 0.0111$. The white dot locates baseline values for α_p and ρ. **(b)** Testing frequency twice every year: $f_p = 1/182 \approx 0.0055$. **(c)** Testing frequency once every two months: $f_p = 1/60 \approx 0.0167$. **(d)** Testing frequency once every 5 years: $f_p = 1/1825 \approx 0.0005$. Black regions represent regions of lower gonorrhea prevalence. Yellow regions represent regions of higher gonorrhea prevalence. Note the difference in vertical scale between the four subpanels. 57

4.4 Gonorrhea prevalence heatmaps. PrEP recruitment rate (ρ) and testing frequency for PrEP users (f_p) are varied and all other parameters are held at baseline values. Different values of gonorrhea transmission risk factor for PrEP users (α_p) are considered. **(a)** gonorrhea transmission risk factor for PrEP users baseline value: $\alpha_p = 12.75$. The white dot locates baseline values for f_p and ρ. **(b)** gonorrhea transmission risk factor for PrEP users reduced by a factor of 2: $\alpha_p = 6.375$. **(c)** gonorrhea transmission risk factor for PrEP users augmented by a factor of 2: $\alpha_p = 25.5$. **(d)** gonorrhea transmission risk factor for PrEP users multiplied by 5: $\alpha_p = 63.75$. Black regions represent regions of lower gonorrhea prevalence. Yellow regions represent regions of higher gonorrhea prevalence. Note the difference in vertical scale between the four subpanels. 60

4.5 Time series of gonorrhea prevalence over different time scales. In each subfigure, all parameters but one are kept at baseline values. **(a,d)** gonorrhea transmission risk factor for PrEP users (α_p) is varied: baseline value in red (12.75), reduced by a factor of 2 in black (6.375), augmented by a factor of 3 in yellow (38.25). **(b,e)** Testing frequency for PrEP users (f_p) is varied: baseline value in red (1/90: once every three months), testing once every 1.5 months in black (1/45), testing twice per year in yellow (1/182). **(c,f)** PrEP recruitment rate (ρ) is varied: baseline value in red (2.375×10^{-6}), No PrEP recruitment in black (0), PrEP recruitment rate 5 times greater than baseline value in yellow (1.1875×10^{-5}). 62

4.6 Time series of gonorrhea and HIV prevalence over long time scales. In the first row, we compute HIV prevalence. We vary **(a)** PrEP recruitment rate ρ (no PrEP recruitment $\rho = 0$, basline value PrEP recruitment rate and 5 times baseline value), **(b)** testing frequency for individuals in the susceptible class f (once every two years, once every year, twice per year), **(c)** efficacy of HIV treatment ϵ_h (90% effective:baseline value, 100% effective, 60% effective). In the second row, we compute gonorrhea prevalence. We vary **(d)** gonorrhea transmission risk factor for individuals who are treated for HIV ($\alpha_t = 3.875$ baseline value, twice lower than baseline value, three times higher than baseline value), **(e)** testing frequency for individuals who are treated for HIV f_t (twice per year, once per year, once every three months), **(f)** efficacy of gonorrhea treatment ϵ_g (83% effective: baseline value, 100% effective, 60% effective). 63

4.7 Sensitivity analysis for model parameters. For each parameter, an interval centered at the baseline value is considered and the equilibrium value of Gonorrhea infections is measured and plotted. 66

5.1 Diagram depicting the dynamics of the stochastic model presented in this paper. There are 12 continuous random variables. Arrows represent transition probabilities per time step. 74

5.2 Human Immunodeficiency Virus (HIV) prevalence: fitting of epidemiological parameters (transmission rates, testing frequencies, and Pre-Exposure Prophylaxis (PrEP) recruitment rate) to data on HIV from 1980-2016 in Toronto. Data reflects both diagnosed and undiagnosed cases. 80

5.3 HIV prevalence (%) for different testing strategies. PrEP recruitment is at baseline value. Labels on the horizontal axes denote testing frequency. **(D-F)** Testing frequency is at baseline outside the summer months. 84

5.4 HIV prevalence (%) for different testing strategies. Testing frequency is at baseline value. Labels on the horizontal axes denote PrEP recruitment rates. **(D-F)** PrEP recruitment rate is at baseline value outside the summer months. 85

5.5 HIV prevalence (%) for different testing and PrEP recruitment strategies. Labels on the horizontal axes denote testing frequencies and PrEP recruitment rates, respectively. **(D-F)** PrEP recruitment rate and test frequency are at baseline value outside the summer months. 86

5.6 Sensitivity analysis for model parameters. 100 sample paths were produced for each parameter value. For each parameter, three values were considered one at a time: baseline value, half baseline value (lower end), one and a half baseline value (upper end). 88

A.1 Transition rate from low risk to high risk 130

A.2 Transition rate from high risk to low risk 131

Abbreviations

AIDS Acquired Immuno-Deficiency Syndrome 35, 37, 45, 48

DNA Deoxyribonucleic acid 34, 35

GbMSM Gay and Biseuxal Men who have Sex with Men ix, 35, 36, 44–47, 67, 68, 70–73, 89, 90, 92

GC Gonorrhea 44–48, 51–53, 55, 56, 58, 59, 61, 64, 65, 67–69

GRID Gay Related Immune Deficiency 36

HAART Higly Active Anti-Retroviral Therapy 45, 51

HIV Human Immunodeficiency Virus xv, 17, 33–36, 41, 44–49, 51, 52, 55, 56, 61, 64, 65, 67–69, 71–75, 77, 79–83, 87, 89, 90, 92

MSM Men who have Sex with Men 51

ODE ordinary differential equation 3, 6, 12, 13, 47

PrEP Pre-Exposure Prophylaxis xv, xvi, 41, 44, 46–48, 52, 55, 56, 58, 59, 61, 64, 65, 67, 68, 71–74, 76, 79–87, 89, 90, 92

RNA Ribonucleic Acid 35, 45

SARS Severe Acute Respiratory Syndrome 17

SEIR Susceptible-Exposed-Infected-Recovered 10

SIR Susceptible-Infected-Recovered 2, 3, 5, 6, 9, 16

SIS Susceptible-Infected-Susceptible 9

SIV Simian Immuno-deficiency Virus 33, 34

SPVL Set-Point Viral Load 35

STI Sexually Transmitted Infection 36, 44–46, 52, 56, 61, 67–69, 92

Chapter 1

The Basics of Mathematical Epidemiology

1.1 A brief introduction to epidemiology

Epidemiology is the study of the spread of disease. The word derives from ancient Greek and Latin and it became a distinct discipline in the earlier part of the 19^{th} century. For a historical overview of the development of this field, we recommend the second chapter of the first part of *Foundations of Epidemiology* [137].

The lexicon of epidemiology is rich. Our focus is on key terms pertaining to the principles and mechanisms involved in the spread of infectious diseases. The most important mechanism is *transmission*. The transmission of a disease occurs between a host who carries the pathogen and is infectious, and a host who is susceptible to infection. There are different modes of transmission. A pathogen can either be transmitted through air [57], through food or water [189], through blood and other bodily fluids [116], or through physical contact [51]. Transmission rate can vary over the infectivity period [98] and this is mostly related to the within host dynamics [201]; i.e. the reproductive cycle of the virus in the host. Another important mechanism that is common to a lot of communicable diseases

is *recovery*. Recovery happens when the host clears the virus and is no longer infected or infectious. Recovery can either happen naturally through the immune system [38], or with the aid of antibiotics and other pharmaceutical products. For certain diseases, recovery yields a life long immunity where the host does no longer contract the disease. In other cases, immunity wanes over time and the host becomes susceptible again to infection [243]. The period of *waning immunity* can vary depending on the disease itself. The *incubation period* is an important epidemiological quantity. It specifies the period from the time the host gets infected until the host shows symptoms of infection [27]. Symptoms vary from one disease to another and they are important for clinical diagnosis and commencement of treatment. The *latent period* is also an important epidemiological quantity. It specifies the period from the time the host gets infected until it becomes infectious [230]. The concept of *Herd immunity* is popular in the control of infectious diseases and refers to the mitigation of the transmission due to a vaccinated pool of hosts, or a to a large number of recovered/immune hosts who practically lower the odds of a susceptible host acquiring the infection [94].

One of the earliest known mathematical models in epidemiology is that of Daniel Bernoulli in 1766 on mortality rate for smallpox [69]. Mathematical analysis in epidemiology became more prominent in the 20^{th} century through the work of William Kermack and Anderson McKendrick in their 1927 paper, entitled "*A contribution to the mathematical theory of epidemics*" [127]. In their dissertation, they have analyzed basic characteristics of disease transmission and they came up with approximations to quantities such as the size of an outbreak, the dynamics of early stages of an outbreak and thresholds for disease persistence in a population. Perhaps, one of the most famous attributions of their work is the development of the simple Susceptible-Infected-Recovered (SIR) model [32, 208]. This approach seeks to divide a population into compartments based on their disease status. In a human population, each individual can either be susceptible to a disease, infected by the disease, or recovered from the disease. A susceptible individual can move to the infected compartment if they acquire the infection and can then progress to the recovered compartment upon recovery.

1.2 Analysis of an elementary model

The SIR model is described mathematically by a set of three ordinary differential equation (ODE)s that track the number of individuals in each compartment over time. The system is given as follows:

$$\begin{aligned} \frac{dS}{dt} &= -\beta \frac{I(t)}{N} S(t), \\ \frac{dI}{dt} &= \beta \frac{I(t)}{N} S(t) - \gamma I(t), \\ \frac{dR}{dt} &= \gamma I(t), \end{aligned} \tag{1.1}$$

where $S(t)$ is the number of susceptible individuals at time t, $I(t)$ is the number of infected individuals at time t, $R(t)$ is the number of recovered individuals at time t, β is the transmission rate, γ is the recovery rate, N is the total population. Both parameters have units *per unit time*. The population is assumed to be constant over the course of the spread of the disease.

The term $\beta \frac{I(t)}{N} S(T)$ is called the incidence term. In this particular set up, we have standard incidence due to dividing $I(t)$ by N. This form of incidence is used when the likelihood of infection increases when surrounded by more infectious individuals. Other forms of incidence include mass-action incidence, saturated incidence, etc [77].

The assumption of a constant population is justified by the relative short length of the course of an outbreak to the lifespan of an individual. Therefore, instead of analyzing all three ODEs, we let $R(t) = N - S(t) - I(t)$ and reduce the system to two equations:

$$\begin{aligned} \frac{dS}{dt} &= -\beta \frac{I(t)}{N} S(t), \\ \frac{dI}{dt} &= \beta \frac{I(t)}{N} S(t) - \gamma I(t). \end{aligned} \tag{1.2}$$

The second equation in particular offers perspective on the evolution of the outbreak. Suppose $S_0 = S(0)$ represents the initial population of susceptible individuals. Factoring

the second equation, we get:

$$\frac{dI}{dt} = I(t)\Big(\beta\frac{S(t)}{N} - \gamma\Big). \tag{1.3}$$

If initially $\beta\frac{S_0}{N} - \gamma < 0$ then $\frac{dI}{dt} < 0$ and therefore $I(t)$ decreases and there is no outbreak. On the other hand, if $\beta\frac{S_0}{N} - \gamma > 0$, $I(t)$ increases and reaches a maximum. In the latter case, we observe an *epidemic*. An epidemic is characterized by a significant increase in the number of infected individuals over a relatively short period of time followed by a drop in that number. Note that at the start of an epidemic we have $\frac{S_0}{N} \approx 1$. From here, we obtain a threshold value that is known as the *basic reproductive number* $\mathcal{R}_0$:

$$\mathcal{R}_0 = \frac{\beta}{\gamma}. \tag{1.4}$$

By definition, $\mathcal{R}_0$ is the average number of secondary infections that an infectious individual generates over the course of their infectivity period in a completely susceptible population. In a simple scenario, it is the product of the transmission rate by the average length of infection (the reciprocal of the recovery rate).

Theorem 1. *If $\mathcal{R}_0 > 1$, an epidemic occurs. If $\mathcal{R}_0 < 1$, the number of infected individuals exponentially decreases to 0.*

The proof of this theorem is the analysis conducted on 1.3 in the last paragraph. To illustrate the above theorem, we present an example in figure 1.1 using the solver *ode45* in MATLAB.

A simple SIR simulation

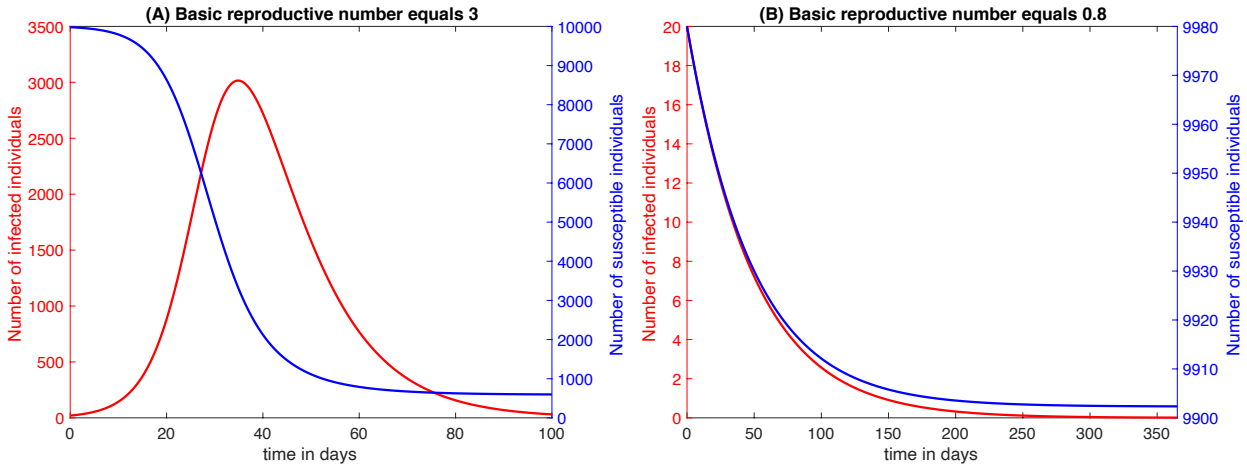

Figure 1.1: SIR model with $\gamma = 0.1$ per day, $N = 10000$, $S(0) = 9980$, $I(0) = 20$. **(A)** The transmission rate is $\beta = 0.3$ per day giving a basic reproductive number $\mathcal{R}_0 = 3$. An epidemic occurs that peaks at about 3000 infections after about 40 days. **(B)** The transmission rate is $\beta = 0.08$ per day giving a basic reproductive number $\mathcal{R}_0 = 0.8$. There is no outbreak and the number of infected individuals decreases exponentially to 0.

Adding vital dynamics to an SIR model allows us to investigate interesting situations such as an *endemic* state of a disease. A disease is endemic in a population if it is constantly present in relatively stable values. The system 1.1 becomes:

$$\begin{aligned} \frac{dS}{dt} &= \mu N - \delta S(t) - \beta \frac{I(t)}{N} S(t), \\ \frac{dI}{dt} &= \beta \frac{I(t)}{N} S(t) - \gamma I(t) - \delta I(t), \\ \frac{dR}{dt} &= \gamma I(t) - \delta R(t), \end{aligned} \tag{1.5}$$

where δ represents a natural death rate, μ is a birth rate. Adding up all three equations

in 1.5, we obtain an equation that describes changes in total population size:

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dI}{dt} + \frac{dR}{dt} = \mu N - \delta\Big(S(t) + I(t) + R(t)\Big) = (\mu - \delta)N. \tag{1.6}$$

If birth rate equals death rate, then the population remains constant. Otherwise, it either decreases exponentially (if $\mu < \delta$) or increases exponentially (if $\mu > \delta$). This simplistic change in population size is based on Malthusian growth and it can be modified to logistic growth or other growth models as needed.

For the purposes of simplicity, we assume that we are dealing with a constant population and therefore we can omit $R(t)$ from the analysis. To analyze this complex model, we would need to obtain equilibria values of the variables $S(t)$ and $I(t)$. We set the first two ODEs in 1.5 equal to 0. In particular, the second equation can be written as:

$$\frac{dI}{dt} = I_\infty\Big(\beta\frac{S_\infty}{N} - (\gamma + \delta)\Big) = 0, \tag{1.7}$$

where I_∞ denotes the number of infected individuals as t approaches infinity (at equilibrium) and S_∞ denotes the number of susceptible individuals as t approaches infinity. Equation 1.7 has two solutions. The first solution is known as the *disease free* state where $I_\infty = 0$. We shall call this equilibrium E_0. Substituting 0 for I_∞ in the first equation of 1.5 gives $S_\infty = \frac{\mu N}{\delta} = N$ (since we are assuming a constant population and therefore birth and death rates are equal). The disease free equilibrium is:

$$E_0 = (N, 0). \tag{1.8}$$

The second solution is known as the endemic state where $I_\infty \neq 0$. We shall call this equilibrium E_1. Solving for S_∞ in 1.7, we get $S_\infty = N\Big(\frac{\gamma+\delta}{\beta}\Big)$. This equilibrium only exists provided $\frac{\gamma+\delta}{\beta} < 1$. It is not surprising that the last inequality is related to the basic reproductive number.

Theorem 2. *In an SIR model with vital dynamics with constant population size, we have two equilibria: a disease free equilibrium E_0 and an endemic equilibrium E_1. If $\mathcal{R}_0 = \frac{\beta}{\gamma+\delta} < 1$ then $E_0 = (N, 0)$ is the only equilibrium and is always locally asymptotically stable. If $\mathcal{R}_0 = \frac{\beta}{\gamma+\delta} > 1$ then $E_1 = \Big(\frac{N}{\mathcal{R}_0}, \frac{\delta N}{\beta}(\mathcal{R}_0 - 1)\Big)$ and is stable.*

Proof. The condition for the existence of the endemic equilibrium is straightforward. We focus on the stability of equilibria. We compute the Jacobian of the first two equations in 1.5.

$$J(S,I) = \begin{bmatrix} -\delta - \beta\frac{I}{N} & -\beta\frac{S}{N} \\ \beta\frac{I}{N} & \beta\frac{S}{N} - (\gamma+\delta) \end{bmatrix}$$

Substituting the disease free equilibrium into the Jacobian gives:

$$J(E_0) = \begin{bmatrix} -\delta & -\beta \\ 0 & \beta - (\gamma+\delta) \end{bmatrix}$$

The first eigenvalue is $\lambda_1 = -\delta$ which is always negative. The second eigenvalue is $\lambda_2 = \beta - (\gamma+\delta)$ which is negative if $\beta - (\gamma+\delta) < 1$ i.e. $\mathcal{R}_0 < 1$, concluding the stability of the disease free equilibrium.

Substituting the endemic equilibrium into the Jacobian gives:

$$J(E_1) = \begin{bmatrix} -\delta\mathcal{R}_0 & -\frac{\beta}{\mathcal{R}_0} \\ \delta(\mathcal{R}_0 - 1) & 0 \end{bmatrix}$$

The trace of this matrix is $Tr = -\delta\mathcal{R}_0 < 0$ and the determinant is $Det = \delta\beta\left(1 - \frac{1}{\mathcal{R}_0}\right) > 0$ and therefore E_1 is stable whenever it exists [75]. □

We illustrate Theorem 2 with an example. The natural death rate δ is estimated as the reciprocal of a lifespan of an individual. If we are discussing a disease that adults are primarily susceptible to then we can assume an average adult life span of 50 years. Notice that the natural death rate slightly decreases the basic reproductive number but not significantly so.

SIR with vital dynamics

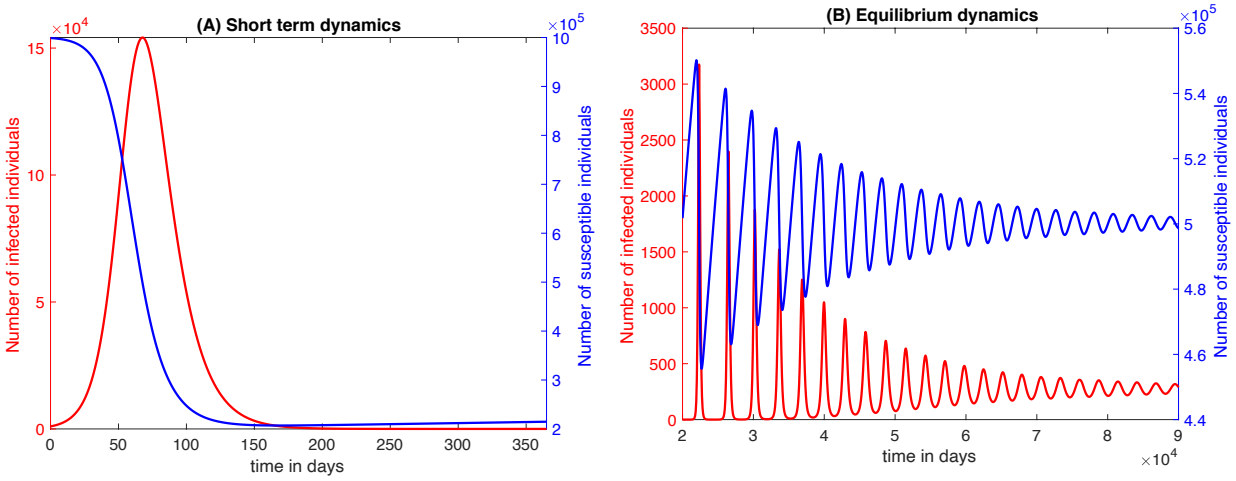

Figure 1.2: SIR model with vital dynamics. $\gamma = 0.1$ per day, $N = 1000000$, $S(0) = 999000$, $I(0) = 1000$, $\delta = 1/(50 \times 365.25)$, $\beta = 0.2$ per day. The basic reproductive number $\mathcal{R}_0$ is approximately 2. **(A)** Short term dynamics: an epidemic occurs and the spike peaks at about 150000, roughly 15% of the total population and then the number of infected individuals decreases as they move to the R class. The number however does not decrease to 0. **(B)** Long term dynamics: the system exhibits oscillations on the long run where the number of infected individuals hovers around 300 (closer to the theoretical value). The period of the oscillations is roughly 8 years.

In some instances, we might be interested in learning about the sensitivity of an outcome, such as infection prevalence to a particular parameter. In this case, we perform a sensitivity analysis [256, 70, 199, 42]. There are different methods, among them the OAT (one at a time) approach. In this method, we allocate a range for the parameter of interest centered at the baseline value and we measure outcomes for a set of values of the parameter. The purpose is to determine how sensitive is the outcome of a particular model to a particular input (usually a parameter). We perform sensitivity analysis in chapters 4 and 5.

1.3 A selection of other models and tools

The SIR model is suitable for diseases when upon recovery, individuals gain permanent immunity. A lot of viral diseases can be modelled with the SIR set up such as Measles, Mumps, Smallpox, Pertussis, etc [83, 112, 48]. However, there are different setups for other diseases.

The Susceptible-Infected-Susceptible (SIS) model is applicable for diseases when upon recovery, an individual becomes susceptible immediately again. An example of a disease that falls under the SIS category is the common cold. The set of differential equations would have the following form:

$$\begin{aligned} \frac{dS}{dt} &= \mu N - \delta S(t) - \beta \frac{I(t)}{N} S(t) + \gamma I(t), \\ \frac{dI}{dt} &= \beta \frac{I(t)}{N} S(t) - \gamma I(t) - \delta I(t). \end{aligned} \tag{1.9}$$

With a constant population size, we can solve for $I(t)$ analytically by substituting in the second equation of 1.9, $S(t)$ by $(N - I(t))$ and then use separation of variables. The solution is given by

$$I(t) = \frac{\dfrac{N(\mathcal{R}_0 - 1)}{\mathcal{R}_0}}{1 - \left(1 - \dfrac{N(\mathcal{R}_0 - 1)}{\mathcal{R}_0 I_0}\right) e^{-\dfrac{\beta(\mathcal{R}_0 - 1)t}{\mathcal{R}_0}}}, \tag{1.10}$$

where I_0 is the initial number of infected individuals and $\mathcal{R}_0 = \frac{\beta}{\gamma+\delta}$ is the basic reproductive number. The asymptotic behaviour depends on the value of $\mathcal{R}_0$ as can be seen from the exponential term in 1.10. If $\mathcal{R}_0 < 1$, then $I(t)$ eventually reaches 0 and we get a disease free state. On the other hand, if $\mathcal{R}_0 > 1$, $I(t)$ approaches the value $\dfrac{N(\mathcal{R}_0 - 1)}{\mathcal{R}_0}$ and we have endemic state. Both cases are portrayed in figure 1.3.

SIS with vital dynamics

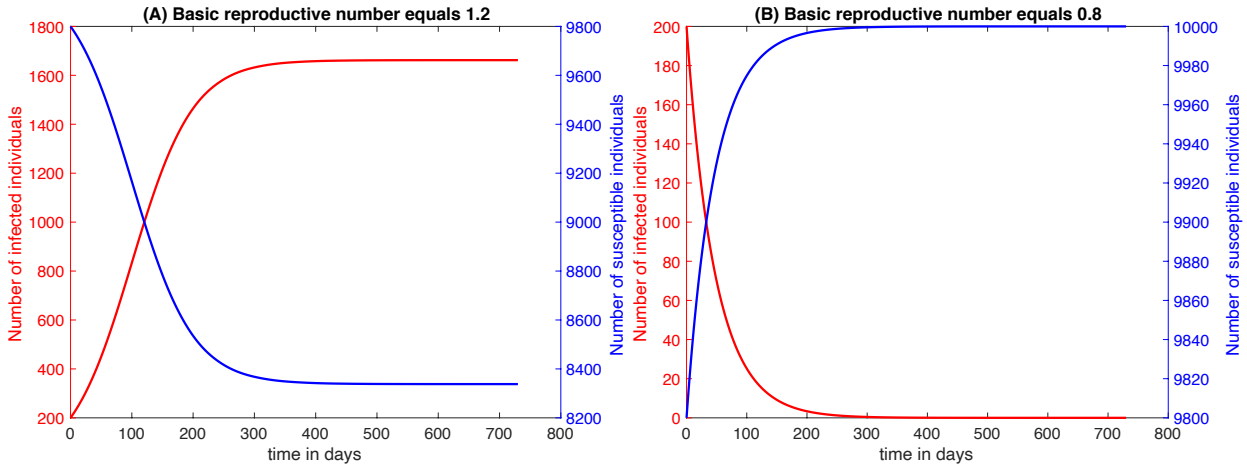

Figure 1.3: SIS model with vital dynamics. $\gamma = 0.1$ per day, $N = 10000$, $S(0) = 9800$, $I(0) = 200$, $\delta = \mu = 1/(50 \times 365.25)$. **(A)** $\beta = 0.12$ per day. The basic reproductive number is greater than 1 and this results in an endemic state with roughly 1666 cases (as predicted by the limiting value) present at all times. **(B)** $\beta = 0.08$ per day. The basic reproductive number is less than 1 and there is no outbreak. The number of infected individuals exponentially decreases to 0.

Another common model is the Susceptible-Exposed-Infected-Recovered (SEIR) model. The exposed class is added to account for the latent period. When an individual gets infected, they move to the exposed class where they remain non-infectious and then progress to the infected class once they become infectious. The system with vital dynamics is given

by 1.11.

$$\begin{aligned}
\frac{dS}{dt} &= \mu N - \beta \frac{I(t)}{N} S(t) - \delta S(t), \\
\frac{dE}{dt} &= \beta \frac{I(t)}{N} S(t) - \sigma E(t) - \delta E(t), \\
\frac{dI}{dt} &= \sigma E(t) - \gamma I(t) - \delta I(t), \\
\frac{dR}{dt} &= \gamma I(t) - \delta R(t),
\end{aligned} \tag{1.11}$$

where $\sigma > 0$ is the reciprocal of the latent period. We will not perform a full analysis of 1.11. However, we refer the reader to the work of Pauline Van den Driessche and James Watmough [238] on how to compute the basic reproductive number. Using the next generation matrix method, we get:

$$\mathcal{R}_0 = \frac{\beta\sigma}{(\sigma + \delta)(\gamma + \delta)}.$$

1.4 Virulence of a pathogen

There are many models that describe the spread of infectious diseases. Every model can be customized based on the transmission and recovery cycles and possibly other disease specific mechanisms. Co-infection is a situation where a host can be infected by two different diseases simultaneously. Super-infection is a situation where often a more *virulent* pathogen strain replaces a less virulent pathogen strain in the host. Virulence is a measure of harm inflicted by the disease on the host. This harm can be characterized by a much higher transmission rate, a much lower chance of recovery, or other means [40].

One way to model virulence is to define a new parameter that measures the excess death rate for two different strains of the same pathogen. The more virulent strain would have a higher virulence. Consider the model in 1.12

$$\begin{aligned}
\frac{dS}{dt} &= \mu N - \beta_1 \frac{I_1(t)}{N} S(t) - \beta_2 \frac{I_2(t)}{N} S(t) - \delta S(t), \\
\frac{dI_1}{dt} &= \beta_1 \frac{I_1(t)}{N} S(t) - \gamma_1 I_1(t) - \nu_1 I_1(t) - \delta I_1(t), \\
\frac{dI_2}{dt} &= \beta_2 \frac{I_2(t)}{N} S(t) - \gamma_2 I_2(t) - \nu_2 I_2(t) - \delta I_2(t), \\
\frac{dR}{dt} &= \gamma_1 I_1(t) + \gamma_2 I_2(T) - \delta R(t),
\end{aligned} \tag{1.12}$$

where ν_i represents the excess death rate due to the pathogen for strain i. Without loss of generality, we consider $I_2(t)$ to be the compartment representing individuals infected by the more virulent strain, and therefore $\nu_2 > \nu_1$. We compute the basic reproductive number for each strain as we did in section 1.3 and we get:

$$\mathcal{R}_{0,1} = \frac{\beta_1}{\gamma_1 + \nu_1 + \delta}, \qquad \mathcal{R}_{0,2} = \frac{\beta_2}{\gamma_2 + \nu_2 + \delta}.$$

In this very simple model, if we assume both strains have the same transmission rates and recovery rates (which is not necessarily true), the more virulent strain has a lower basic reproductive number since individuals infected by that strain exit the I_2 class faster due to a higher death rate, and thus have less time to transmit the strain. In reality, the dynamics of different strains for the same pathogen are complex and are discussed at length in the next chapter.

Several approaches to studying the spread of infectious diseases exist. In this chapter so far, we have considered ordinary differential equations which are deterministic. However, in real life, random events can occur that can influence the course of an epidemic. In that case, we can use Markov chains (discrete or continuous) and stochastic differential equations to analyze a disease outbreak. For a comprehensive formulation in stochastic differential equations we refer the reader to the work of Linda Allen [8].

ODEs assume homogeneity in a given population. In reality, individuals are unique and differ in their behaviour. They also have different health conditions and disease resistance thresholds. This creates heterogeneity in the population of study. From that perspective,

one can use network models to analyze disease outbreaks in communities [145]. Network models come with challenges. Computationally, they can be very time consuming. They also require large data sets.

Every approach and tool utilized in understanding the spread of infectious diseases is relevant to certain questions we ask. The implementation of ODEs is crucial to understanding long term dynamics and is a good approximation for well-mixed large populations. Every approach comes with uncertainties but also offers a perspective on what needs to be done to control outbreaks and mitigate threats. Very often, risk mitigation is largely dependent on social behaviour [237, 148, 82]. The next chapter introduces social behaviour in the context of epidemiology and discusses its influence on the spread of infectious diseases.

Chapter 2

The Influence of Social Behaviour on Competition between Virulent Pathogen Strains

2.1 Publication record

This chapter is based on the paper "*The Influence of Social Behaviour on Competition between Virulent Pathogen Strains*", submitted to the Journal of Theoretical Biology on the 11^{th} day of November in 2017 and published on the 18^{th} day of June in 2018 (volume 455, pages 47-53).

- Model conceptualization: Chris Bauch.
- Model analysis: Joe Pharaon.
- Manuscript write up: Joe Pharaon and Chris Bauch.
- Edits and Revisions: Joe Pharaon and Chris Bauch.

2.2 Abstract

Infectious disease intervention like contact precautions and vaccination have proven effective in disease control and elimination. The priority given to interventions can depend strongly on how virulent the pathogen is, and interventions may also depend partly for their success on social processes that respond adaptively to disease dynamics. However, mathematical models of competition between pathogen strains with differing natural history profiles typically assume that human behaviour is fixed. Here, our objective is to model the influence of social behaviour on the competition between pathogen strains with differing virulence. We couple a compartmental Susceptible-Infectious-Recovered model for a resident pathogen strain and a mutant strain with higher virulence, with a differential equation of a population where individuals learn to adopt protective behaviour from others according to the prevalence of infection of the two strains and the perceived severity of the respective strains in the population. We perform invasion analysis, time series analysis and phase plane analysis to show that perceived severities of pathogen strains and the efficacy of infection control against them can greatly impact the invasion of more virulent strains. We demonstrate that adaptive social behaviour enables invasion of the mutant strain under plausible epidemiological scenarios, even when the mutant strain has a lower basic reproductive number than the resident strain. Surprisingly, in some situations, increasing the perceived severity of the resident strain can facilitate invasion of the more virulent strain. Our results demonstrate that for certain applications, it may be necessary to include adaptive social behaviour in models of the emergence of virulent pathogens, so that the models can better assist public-health efforts to control infectious diseases.

2.3 A background on social behaviour in the context of epidemiology

Modern approaches to developing a theory of the spread of infectious diseases can be traced to 1927 when Kermack and McKendrick developed an integro-differential equation model now widely described as the SIR [126]. The model tracks changes in the number of individuals susceptible to an infection $S(t)$, the number of infected individuals $I(t)$, and (implicitly) the number of recovered individuals $R(t)$. Compartmental models such as the SIR model are useful for mechanistic modelling of infection transmission in populations. They have since been further developed to study the evolution and epidemiology of multiple species of pathogens in a population or different strains of the same species [88]. Some models focus on between-host competition while some others on within-host competition [150]. Bull suggested in the 1990s that coupling inter-host and intra-host dynamics in models may be desirable [40]. Models linking between-host transmission dynamics to within-host pathogen growth and immune response are now becoming commonplace [5, 80, 211, 107, 150]. One such approach is to link host viral load (which is a necessary condition of virulence) to the between-host transmission rate.

Compartmental models have also been used to study the phenomenon of pathogen virulence- the rate at which a pathogen induces host mortality and/or reduces host fecundity [13, 59, 162, 227]. It was initially believed that hosts and parasites co-evolved to a state of commensalism (whereby parasites benefit from their host without harming them) [211, 221] but this hypothesis was later challenged [6]. In mathematical models, virulence is often treated as a fixed model parameter expressing the excess mortality rate caused by the pathogen. For instance, virulence has been assumed to depend on the intrinsic reproductive rate of the parasite [37]. Other research expresses the transmission rate β and the recovery rate μ in terms of a parameter ν that represents virulence [63]. When the impact of human behaviour is discussed in such models, it is discussed in terms of hypothesized effects of human behaviour on the value of the fixed parameter representing

virulence. HIV virulence model by Massad [144] shows that reducing the number of sexual partners could possibly drive HIV to be a more benign pathogen. However, the model assumes that the number of sexual partners can simply be moved up or down as a model parameter, whereas in reality the number of sexual partners in a population is the outcome of a dynamic socio-epidemiological process that merits its own mechanistic modelling, and itself responds to pathogen virulence. In general, these models do not treat human behaviour as a dynamic variable that can evolve in response to transmission dynamics and influence the evolution of virulence. (A few exceptions exist, including work that allows virulence to be a function of the number of infected hosts, thus capturing a situation where the magnitude of the epidemics affects the ability of health care services to host patients [66]). However, as human responses to both endemic and emerging infectious diseases show, human behaviour can have a significant influence on how infections get transmitted. For instance, an early and well-documented example shows how the residents of the village of Eyam, England quarantined themselves to prevent the spread of plague to neighbouring villages [202]. Individuals moved to less populated areas during the Spanish Influenza pandemic in the early 20^{th} century [60]. More recently, masks became widely used during the outbreak of Severe Acute Respiratory Syndrome (SARS) at the beginning of the 21^{st} century [132], and it has been shown pathogen virulence in Marek's disease can evolve in response to how vaccines are used [193].

Theoretical models of the interactions between human behaviour and the spread of infectious diseases are increasingly studied [19, 21, 18, 79, 91, 172, 207]. For instance, Bagnoli et al. [16] found that under certain conditions, a disease can be driven extinct by reducing the fraction of the infected neighbours of an individual. Zanette and Risau-Gusman [261] showed that if susceptible individuals decide to break their links with infected agents and reconnect at a later time, then the infection is suppressed. Gross et al. [102] also shows that rewiring of edges in a network (and thus social interaction) can greatly influence the spread of infectious diseases. Of the compartmental models, we focus on those that have used concepts from evolutionary game theory such as imitation dynamics [20] to describe the evolution of behaviour and its interplay with the epidemics. An example

of imitation dynamics concerns, as described in detail in [18], the effect of vaccination on the spread of infectious diseases. Each individual in the population picks one strategy and adopts it: "to vaccinate"or "not to vaccinate". The proportion of vaccinators is modelled using an ordinary differential equation and is coupled with a standard SIR model. An important aspect of behavioural models is to couple them with epidemiological processes such as transmission. This coupling creates a feedback loop between behaviour and spread of the disease.

Given that adaptive social behaviour is important in many aspects of infection transmission, we hypothesize that adaptive social behaviour can also influence selection between pathogen strains with differing virulence in ways that cannot be captured by assuming it to be represented by a fixed parameter. Our objective in this paper was to explore how behaviour and virulence influence one another, in a coupled behaviour-disease differential equation model. The model allows individuals who perceive an increase in the prevalence of infection to increase their usage of practices that reduce transmission rates (such as social distancing and hand washing) and thereby boost population-level immunity. This approach can help us understand the effects specific social dimensions, such as level of concern for a strain or the rate of social learning, have on the coupled dynamics of pathogen strain emergence and human behaviour in a situation where virulence imposes evolutionary trade-offs and is strain-specific. Instead of considering long-term evolutionary processes with repeated rounds of mutation and selection, we focus on the case of invasion of a single mutant strain with a large phenotypical difference compared to the resident strain. In the next section, we describe a model without adaptive social behaviour as well as a model that includes it, and in the following Results section we will compare their dynamics.

2.4 Coupling an epidemiological system with adaptive social behaviour

We compare dynamics of a two-strain compartmental epidemic model in the presence and absence of adaptive social behaviour. Individuals are born susceptible (S). They may be infected either by a resident strain (I_1) or a mutant strain (I_2). For simplicity, we assume that co-infection and super-infection are not possible. Infected individuals can either recover (R) or die from infection. We furthermore assume that recovery from either strain offers permanent immunity to both strains. The system of differential equations representing the SI_1I_2R model in the absence of adaptive social behaviour (we will refer to this as the "uncoupled model" throughout) is given by 2.1:

$$\begin{aligned}
\frac{dS}{dt} &= \mu - \beta_1 I_1(t)S(t) - \beta_2 I_2(t)S(t) - \delta S(t), \\
\frac{dI_1}{dt} &= \beta_1 I_1(t)S(t) - (\gamma_1 + \nu_1 + \delta)I_1(t), \\
\frac{dI_2}{dt} &= \beta_2 I_2(t)S(t) - (\gamma_2 + \nu_2 + \delta)I_2(t), \\
\frac{dR}{dt} &= \gamma_1 I_1(t) + \gamma_2 I_2(t) - \delta R(t),
\end{aligned} \tag{2.1}$$

where β_1 (β_2) represents the transmission rate of the resident (mutant) strain; γ_1 (γ_2) represents the recovery rate from the resident (mutant) strain; ν_1 (ν_2) represents the death rate from the resident (mutant) strain due to infection (virulence); μ is a birth rate and δ is the background death rate. All variables represent the proportions of individuals with the given infection status (for instance, S is the proportion of susceptible individuals). Since R does not appear in the other equations, we can omit R from the analysis.

The system of differential equations in the presence of adaptive human behaviour couples the SI_1I_2R epidemic spread with a differential equation for human behaviour ("coupled model"). Each individual in the population can choose to accept or reject behaviours that reduce infection risk (e.g. washing hands, wearing a mask, social distancing), and individuals imitate successful strategies observed in others. Let x represent the proportion of

individuals accepting preventive behaviour (we will call these "protectors"). Individuals sample others in the population at rate κ, representing social learning. The choice is based on the perceived severity ω_1 (resp. ω_2) from the resident (resp. mutant) strain, where ω_1 (resp. ω_2) can be quantified as the probability that an infection by the resident (resp. mutant) strain results in a severe case of disease. The more severe cases the population observes, the more attractive preventive behaviour becomes: we assume that individuals respond to the total number of severe cases $\omega_1 I_1 + \omega_2 I_2$ they observe at a given time. Preventive behaviour is not always completely effective. We introduce efficacy of infection control ϵ_1 (ϵ_2) against the resident (mutant) strain. The efficacy of infection control influences the transmission process. The more effective infection control is against a strain, the less likely it will be transmitted.

More formally, the preceding imitation dynamic (or equivalently, replicator dynamic) assumes that each individual samples others at a fixed rate, and if another person is found to be playing a different strategy but is receiving a higher payoff, the individual switches to their strategy with a probability proportional to the expected gain in payoff [113]. These assumptions give rise to a differential equation of the form $dx/dt = \kappa x(1-x)\Delta U$ where κ is the sampling rate and ΔU is the payoff difference between the two strategies. This equation is derived elsewhere and is used in other socio-ecological and socio-epidemiological models [18, 170, 109, 25]. The augmented system of differential equations representing the coupled social-epidemiological SI_1I_2R-x model with adaptive human behaviour is therefore given by 2.2:

$$\begin{aligned}
\frac{dS}{dt} &= \mu - \beta_1(1-\epsilon_1 x)I_1(t)S(t) - \beta_2(1-\epsilon_2 x)I_2(t)S(t) - \delta S(t),\\
\frac{dI_1}{dt} &= \beta_1(1-\epsilon_1 x)I_1(t)S(t) - (\gamma_1+\nu_1+\delta)I_1(t),\\
\frac{dI_2}{dt} &= \beta_2(1-\epsilon_2 x)I_2(t)S(t) - (\gamma_2+\nu_2+\delta)I_2(t),\\
\frac{dR}{dt} &= \gamma_1 I_1(t) + \gamma_2 I_2(t) - \delta R(t),\\
\frac{dx}{dt} &= \kappa x(1-x)(\omega_1 I_1 + \omega_2 I_2 - 1).
\end{aligned} \tag{2.2}$$

We apply the restrictions $\epsilon_i \in [0,1]$ and $\omega_i \geq 0$. Baseline parameter values are summarized in Table 2.1.

Parameter	Definition	Value
δ	death rate	1/18250 per day, [20].
μ	birth rate	1/18250 per day, [20].
γ_1	recovery rate for strain 1	0.2 per day (assumed).
ν_1	disease death rate for strain 1	0.0 per day (assumed).
γ_2	recovery rate for strain 2	0.2 per day (assumed).
ν_2	disease death rate for strain 2	0.05 per day (assumed).
β_1	transmission rate for strain 1	0.4 per day (assumed).
β_2	transmission rate for strain 2	0.4 per day (assumed.)
κ	sampling rate	1/365 per day, [170].
ω_1	perceived severity from strain 1	10000 (assumed)
ω_2	perceived severity from strain 2	100000 (assumed)
ϵ_1	efficacy of infection control against strain 1	0.7 (assumed)
ϵ_2	efficacy of infection control against strain 2	0.4 (assumed)

Table 2.1: Baseline parameter values. Strain 1 is taken to be an avirulent resident strain, and strain 2 is taken to be a more virulent mutant strain.

We chose parameter values to represent an emerging infectious disease with a relatively low basic reproduction number and an acute-self limited infection natural history, as might occur for viral infections such as Ebola or Influenza. Recruitment is assumed to occur due to births and immigration at a constant rate μ, while the per capita death rate due to all causes other than the infection is δ. The values of μ and δ are obtained as the reciprocal

of an average human lifespan of 50 years. Note that $\gamma_i + \nu_i$ is the reciprocal of the average time spent in the infected class before the individual recovers or dies from infection. Since we are assuming that strain 2 is more virulent, $\nu_2 - \nu_1 = 0.05$ per day can be considered as the excess death rate due to infection from the more virulent strain 2. We assume $\beta_1 = \beta_2$ and therefore $\mathcal{R}_{0,2} \approx 1.6 < 2 \approx \mathcal{R}_{0,1}$. Hence, all else being equal, the more virulent strain has a lower reproductive number and is therefore at a disadvantage to invade. We note that R does not appear in the other equations and hence could be omitted.

We identify all equilibria of the uncoupled and coupled systems and determine their local stability properties. We study conditions under which the mutant strain successfully invades. Due to the analytical complexity of the coupled model, we rely primarily on numerical simulations. We used MATLAB to run our simulations and generate parameter planes (ODE45, ODE23tb, and ODE15s). We also wrote MATLAB code to analyse the stable regions of all equilibria versus a combination of parameters of interest.

2.5 Invasion analysis of the uncoupled and coupled systems.

The SI_1I_2R model has 3 equilibria [31]. One equilibrium is disease free and is stable when

$$\max\left\{\mathcal{R}_{0,1}, \mathcal{R}_{0,2}\right\} < 1.$$

$\mathcal{R}_{0,1}$ (resp. $\mathcal{R}_{0,2}$) is the basic reproductive number of the resident (mutant) strain, where $\mathcal{R}_{0,i}$ is given by

$$\mathcal{R}_{0.i} = \frac{\beta_i}{\gamma_i + \nu_i + \delta_i}$$

The other two equilibria are endemic. Assuming that basic reproductive numbers are not equal, strains can not co-exist and the strain with the higher basic reproductive number always invades.

In contrast, the addition of a dynamic social variable $x(t)$ generates 9 equilibria for the $SI_1I_2R - x$ model. Two equilibria are disease free and the other equilibria are endemic. One of the 7 endemic equilibria represents a state of coexistence of both strains (which can occur even if basic reproductive numbers are not the same). The analytical expression and stability criteria for the equilibrium with co-existing strains are difficult to compute and therefore, we determine them numerically.

If both basic reproductive numbers are less than 1, then the system evolved to a disease free state and social behaviour is not relevant. Assume, on the other hand, that $1 < \mathcal{R}_{0,2} < \mathcal{R}_{0,1}$ (as in our baseline parameter values, Table 2.1, and where the expressions for $\mathcal{R}_{0,1}$ and $\mathcal{R}_{0,2}$ are the same as in the SI_1I_2R model and assume $x = 0$. This corresponds to a scenario where the resident strain is more transmissible than the mutant strain. As already noted the mutant strain can not invade in the absence of adaptive social behaviour (SI_1I_2R model). However, in the presence of adaptive social behaviour, we can derive necessary and sufficient conditions for the mutant strain to invade when $1 < \mathcal{R}_{0,2} < \mathcal{R}_{0,1}$:

$$\omega_2 > \frac{\beta_2}{\delta} \frac{1}{\mathcal{R}_{0,2} - \frac{1}{1-\epsilon_2}}, \qquad \epsilon_1 > 1 - \frac{\mathcal{R}_{0,2}}{\mathcal{R}_{0,1}}(1 - \epsilon_2).$$

These results show that a high level of perceived severity from the mutant strain is a necessary condition for invasion. However, it has to be coupled with a sufficiently high efficacy of infection control against the resident strain (with $\epsilon_1 > \epsilon_2$). A high efficacy of infection control against the resident strain will effectively reduce its transmission and therefore creating a larger pool of susceptible individuals for the mutant strain. The two conditions must be met simultaneously to provide a necessary and sufficient condition for invasion. The condition that $\epsilon_1 > \epsilon_2$ could easily be met in a real population if the two strains differ in their mode of transmission, and the population has more experience with controlling the resident strain than with the new mutant strain. Moreover, a high value of ω_2 could easily be met in a real population due to spreading panic about a new and more virulent strain that public health does not yet know how to best control.

We also consider necessary and sufficient conditions for failure of invasion of the mutant

strain:

$$\omega_1 > \frac{\beta_1}{\delta}\frac{1}{\mathcal{R}_{0,1} - \frac{1}{1-\epsilon_1}}, \qquad \epsilon_2 > 1 - \frac{\mathcal{R}_{0,1}}{\mathcal{R}_{0,2}}(1-\epsilon_1), \qquad \omega_2 < \frac{\beta_2}{\delta}\frac{1}{\mathcal{R}_{0,2} - 1}.$$

Invasion fails when perceived severity of the mutant strain is low enough but also that of the resident strain high enough. Note the difference between invasion and failure to invade. Here, we require conditions on both perceived severities. As predicted, if the efficacy of infection control against the mutant strain is high enough (relative to that of the resident strain) then invasion fails. Again, all three conditions must be met jointly. Together, they create a necessary and sufficient condition for the failure of invasion.

Finally assume that $\mathcal{R}_{0,1} < \mathcal{R}_{0,2}$ (this scenario is not discussed at length in this paper). In the absence of social behaviour, the mutant strain is bound to invade. However, we derive necessary and sufficient conditions for the failure of invasion when social behaviour is added to the system:

$$\omega_1 > \frac{\beta_1}{\delta}\frac{1}{\mathcal{R}_{0,1} - \frac{1}{1-\epsilon_1}}, \qquad \epsilon_2 > 1 - \frac{\mathcal{R}_{0,1}}{\mathcal{R}_{0,2}}(1-\epsilon_1).$$

Note the difference between this case and the case when $\mathcal{R}_{0,1} < \mathcal{R}_{0,2}$: there is no conditioning on ω_2. If the mutant strain has a higher fitness, it does not matter how severely it is perceived (since individuals respond to the weighted sum of mutant and resident prevalence and the mutant is initially rare, hence the early response is dominated by the resident). It will fail to invade provided that the perceived severity of the resident strain is high enough and that efficacy of infection control against the mutant strain is high enough relative to the resident strain (with $\epsilon_2 > \epsilon_1$). Once again we require both inequalities to be satisfied and together they provide necessary and sufficient conditions for the mutant strain to fail invasion.

We finally turn our attention to the invasion of the mutant strain when it is more transmissible. The invasion is conditional: necessary and sufficient conditions for the invasion of the mutant strain are:

$$\omega_1 < \frac{\beta_1}{\delta}\frac{1}{\mathcal{R}_{0,1} - 1}, \qquad \epsilon_1 > 1 - \frac{\mathcal{R}_{0,2}}{\mathcal{R}_{0,1}}(1-\epsilon_2).$$

In this scenario, a low perceived severity of the resident strain will allow invasion of the mutant strain provided that the efficacy of infection control against the resident strain is high enough.

The addition of adaptive social behaviour to the epidemic model introduced four new parameters, and it is clear that the model permits conditions for the mutant strain to invade on account of behaviour, even when the mutant strain has a lower basic reproductive ratio, as long as certain conditions for efficacy of infection control are satisfied and level of concern about the severity of the mutant strain are satisfied. To gain further insight into how adaptive social behaviour influences the invasion of the more virulent strain, we turn to numerical simulation and generation of time series and parameter planes.

2.6 What do time series and parameter plane analysis tell us?

We use time series of model simulations to illustrate some of the model's dynamical regimes. We consider the case where $\nu_1 = 0$ and $\nu_2 = 0.25$ and therefore $\mathcal{R}_{0,1} > \mathcal{R}_{0,2}$ while assuming (for simplicity) that $\beta_1 = \beta_2$ and $\gamma_1 = \gamma_2$. Hence, the mutant strain is more virulent and kills its hosts more quickly, giving it a significantly lower basic reproduction number. We use a simulation time horizon on the order of hundreds of years–although both pathogen and social parameters could vary over this period, a long time horizon ensures that the asymptotic model states are correctly characterized, and thus enables us to meet our objective of gaining insight into the types of dynamics exhibited by the model.

We first consider a scenario where the mutant strain, on account of its greater virulence, is perceived to be ten times more severe than the resident strain ($\omega_2 = 10^5 = 10\omega_1$). Moreover, infection control against the resident strain is much more effective, on account of less being known about the modes of transmission of the mutant strain (baseline values: $\epsilon_1 = 0.7 > 0.4 = \epsilon_2$). In this scenario, the mutant strain invades (Fig 2.1a).

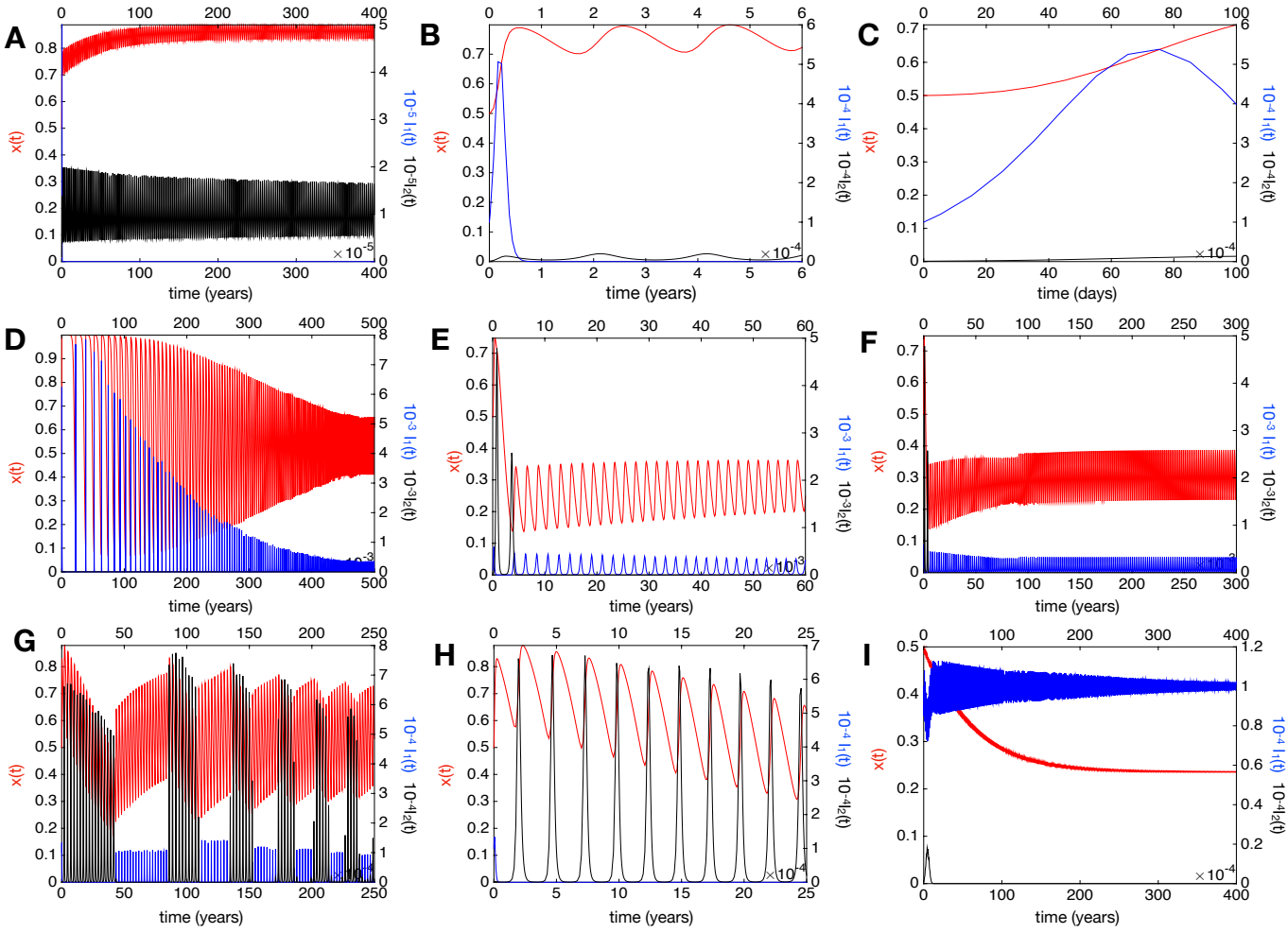

Figure 2.1: Numerical simulations for the SI_1I_2R-x model at various values for the social and infection control parameters. **(a,b,c)** show baseline values where the mutant strain is perceived to be 10 times more severe ($\omega_2 = 10\omega_1 = 10^5$) and where efficacy of infection control against the resident strain is greater $\epsilon_1 = 0.7 > \epsilon_2 = 0.4$. The dynamics are shown at different timescales in **(a)**, **(b)** and **(c)**. **(d)** $\epsilon_1 = 0.4$. **(e,f)** $\omega_2 = 10^2$, $\epsilon_2 = 0.3$. **(g,h)** $\omega_1 = 10\omega_2 = 10^5$. **(i)** $\omega_1 = \omega_2 = 10^4$. $\epsilon_1 = 0.9$, $\epsilon_2 = 0.6$. All other parameters are held at their baseline values. Red line represents prevalence of protectors x. Blue line represents prevalence of the resident strain I_1. Black line represents prevalence of the more virulent mutant strain I_2.

This agrees with the conditions determined in our invasion analysis. We observe that the mutant strain quickly displaces the resident strain and converges to an endemic state where the proportion of protectors x remains relatively high (Fig 2.1a). On shorter timescales, we see a transient phase at the start of the simulation with a sharp epidemic of the resident strain, followed by periodic epidemics with much lower incidence of the mutant strain (Fig 2.1b,c). The numerical simulations agree with the values computed from analytical expressions at equilibrium (for sufficiently large values of t).

Decreasing the efficacy of infection control against the resident strain and equating it to that of the more virulent strain ($\epsilon_1 = \epsilon_2 = 0.4$, with all other parameter values at baseline values) prevents the invasion of the mutant strain (Fig 2.1d). This occurs because more susceptible individuals will be infected by the resident strain, thereby significantly decreasing the pool of susceptible individuals available for infection by the mutant strain.

A surprising scenario under which the invasion of the mutant strain fails is when both perceived severity of the mutant strain and the efficacy of infection control against are low (Fig 2.1e,f, $\omega_2 = 10^2$, $\epsilon_2 = 0.3$ with other parameter values at baseline). It is worth noting in this case that we initially have a few outbreaks of the mutant strain with high incidence. (Fig 2.1f) represents the same dynamics as (Fig 2.1e) but on a longer timescale. The oscillations in the prevalence of infection and the prevalence of protectors is typical of coupled behaviour-disease models with adaptive social behaviour [23].

It is difficult for both strains to co-exist without imposing $\omega_1 = 10^5 > \omega_2 = 10^4$. If the resident strain is perceived to be ten times more severe, then co-existence is achieved via a transient but very long-term pattern of switching between oscillatory regimes before the system finally converges to an equilibrium of co-existence (Fig 2.1g). The system switches between a longer-lived regime with relatively small epidemics of the resident strain, and a shorter-lived regime with very large epidemics of the mutant strain. Changes in the proportion adopting contact precautions, x , facilitates the switching. As x rises, it allows a series of periodic outbreaks of the mutant strain which in turn decreases the proportion of people adopting prevention and starts a series of outbreaks of the resident strain. This

loop continues with diminishing switching-period as well as amplitude. If we bring back efficacies of infection control to baseline values, this phenomenon persists but with wilder oscillations in x . This happens because lower values of ϵ increase the effective transmission rate which in turns leads to rapid changes in x. (Fig 2.1h) shows the same dynamics as in (Fig 2.1g) but on a shorter timescale.

We also allowed the perceived severities to be equally high ($\omega_1 = \omega_2 = 10^4$) and we have increased the efficacies from their baseline values ($\epsilon_1 = 0.9$ and $\epsilon_2 = 0.6$) (Fig 2.1i). We observe that the mutant strain fails to invade and the prevalence of the resident strain remains relatively close to the initial condition.

In order to refine our understanding of the influence of social parameters on the invasion of the mutant strain, we proceed in the next subsection with phase plane analysis that studies the interplay between the parameters determining regions of invasion.

Surprisingly, there are parameter regimes where increasing the perceived severity of the resident strain (ω_1) allows the mutant strain to invade (Fig 2.2a-c). This occurs across a nontrivial portion of parameter space despite the fact that $\mathcal{R}_{0,2} < \mathcal{R}_{0,1}$. This regime shift occurs because a sufficiently high perceived severity of the resident strain creates a large pool of susceptible individuals, and coupled with a higher efficacy of infection control against the resident strain, this means that the invading mutant strain can take advantage of the increased pool of susceptible individuals to invade. This effect occurs only when the efficacy of infection control against the resident strain is relatively high (e.g. $\epsilon_1 = 0.9$ and $\epsilon_2 = 0.6$). However, this phenomenon does not hold when ϵ_1 and ϵ_2 are low, in which event the model behaves similar to the SI_1I_2R model where the strain with the higher basic reproductive number invades, as expected. Similarly, increasing ω_2 can push the system from a regime of co-existence of the two strains to a region where only strain 2 persists.

In $\epsilon_1 - \epsilon_2$ parameter planes we again find parameter regimes where the more virulent strain can invade due to adaptive social behaviour, despite the fact that $\mathcal{R}_{0,2} < \mathcal{R}_{0,1}$, if there is an imbalance in the perceived severity of the two strains. When perceived severities

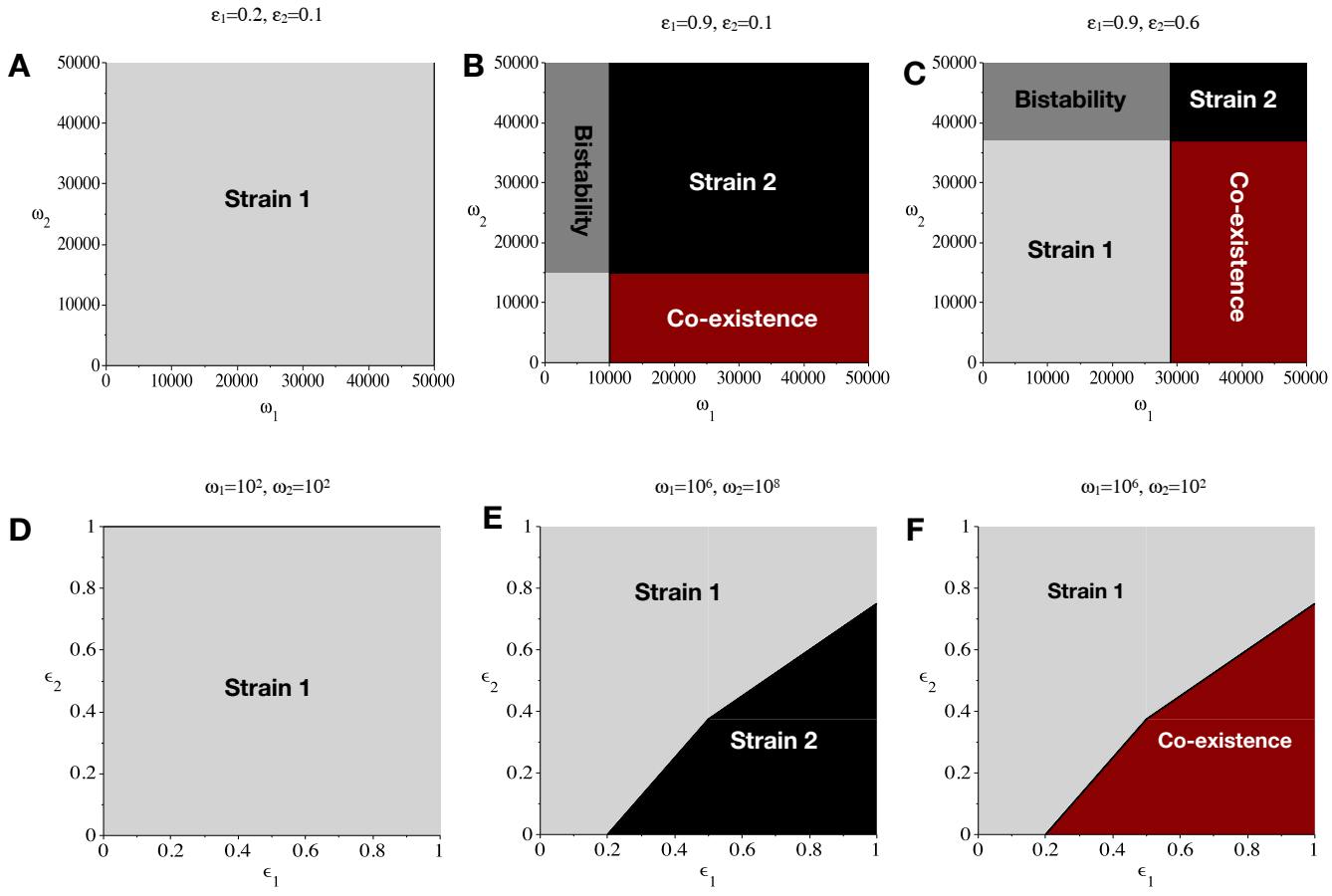

Figure 2.2: Parameter plane analysis of the $SI_1I_2R - x$ model. These dynamics are more complex than those exhibited by the SI_1I_2R model, which only predicts persistence of strain 1 for equivalent parameter values. The epidemiological parameters are at baseline values (Table 2.1). The social parameters are varied. **(a)** and **(d)** show no invasion of the mutant strain when $\epsilon_1 = 0.2$ and $\epsilon_2 = 0.1$ in the $\omega_1 - \omega_2$ parameter plane **(a)** and when $\omega_1 = \omega_2 = 10^2$ in the $\epsilon_1 - \epsilon_2$ parameter plane **(d)**. **(b)** and **(c)** represent similar qualitative results when for large $\epsilon_1 = 0.9$ we get invasion of the mutant strain in the black region and co-existence with the resident strain in the red region. The invasion region is bigger when

ϵ_2 is lower ($\epsilon_2 = 0.1$ in **(b)** and $\epsilon_2 = 0.6$ in **(c)**). Finally, in **(e)** and **(f)** we observe qualitatively different results when we vary ω_2 in the $\epsilon_1 - \epsilon_2$ parameter plane. In **(e)** , $10^8 = \omega_2 > \omega_1$, we have invasion of the mutant strain. In **(f)** , $\omega_1 = 10^6 > \omega_2$, we have co-existence of the strains. The light gray region in the lower-left hand corner of subpanel **(b)** corresponds to both strains being extinct.

are sufficiently low, the mutant strain can never invade (Fig 2.2d). But when $\omega_2 \gg \omega_1$, the mutant strain can invade and remove the resident strain if ϵ_1 is sufficiently large and ϵ_2 is sufficiently small (Fig 2.2e). When $\omega_1 \gg \omega_2$, the mutant strain and the resident strain coexist, when ϵ_1 is sufficiently large and ϵ_2 is sufficiently small (Fig 2.2f). Increasing the efficacy of infection control against the resident strain (ϵ_1) or decreasing efficacy of control against the mutant strain (ϵ_2) can allow the mutant strain to invade (Fig 2.2e-f). We note again that, surprisingly, invasion can result in the elimination of the resident strain if the perceived severity of the mutant strain is significantly higher than that of the resident strain ($\omega_2 \gg \omega_1$), but when the opposite applies, coexistence results.

2.7 Human social behaviour can be critical in the mitigation of highly virulent strains

We have showed how adaptive social behaviour greatly impacts the evolution of virulence in a coupled behaviour-disease model. If we neglect social behaviour, the basic reproductive numbers of the two strains are sufficient to predict which of the strains will invade a population. However, adding adaptive social behaviour with asymmetric stimulation and effects on either strain to an epidemiological system completely shifts how we view whether a more virulent strain will be selected for. As we have seen, social behaviour can either act in favour or against the invasion of a more virulent strain, and we can describe these effects with reference to specific social parameters ($\omega_{1,2}$) quantifying how concerned individuals are about the two strains, and control parameters ($\epsilon_{1,2}$) quantifying how well infection

control measures like hand-washing work. Most interestingly, adaptive social behaviour enables invasion of the mutant strain under plausible epidemiological and social conditions even when it has a lower basic reproductive number.

Future work can generate further insights into how behaviour and virulence interact for specific infectious diseases, by building on existing research on the coupled dynamics of behaviour and infection transmission. For instance, an increase in the average number of sexual partners of an individual has been predicted by mathematical models to cause increased HIV virulence [144, 174]. These models use a fixed parameter to quantify the number of sexual partners, but the number of sexual partners could be made to evolve dynamically based on the number of infected individuals in a particular population, similar to seminal work using compartmental models to model core group dynamics [105]. An increase in the number of sexual partners will decrease the efficacy of infection control against the more virulent strain and effectively increase its transmission and hence leads to higher virulence. Other future research could explore how adaptive social behaviour interacts with evolutionary trade-offs to determine virulence evolution. One of the most common hypotheses is that a trade-off exists for between-host transmission and virulence. To increase its probability of transmission, the parasite must replicate within the host. This replication, on the other hand, must be controlled because otherwise it might lead to the host's death and therefore prevent transmission. However, other trade-offs have been suggested, such as between transmission rate and host recovery rate [4]. Moreover, complicated host life cycles imply that many other types of trade-offs are also possible [65], and the presence of multiple trade-offs may complicate the relationship between transmission rate and virulence [7]. Social behaviour could interact with evolutionary trade-offs to alter the virulence evolution of an emerging pathogen, and this process could be modelled by building on existing virulence evolution models.

While the model discussed in this paper serves as a general framework for studying the influence of social behaviour on strain competition and emergence, further research needs to be carried out to understand the interplay between the epidemiological and social parameters. For instance, we did not model virulence evolution explicitly but rather by assuming

two strains have already emerged due to mutation and addressing conditions under which the more virulent mutant strain is more fit. Future research could instead model virulence by defining transmission and recovery rates in terms of a virulence parameter, or by using an adaptive dynamics approach. Future research could also explore different possible relationships between the virulence parameters $\nu_{1,2}$ and the perceived severity parameters $\omega_{1,2}$, or the interaction between social learning timescales and pathogen evolutionary timescales. We did not study the influence of the social learning parameter κ in this paper, but previous research on other socio-ecological and socio-epidemiological systems suggests that the social learning rate can destabilize interior equilibria [25, 109]. A model that accounts for multiple rounds of mutation would enable studying how pathogen evolutionary timescales interact with social learning dynamics. Finally, we assumed no specific relationship between the perceived severity $\omega_{1,2}$ and the virulence $\nu_{1,2}$ although a non-trivial relationship certainly exists, and future research could explore possible assumptions for their formal relationship.

In conclusion, our model shows how social behaviour can influence the virulence of emerging strains under plausible parameter regimes when using standard models for social and infection dynamics. When analyzing emerging and re-emerging pathogens and continually evolving infectious diseases such as influenza, it is worthwhile further considering aspects of social behaviour in efforts to mitigate serious threats.

Chapter 3

A brief history of the Human Immuno-deficiency Virus (HIV) and HIV in MSM populations

3.1 The origins of HIV

The origins of the Human Immuno-deficiency Virus HIV are still debated and several virologists and HIV specialists keep attempting to trace it back to its earliest days. Jacques Pepin, a professor at the University of Sherbrooke in Quebec has published the book on "*The Origins of AIDS*" [178]. He argued that the colonization of Africa has helped the circulation of HIV. There have been many pre-pandemic samples that tested positive for HIV. One of the earliest is a serum sample, tested in 1998, from an adult male from the Democratic Republic of Congo from 1959 [263]. Samples that have been tested suggest that an HIV strain was present in several locations in Central Africa in the 1960s and 1970s [254]. Scientists have looked into the genetic material of related primates of humans and discovered the Simian Immuno-deficiency Virus (SIV) in chimpanzees in 1989 [92]. They have analyzed more than 7000 fecal samples from chimpanzees from 90 different field sites,

where they found SIV and then confirmed that chimpanzees were the reservoir host for SIV through mitochondrial Deoxyribonucleic acid (DNA) sequencing. Sequencing analysis of HIV and SIV found that these two viruses are highly related [184].

HIV started crossing over from primates to humans multiple times in the early parts of the 20^{th} century [206]. Four cross-overs happened from chimpanzees and gorillas creating strain HIV-1. Eight cross-overs happened from sooty mangabeys creating strain HIV-2. The *cut hunter* hypothesis is one of the most widely accepted hypotheses on how HIV crossed over to humans [191, 158, 135]. This theory suggests that the crossover happened through exposure to chimpanzee blood, or other bodily fluids through bush-meat hunting. Calculations suggest that in the second decade of the 20^{th} century, there were less than 10 people infected by SIV [178]. The population growth in Kinshasa (formerly known as Leopoldville) located in the Democratic Republic of Congo likely contributed to the spread of HIV [78].

In the late 1960s, Haitian physicians came to the Democratic Republic of Congo (known as the Belgian Congo until 1960) to help treat patients and it is suspected that they brought back HIV with them to Haiti [255], which then spread to New York and California in the early 70s.

3.2 The biology and epidemiology of HIV

In the first half of the 20^{th} century, HIV crossed over from primates multiple times creating two main strains and several groups. The first strain HIV-1 came from SIVcpz (cpz: chimpanzee). It is very diverse genetically and has four groups: M (Main) is the most common and accounts for more than 99% of all HIV-1 infections and is further divided into 9 subtypes [134], while the O (Outlier) group has less than 1% of all HIV-1 infections and is limited to Cameroon, Gabon and neigbouring countries [72]. Two other groups P and N are rare and together infect about 15 individuals in Cameroon [236]. The second strain HIV-2 came from SIVsmm and is not common [64].

HIV belongs to the genus lentivirus within the family of retroviruses [33]. A retrovirus is an Ribonucleic Acid (RNA) virus that inserts a copy of its genome into the DNA of the host that it is invading [39]. A lentivirus is a genus of retroviruses that causes illnesses characterized by long incubation periods [163]. HIV can be transmitted through sexual intercourse (anal and vaginal), drug injection and sharing needles and from mother to child [241]. Once HIV enters the host, it attacks CD4 cells found within the immune system. Those cells are responsible for helping the body fight infections.

In the earliest stage of infection, a patient would experience flu-like symptoms ranging in severity. This stage is known as the acute phase. During the acute phase, the presence of virus particles in the bloodstream can be as high as 10^6 virions per milliliter of blood [53]. Within 4 weeks, the patient moves to the chronic phase characterized by no symptoms shown. This phase can last up to 10 years [89]. During this phase, the viral load decreases and reaches asymptotically a stable value called the Set-Point Viral Load (SPVL) [89]. The only way to detect the virus is through testing. Finally, the immune system collapses and the patient enters the last and final phase known as Acquired Immuno-Deficiency Syndrome (AIDS) where they become susceptible to opportunistic illnesses leading to death. This phase can last up to 3 years [155, 186].

About 39 million individuals worldwide live with HIV and there are about 2 million new infections every year [173]. In Canada, there have been a cumulative of 84,409 cases since 1985 and the incidence rate in 2016 was 6.4 cases per 100,000 (an increase from 5.4 cases per 100,000 since 2015) [35]. The GbMSM population represents about 44.1% of total cases reported in Canada.

3.3 HIV in MSM communities

HIV in the GbMSM community was first reported in the *Morbidity and Mortality Weekly Report* on the 5^{th} day of June of 1981, titled: "Pneumocystis Pneumonia - Los Angeles". The first paragraph reads as follows:

> In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed Pneumocystis carinii pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

The rest of the article can be found here. The report mentioned that five young, otherwise healthy, homosexual men were diagnosed with Pneumocystis Pneumonia, a disease usually affecting immunosuppressed individuals. HIV was first labeled Gay Related Immune Deficiency (GRID). When it first emerged, it was thought that it only affected gay men [11, 240].

Prior to the HIV pandemic, there was a prevalence of bacterial Sexually Transmitted Infection (STI)s in the population and a survey found a strong connection between the lifetime number of sexual partners and the number of venereal infections in the population [62]. We now know that infection by one particular STI increases risks of infection by another one [28]. Dale O'Leary discusses other factors that favoured the transmission of HIV among the GbMSM population [169]. Early HIV models were limited in their knowledge of the transmission dynamics. In the next section, we present an early mathematical model of HIV

3.4 An early HIV model

We explore a basic HIV model from 1991 [138]. The model examines the uniqueness of the endemic equilibria in a heterogeneous population of homosexuals. As such the author divides the population into n sub-populations and each sub-population to three epidemiological classes as follows:

$$
\begin{aligned}
\frac{dx_i}{dt} &= U_i - \mu x_i - c_i x_i \sum_{j=1}^{n} \rho_{ij}\beta_{ij}\frac{y_i}{x_j + y_j}, \\
\frac{dy_i}{dt} &= -(k_i + \mu)y_i + c_i x_i \sum_{j=1}^{n} \rho_{ij}\beta_{ij}\frac{y_i}{x_j + y_j}, \quad (i = 1, \ldots, n) \\
\frac{dz_i}{dt} &= k_i y_i - \delta_i z_i,
\end{aligned}
\tag{3.1}
$$

where x_i is the number of susceptible individuals in sub-population i, y_i is the number of infected and infectious individuals in sub-population i and z_i is the number of individuals with severe AIDS symptoms. U_i is a recruitment rate to sub-population i. c_i is the average number of sexual partners per person in the ith sub-population per unit time. ρ_{ij} is the proportion of contacts of a person in sub-population i with persons in sub-population j. In their paper, the author uses proportionate mixing, i.e.

$$
\rho_{ij} = \frac{c_j(x_j + y_j)}{\sum_{k=1}^{n} c_k(x_k + y_k)}.
$$

At this point, we note that the author doesn't include z_i's in sexual partnership and transmission dynamics due to the fact that persons with severe AIDS symptoms are generally not involved in sexual acts. β_{ij} is the transmission rate between susceptible persons in sub-population i and infected persons in sub-population j. k_i is the transfer rate from y_i to z_i. μ is the mortality rate from all other sources except AIDS related. δ_i is the excess death rate due to AIDS related illnesses in sub-population i.

The author does not specify the characteristics that define each sub-population. Therefore, it is left out of the discussion. The main result in the study give conditions (depending exclusively on the model parameters) under which a unique endemic equilibrium exists. The case of two sub-populations is considered and it is shown that under certain conditions (by properly choosing the parameters), there can be at least three endemic equilibria. We present this case in here.

Let us consider the case of two sub-populations. The system of differential equations is given by 3.2.

$$\begin{aligned}
\frac{dx_1}{dt} &= U_1 - \mu x_1 - c_1 x_1 \Big(\rho_{11}\beta_{11}\frac{y_1}{x_1+y_1} + \rho_{12}\beta_{12}\frac{y_1}{x_2+y_2}\Big),\\
\frac{dy_1}{dt} &= -(k_1+\mu)y_1 + c_1 x_1 \Big(\rho_{11}\beta_{11}\frac{y_1}{x_1+y_1} + \rho_{12}\beta_{12}\frac{y_1}{x_2+y_2}\Big),\\
\frac{dz_1}{dt} &= k_1 y_1 - \delta_1 z_1,\\
\frac{dx_2}{dt} &= U_2 - \mu x_2 - c_2 x_2 \Big(\rho_{21}\beta_{21}\frac{y_2}{x_1+y_1} + \rho_{22}\beta_{22}\frac{y_2}{x_2+y_2}\Big),\\
\frac{dy_2}{dt} &= -(k_2+\mu)y_2 + c_2 x_2 \Big(\rho_{21}\beta_{21}\frac{y_2}{x_1+y_1} + \rho_{22}\beta_{22}\frac{y_2}{x_2+y_2}\Big),\\
\frac{dz_2}{dt} &= k_2 y_2 - \delta_2 z_2.
\end{aligned} \tag{3.2}$$

The variables z_1 and z_2 only appear in differential equations for $z_1^{'}$ and $z_2^{'}$, respectively. Therefore, we will omit them from the analysis. Note that the total population is not necessarily constant. The reduced system for analytical purpose is given by 3.3.

$$\begin{aligned}
\frac{dx_1}{dt} &= U_1 - \mu x_1 - c_1 x_1 \Big(\rho_{11}\beta_{11}\frac{y_1}{x_1+y_1} + \rho_{12}\beta_{12}\frac{y_1}{x_2+y_2}\Big),\\
\frac{dy_1}{dt} &= -(k_1+\mu)y_1 + c_1 x_1 \Big(\rho_{11}\beta_{11}\frac{y_1}{x_1+y_1} + \rho_{12}\beta_{12}\frac{y_1}{x_2+y_2}\Big),\\
\frac{dx_2}{dt} &= U_2 - \mu x_2 - c_2 x_2 \Big(\rho_{21}\beta_{21}\frac{y_2}{x_1+y_1} + \rho_{22}\beta_{22}\frac{y_2}{x_2+y_2}\Big),\\
\frac{dy_2}{dt} &= -(k_2+\mu)y_2 + c_2 x_2 \Big(\rho_{21}\beta_{21}\frac{y_2}{x_1+y_1} + \rho_{22}\beta_{22}\frac{y_2}{x_2+y_2}\Big).
\end{aligned} \tag{3.3}$$

Note that the model presented in the paper [138] considers standard incidence rates since we are dividing the number of infected individuals by the total number of (sexually active) persons in the appropriate sub-population. To prove the existence of at least three

(positive) endemic equilibria, the author proceeds by defining a new system equivalent to 3.3 and is given by 3.4.

$$\begin{aligned}
\frac{d\nu_1}{dt} &= -\mu\nu_1 + k_1 y_1, \\
\frac{dy_1}{dt} &= -(k_1+\mu)y_1 + c_1(U_1 - \mu\nu_1 - \mu y_1)\frac{c_1\beta_{11}y_1 + c_2\beta_{12}y_2}{c_1(U_1-\mu\nu_1)+c_2(U_2-\mu\nu_2)}, \\
\frac{d\nu_2}{dt} &= -\mu\nu_2 + k_2 y_2, \\
\frac{dy_2}{dt} &= -(k_2+\mu)y_2 + c_2(U_2 - \mu\nu_2 - \mu y_2)\frac{c_1\beta_{21}y_1 + c_2\beta_{22}y_2}{c_1(U_1-\mu\nu_1)+c_2(U_2-\mu\nu_2)},
\end{aligned} \tag{3.4}$$

where $\nu_i = \frac{U_i}{\mu} - x_i - y_i$. Note that the disease free equilibrium for 3.3: $(\frac{U_1}{\mu}, 0, \frac{U_2}{\mu}, 0)$ is equivalent to the disease free equilibrium 3.4: $(0,0,0,0)$. Next, define the following matrices:

$$K = \begin{bmatrix} k_1 & 0 \\ 0 & k_2 \end{bmatrix}, \quad L = \frac{1}{c_1U_1 + c_2U_2}\begin{bmatrix} c_1^2U_1\beta_{11} & c_1c_2U_1\beta_{12} \\ c_1c_2\beta_{21}U_2 & c_2^2U_2\beta_{22} \end{bmatrix}, \quad A(\mu) = -K - \mu E + L,$$

where E is the 2×2 identity matrix. The Jacobian of system 3.4 at the disease free equilibrium is given by:

$$J_0 = \begin{bmatrix} -\mu E & K \\ 0 & A(\mu) \end{bmatrix} = \begin{bmatrix} -\mu & 0 & k_1 & 0 \\ 0 & -\mu & 0 & k_2 \\ 0 & 0 & A(\mu)_{11} & A(\mu)_{12} \\ 0 & 0 & A(\mu)_{21} & A(\mu)_{22} \end{bmatrix}.$$

Thus, the disease free equilibrium is stable if the eigenvalues of $A(\mu)$ both have negative real parts. At this point, the author assumes the existence of μ_0 such that $s(A(\mu_0)) = 0$, where $s(A)$ denotes the maximum value of the real part of all eigenvalues of A. For $\mu < \mu_0$, $s(A(\mu)) > 0$ (disease free equilibrium unstable) and conversely for $\mu > \mu_0$, $s(A(\mu)) < 0$ (disease free equilibrium stable). The author presents results from other studies [45, 46] to define multiple conditions, using different lemmas, under which the (positive) endemic

equilibrium is unique. However, for the main result, i.e. the case where there exist at least three positive endemic equilibria, they present a counter example. They first define all transmission rates in terms of a parameter ϵ as follows (with the condition that $0 < \epsilon < \frac{1}{3}$):

$$\begin{aligned}
\beta_{12} &= \frac{3}{\epsilon}, \\
\beta_{11} &= 3(3-\epsilon) - \epsilon\beta_{12}, \\
\beta_{22} &= \frac{9}{4}, \\
\beta_{21} &= \frac{3\epsilon(3-\epsilon)}{4-3\epsilon} - \epsilon\beta_{22}.
\end{aligned} \tag{3.5}$$

They also, for simplicity, let $U_i = k_i = c_i = 1$ and $\mu = \frac{1}{2}$. A lemma is used to state that the number of positive endemic equilibria for the model in 3.4 (or equivalently 3.3), is equal to the number of equilibria for an auxiliary system of differential equations, given by:

$$\begin{aligned}
\frac{dy_1}{dt} &= -\frac{3}{2}y_1 + \left(1 - \frac{3}{2}y_1\right)\frac{\beta_{11}y_1 + \beta_{12}}{(1-y_1)+(1-y_2)}, \\
\frac{dy_2}{dt} &= -\frac{3}{2}y_2 + \left(1 - \frac{3}{2}y_2\right)\frac{\beta_{21}y_1 + \beta_{22}}{(1-y_1)+(1-y_2)},
\end{aligned} \tag{3.6}$$

where $y_1 \in (0, \frac{2}{3})$ and $y_2 \in (0, \frac{2}{3})$. We would like to point out that y_1 and y_2 in 3.6 are not exactly the same as y_1 and y_2 in 3.3. The region G defined by the intervals for y_1 and y_2 is required for the lemma to work. It suffices to show, at this point, that 3.6 has at least three positive equilibria on G. The author shows that $y^* = (\frac{1}{2}, \frac{\epsilon}{2})$ is an equilibrium and then proves that there are two other positive equilibria $\overline{y}$ and $\hat{y}$ such that:

$$0 < \hat{y} < y^*, \qquad y^* < \overline{y} < \left(\frac{2}{3}, \frac{2}{3}\right).$$

In this case, $\overline{p} < \overline{q}$ if all the components of $\overline{p}$ are strictly less than all the components of $\overline{q}$. Using the concept of cooperative functions and properties of monotone flows, the author shows that y^* is a repellor, where as $\overline{y}$ and $\hat{y}$ are both attractors.

The value of this study lies in the fact that the transmission of HIV in a heterogeneous population of homosexuals can lead to different endemic equilibria and thus it can be difficult to predict future outcomes. This study is theoretical and requires data to estimate model parameters to get realistic/applicable results. Moreover, the understanding of HIV has evolved over the past three decades and thus at this point, HIV models add a lot more complexity such as individuals who are treated and who no longer transmit the virus [258], or the use of prophylactic measures (other than condoms) such as PrEP. The next chapter discusses PrEP in more details, including its awareness, usage and some of consequences of its usage.

Chapter 4

The Impact of Pre-exposure Prophylaxis for Human Immunodeficiency Virus on Gonorrhea Prevalence

4.1 Publication record

This chapter is based on the paper "*The Impact of Pre-exposure Prophylaxis for Human Immunodeficiency Virus on Gonorrhea Prevalence*", submitted to the Bulletin of Mathematical Biology on the 20^{th} day of August in 2019 and was published on the 1^{st} day of July in 2020 (volume 82, issue 7, pages 1-19).

- Model conceptualization: Joe Pharaon and Chris Bauch.
- Model analysis: Joe Pharaon.
- Manuscript write up: Joe Pharaon and Chris Bauch.

- Edits and Revisions: Joe Pharaon and Chris Bauch.

4.2 Abstract

PrEP has been shown to be highly effective in reducing the risk of HIV infection in GbMSM. However, PrEP does not protect against other STI. In some populations, PrEP has also led to riskier behaviour such as reduced condom usage, with the result that the prevalence of bacterial STIs like Gonorrhea (GC) has increased. Here we develop a compartmental model of the transmission of HIV and GC, and the impacts of PrEP, condom usage, STI testing frequency and potential changes in sexual risk behaviour stemming from the introduction of PrEP in a population of GbMSM. We find that introducing PrEP causes an increase in GC prevalence for a wide range of parameter values, including at the current recommended frequency of STI testing once every three months for individuals on PrEP. Moreover, the model predicts that a higher STI testing frequency alone is not enough to prevent a rise in GC prevalence, unless the testing frequency is increased to impractical levels. However, testing every two months in combination with a 10–25 % reduction in risky behaviour by individuals on PrEP would maintain GC prevalence at pre-PrEP levels. The results emphasize that programs making PrEP more available should be accompanied by efforts to support condom usage and frequent STI testing, in order to avoid an increase in the prevalence of GC and other bacterial STIs.

4.3 An overview of HIV in GbMSM communities

Sexually transmitted infections have long been a public-health concern in the GbMSM community, especially since the sexual liberation movement and the emergence of sex clubs and bath houses in the late 1970s [216, 29]. At around the same time, HIV started spreading and the first cases were recorded. HIV patients progressed to AIDS and subsequently died. An AIDS pandemic began in the 1980s. The origins of HIV are still debated in the scientific community and multiple theories have been laid out [92, 191]. Nevertheless, it is a virus that disproportionately affects sexually active gay and bisexual men in Canada and North America.

HIV has two main types (1 and 2) and several subtypes [191]. The strain that affects most gay and bisexual men is type 1 subtype B [30]. HIV is a retrovirus—a complex group of enveloped RNA viruses with common features, including higher mutation rates [54]—thus making it difficult to cure with antiviral drugs [141]. As the pandemic accelerated, research began to understand the modes of transmission. HIV virus particles (known as virions) are mainly found in pre-ejaculatory fluid and semen and are transmitted through anal intercourse and oral sex [197]. For a long time, condoms have been identified as the main tool for HIV prevention. Condoms lower the transmission risk of HIV by 60% to 90% [182, 245].

Testing for HIV became available in 1985 [47]. Public health agencies and physicians recommend frequent testing, especially for highly sexually active individuals. If an individual tests positive for HIV, they initiate Higly Active Anti-Retroviral Therapy (HAART), which consists in taking a daily regimen of several pharmaceutical drugs to bring viral loads to undetectable levels: lower than 50 copies of virus particles per milliliter of blood. Once the patient achieves undetectable status, they can no longer transmit the virus [258].

Other STIs such as GC, Syphilis and Chlamydia are also mainly transmitted through anal intercourse and oral sex. The three aforementioned diseases are bacterial and are usually treated with antibiotics [253]. However, if they are not diagnosed in their early

stages, they can lead to complications resulting in severe health issues [225]. Condoms also act as a prophylactic measure against them. Individuals can be co-infected by HIV and other STIs [123]. If an individual is already infected by one STI, it is easier to contract another STI. GC is becoming resistant to antibiotics [225] and drug-resistant GC is becoming a public health concern.

In recent years, a treatment protocol based on antiviral drugs called PrEP has been implemented, and has been shown to strongly reduce the transmission of HIV [177, 120]. Recent studies have shown that PrEP efficacy exceeds 90% [147]. However, PrEP doesn't protect against other STIs, such as GC. Studies have associated the use of PrEP with an increase in risky sexual behaviour (such as reduced condom usage) [239, 2, 129] as well as an increase in bacterial STIs including GC [231]. Physicians or nurse practitioners prescribe PrEP in intervals of three months. Before renewing a prescription, the patient has to get tested negative for STIs (including HIV). PrEP is currently on the market and is being prescribed to individuals deemed at risk, as determined by their sex practices. It is covered by most health-insurance companies and provincial and federal governments [118].

HIV transmission and the impact of interventions such as antiviral drugs, condoms, and hypothetical vaccines have been a frequent topic of mathematical modelling efforts [205, 139, 188, 210, 233, 232, 247, 217]. A few of these models have also considered interactions between HIV and other infections, such as the effects of tuberculosis co-infection with HIV [205]. Mathematical models can be useful for anticipating undesirable dynamics that emerge in the wake of infectious disease interventions, and how to best counter them, such as exemplified by increases in congenital rubella syndrome incidence under certain rubella vaccination policies [93]. The observed increase in GC due to use of PrEP in some populations is another example of an undesirable side effect of increased PrEP recruitment. Here, we develop a model of HIV and GC transmission in a population of GbMSM, including STI testing, condom usage, and PrEP adoption. The model is parameterized with data from Canadian and United States GbMSM populations. We use the model to study the relationship between STI testing frequency and GC prevalence after the introduction of PrEP, with a particular focus on how much STI testing frequency needs to be increased

in order to counter a potential rise in GC due to reduced condom usage among individuals taking PrEP. Given the challenges in increasing condom usage in the GbMSM community in the PrEP era, [108, 231, 260, 157] we also seek strategies that can maintain GC prevalence at pre-PrEP levels by combining more frequency testing with a smaller (and thus more achievable) increase in condom usage acting in synergy. The model is described in the following section, followed by the results and finally a discussion section.

4.4 Constructing the model and its parametrization

We introduce a system of ODEs that describes the spread of HIV and GC in the presence of a PrEP regimen in a population of gay and bisexual men. The population is divided into eight compartments and each individual can belong to only one compartment at a time. The compartments and the possible transfers between them appear in Fig 4.1.

$S(t)$ represents the proportion of individuals who are susceptible to HIV and GC infection but are not on PrEP. $P(t)$ represents the proportion of individuals who are both susceptible to GC infection and are also on PrEP. We assume that PrEP users strongly adhere to the regimen recommended by their physicians. The most popular recommended dosage is a daily pill of Tenofovir(TDF)/Emtricitabine(FTC). Studies have shown that strong adherence reduces the transmission of HIV by 94% [147, 218]. A more recent study of HIV transmission among serodiscordant couples (an HIV negative individual in a partnership with an HIV positive individual) has shown 0 cases of transmission when PrEP was administered as recommended [196]. We therefore assume that strong adherence prevents the transmission of HIV. We furthermore assume that PrEP patients stay on PrEP and do not discontinue its use.

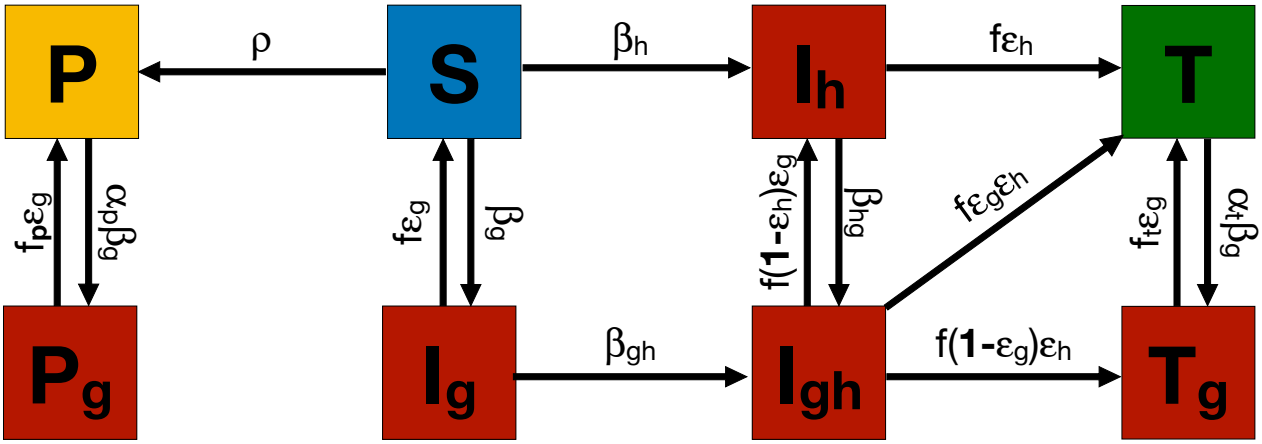

Figure 4.1: Diagram representing model structure. The eight compartments represent possible infection and treatment status for HIV and GC, while arrows represent transfers between those states. See main text and Table 4.1 for definitions of variables and parameters.

$P_g(t)$ is the proportion of individuals who are infected by GC while on PrEP. They can recover when they test positive for GC and start medication with efficacy ϵ_g. $I_g(t)$ represents the proportion of individuals who are infected by GC only. $I_h(t)$ is the proportion of individuals who are infected by HIV only. $I_{gh}(t)$ represents the proportion of individuals who are infected by both HIV and GC. Even though simultaneous co-infection is a possible outcome of a sexual act, we will neglect this outcome and assume that individuals are first infected by one pathogen, and then independently infected by the other.

$T(t)$ represents the proportion of individuals who are on treatment for HIV infection. Individuals who are on an HIV treatment protocol do not transmit HIV [258]. They can, however, contract GC and move to the $T_g(t)$ class. We assume that individuals infected by HIV do not progress to AIDS due to the availability of HIV medication provided by governments and the fact that it can take up to 10 years for HIV to progress into AIDS

[185]. The system of differential equations describing the transfers between these eight compartments is:

$$
\begin{aligned}
\frac{dS}{dt} &= \mu - \delta S - \rho S - \beta_h S(I_h + I_{gh}) - \beta_g S(I_g + I_{gh} + P_g + T_g) + f\epsilon_g I_g. \\
\frac{dP}{dt} &= \rho S - \delta P - \alpha_p \beta_g P(I_g + T_g + P_g + I_{gh}) + f_p \epsilon_g P_g. \\
\frac{dP_g}{dt} &= \alpha_p \beta_g P(I_g + T_g + P_g + I_{gh}) - \delta P_g - f_p \epsilon_g P_g. \\
\frac{dI_g}{dt} &= \beta_g S(I_g + I_{gh} + P_g + T_g) - \delta I_g - f\epsilon_g I_g - \beta_{gh} I_g(I_h + I_{gh}). \\
\frac{dI_h}{dt} &= \beta_h S(I_h + I_{gh}) - \beta_{hg} I_h(I_{gh} + P_g + T_g + I_g) - \delta I_h - f\epsilon_h I_h + f(1-\epsilon_h)\epsilon_g I_{gh}. \\
\frac{dI_{gh}}{dt} &= \beta_{gh} I_g(I_h + I_{gh}) - \delta I_{gh} + \beta_{hg} I_h(I_{gh} + P_g + T_g + I_g) - f\epsilon_g\epsilon_h I_{gh} \\
&\quad - f(1-\epsilon_g)\epsilon_h I_{gh} - f(1-\epsilon_h)\epsilon_g I_{gh}. \\
\frac{dT}{dt} &= f\epsilon_h I_h - \delta T - \alpha_t \beta_g T(I_g + I_{gh} + T_g + P_g) + f_t \epsilon_g T_g + f\epsilon_g\epsilon_h I_{gh}. \\
\frac{dT_g}{dt} &= \alpha_t \beta_g T(I_g + I_{gh} + T_g + P_g) - f_t \epsilon_g T_g - \delta T_g + f(1-\epsilon_g)\epsilon_h I_{gh},
\end{aligned}
\tag{4.1}
$$

where the parameter values are defined in Table 4.1. We note that these equations ostensibly represent a mass-action incidence assumption, where individuals mix homogeneously in the population and infection risk βI is proportional to the number of infected individuals. However, the standard incidence assumption $\beta I/N$ [204] is arguably more realistic for sexually transmitted infections in most settings, since infection risk is better approximated as depending on the proportion of infected personal contacts. In our model, the population size is constant and an individual's infection status does not influence their mortality rate. Hence, standard incidence and mass-action incidence are formally identical (related only by a scaling constant) since $\beta S\frac{I}{N} \equiv \beta_0 SI$ where $\beta_0 = \beta/N$.

Five parameters (ρ,α_p,α_t,β_g and β_h) were fitted to empirical values of disease prevalence to generate the baseline parameter values listed in Table 4.1 (all parameters that represent time rates are in units of per day, unless otherwise specified). The calibration process was carried out in two steps. The first step sets $\rho = \alpha_p = 0$ and $P(0) = P_g(0) = 0$. HIV

Parameter	Description	Value (per day)	Reference
β_h	Transmission rate of HIV	0.001275	Calibrated
β_g	Transmission rate of GC	0.001475	Calibrated
α_p	GC transmission risk factor for PrEP users	12.75	Calibrated
α_t	GC transmission risk factor for HART patients	3.875	Calibrated
β_{hg}	Transmission rate of GC with HIV infection	$3\beta_g$	[175]
β_{gh}	Transmission rate of HIV with GC infection	$3\beta_h$	[175]
ρ	PrEP recruitment rate	0.000002375	Calibrated
δ	Natural death rate	1/20075	Assumed
μ	Migration rate	1/20075	Assumed
f	Testing frequency for HIV/GC	0.54/365	[153]
f_p	Testing frequency for HIV/GC for PrEP users	1/90	[224]
f_t	Testing frequency for HIV/GC for HAART patients	1/180	Assumed
ϵ_h	Efficacy of HAART treatment	0.9 (unitless)	[209]
ϵ_g	Efficacy of GC treatment	0.83 (unitless)	[104, 213]

Table 4.1: Baseline parameter values. The assumed values of δ and μ are based on an average lifespan of 50 years. The parameters β_h and β_g and α_t were first calibrated neglecting all parameters and variables related to PrEP. Finally, α_p and ρ were calibrated.

prevalence in Canada among Men who have Sex with Men (MSM) is roughly 19%. This number was obtained after weighing the prevalence of HIV in the main three metropolitan cities in Canada: Toronto, Vancouver and Montreal [85, 222]. Therefore, at equilibrium, we set $I_h + I_{gh} + T + T_g = 0.19$. The same studies reported that roughly two-thirds of HIV-positive individuals are on HAART, and therefore we set $I_h + I_{gh} = 0.06$ and $T + T_g = 0.13$. We note that estimates of HIV prevalence are subject to a significant degree of statistical uncertainty and that our quantitative model projections could change under different assumptions for HIV prevalence.

GC prevalence in MSM populations was more difficult to obtain, mostly due to disease surveillance being performed at the level of the general population (i.e., not specific to MSM). However a clinical study in California [125] reported that 15% of patients visiting a sexual health clinic were infected by GC. At equilibrium, we set $I_g + I_{gh} + T_g = 0.15$. The study also filters GC infection by HIV status. Taking into account only HIV negative individuals (we discarded unknown HIV status), we obtained, at equilibrium $I_g = 0.10$. We are left with $I_{gh} + T_g = 0.05$. Finally, at equilibrium $S = 1 - 0.19 - 0.1 = 0.71$.

We first identified a region of parameter space in α_t, β_h, and β_g where the model equilibrium values were close to target data. As a result the parameter ranges were narrowed down to $\alpha_t \in [3, 4]$, $\beta_h \in [0.0012, 0.0014]$, and $\beta_g \in [0.0014, 0.0016]$. We then conducted a three-dimensional grid sweep across these ranges. We used the method of least-square error to identify a single set of parameter values for α_t, β_h, and β_g for our baseline analysis. This involved determining which parameter combination of α_t, β_h, and β_g in the grid sweep resulted in the smallest value of the squared difference between the model equilibrium value and the target data value. The grid sweep was performed in MATLAB using ODE45. We also tested the model with other solvers (ODE23S, ODE15S) and obtained very similar results. Initial conditions (aside from P and P_g) were randomly selected, since our focus was on equilibrium values.

We are left with calibrating ρ and α_p. We started by replacing $S = 0.71$ by $S+P = 0.71$ at equilibrium. We have also replaced $I_g+I_{gh}+T_g = 0.15$ by $I_g+I_{gh}+T_g+P_g = 0.15$ and $I_g =$

0.1 by $I_g + P_g = 0.1$. Current estimates of PrEP users average to 5% [192, 160, 106, 97, 176]. Therefore, we added $P + P_g = 0.05$. When calibrating ρ and α_p, we fixed the previously found baseline values for $\alpha_t = 3.875$, $\beta_g = 0.001475$ and $\beta_h = 0.001275$. The baseline parameter values appear in Table 4.1.

In addition to the calibration of parameters, we perform a univariate parameter sensitivity analysis. The results are added to the appendix and, in most parts, show sensitivity of outcomes (Gonorrhea infections) with respect to parameters due to high correlation factors. In the case of f, β_h and β_g, there are sub-intervals in the range where the outcomes are not sensitive to, in particular there would be zero prevalence at equilibrium.

4.5 Increasing PrEP recruitment rate increases Gonorrhea prevalence.

While PrEP prevents the transmission of HIV, it is ineffective against other STIs. Therefore, we examined the equilibrium prevalence of GC ($I_g + I_{gh} + P_g + T_g$) for different rates of PrEP recruitment. In particular, we were interested in optimal combinations of testing frequency for PrEP users (f_p), and condom use or other preventive strategies (α_p) in order to minimize the prevalence of GC.

We ran a two dimensional grid 101×101 of values for f_p ranging from 0.001 (testing roughly once every 3 years) to 0.04 (testing once every 25 days), and for α_p ranging from 0.0 (abstinence from sex, very high condom use or any other preventive strategy) to 20.0 (less precautions, lower condom use). We conducted this simulation for 4 different values of ρ: 0.0 (no PrEP recruitment), 2.375×10^{-6} (baseline value), 3.562×10^{-6} (50% higher than baseline value) and 1.1875×10^{-5} (5 times higher than baseline value).

For the baseline parameter value of PrEP recruitment (Fig 4.2a), we observe that an increase in risky behaviour (α_p) causes a significant increase in GC prevalence. For example, a decline in condom usage sufficient to cause an almost 13-fold increase in the

transmission rate (corresponding to an increase of α_p from 1 to 12.75) causes an increase in GC prevalence by approximately 60%. On the other hand, an increase in the testing frequency (f_p) causes a decrease in GC prevalence (for α_p unchanged). This happens due to the fact that more frequent testing implies less window for transmission. Lines of constant GC prevalence run approximately linearly across the parameter plane, such that the baseline increase in α_p would need to be accompanied by an increase in f_p far in excess of 0.04

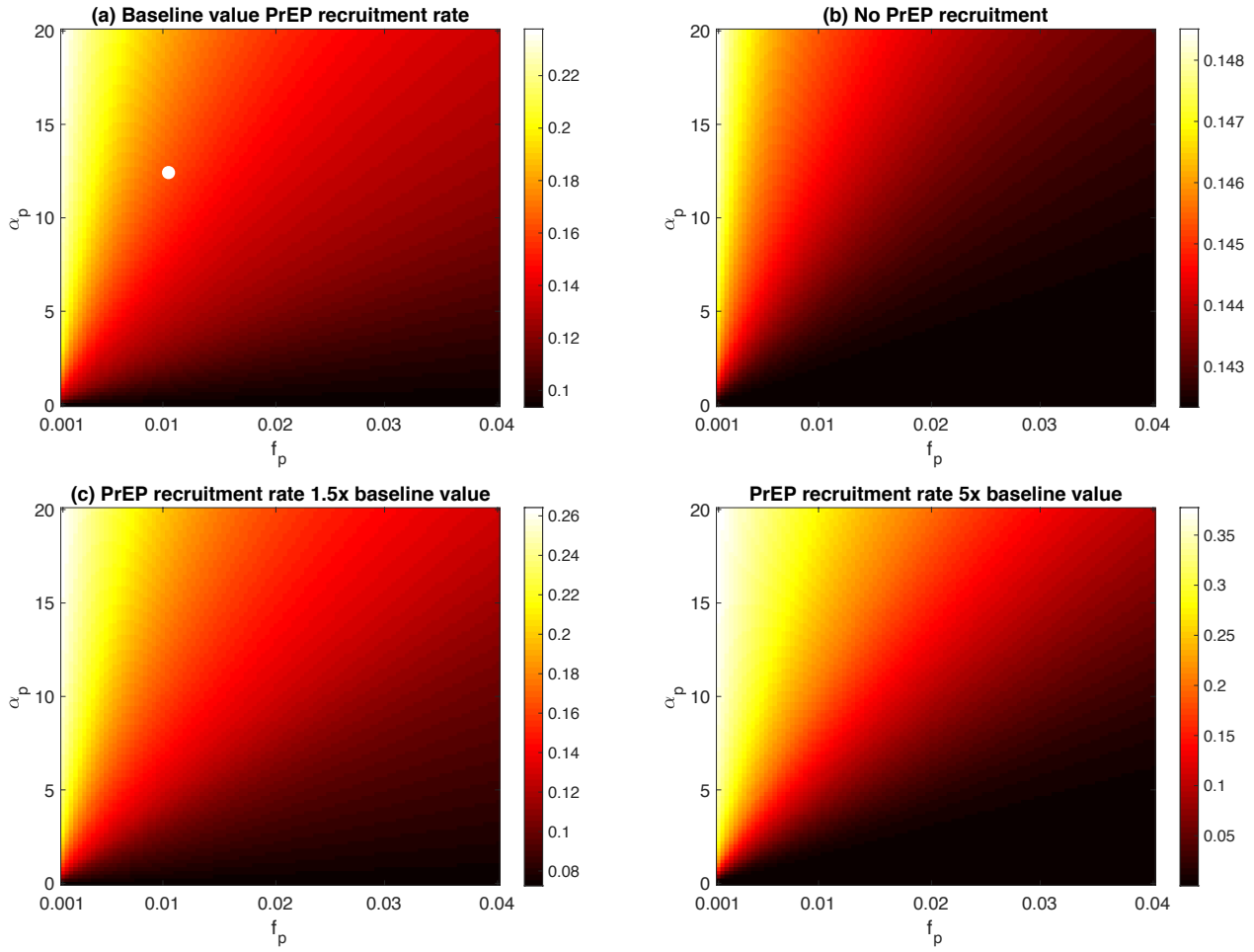

Figure 4.2: Gonorrhea prevalence heatmaps. Testing frequency for PrEP users (f_p) and gonorrhea transmission risk factor for PrEP users (α_p) are varied and all other parameters are held at baseline values. Different values of PrEP recruitment rate (ρ) are considered. **(a)** PrEP recruitment rate baseline value: $\rho = 2.375 \times 10^{-6}$. The white dot locates baseline values for α_p and f_p. **(b)** No PreP recruitment: $\rho = 0.0$. **(c)** PrEP recruitment rate 50% greater than baseline value: $\rho = 3.562 \times 10^{-6}$. **(d)** PrEP recruitment rate 5 times greater than baseline value: $\rho = 1.1875 \times 10^{-5}$. Black regions represent regions of lower gonorrhea prevalence. Yellow regions represent regions of higher gonorrhea prevalence. Note the difference in the ranges of the colour bars.

(testing every 25 days). Unfortunately, this suggests that an increase in GC prevalence in a population where PrEP is widespread is very difficult to prevent, for realistic testing intervals.

When $\rho = 0$ (no PrEP recruitment, Fig 4.2b), we observe a slight variation of about 0.5% in the prevalence of GC in the (f_p, α_p) plane, as expected (note the range of the colour bar of subpanel 2b). This is due to the fact that we have chosen non-zero initial conditions for P and P_g. In particular, we have set $P(0) = 0.08$ and $P_g(0) = 0.02$. We have examined the case when $P(0) = P_g(0) = \rho = 0$ and there was no variation in the levels of GC in the population.

With information propagating through social media and awareness campaigns, more individuals are becoming aware of PrEP and its efficacy in HIV prevention. We suspect that the PrEP recruitment rate will be on the rise within the next decade. We have therefore investigated scenarios where the recruitment rate is increased by 50% from the baseline value (Fig 4.2c) and is 5 times higher than the baseline value (Fig 4.2d). This inevitable increase in ρ can be potentially problematic since greater increases in the prevalence of GC are observed for higher values of ρ. For instance, when ρ is 5 times larger than the baseline value, GC levels can reach 35% of the entire population if no precautions are carefully taken into account (yellow regions in Fig 4.2c,d).

On the other hand, this increase in the recruitment rate offers a wider area in the (f_p, α_p) parameter plane where GC prevalence remains low (compare black regions in Fig 4.2c and Fig 4.2d). In fact, under these scenarios of higher PrEP recruitment, the testing frequency does not need to be increased as much as under the baseline PrEP recruitment, in order for GC prevalence to remain unchanged. This flexibility allows for better control and the prevention of outbreaks. If α_p is too high, the focus would be on increasing the testing frequency to maintain sub-epidemic levels of GC in the population.

We also noticed a linear border between regions of higher and lower GC prevalence. The border separating yellow regions from red regions is much steeper than that separating red regions from black regions. This is an indication of the importance in maintaining a

minimum testing frequency to keep GC from infecting a greater proportion of the population.

4.6 Sufficiently frequent STI testing controls Gonorrhea prevalence.

Before starting a PrEP regimen, every individual needs to go through a series of tests. The individual should test negative for HIV as a first step to qualify. They also have to test for common STIs such as GC, chlamydia, and syphilis. If the results come back positive for any of the STIs, an anti-bacterial treatment is prescribed first, and pending recovery, PrEP qualification is revisited. Finally, testing the liver and kidney functions is also essential before starting PrEP. The pills can have damaging effects on the liver [226]. If ALT (alanine aminotransaminase) and AST (aspartate transaminase) levels are too high, a nurse practitioner (or a physician) recommends lowering the levels before starting PrEP.

Public-health agencies in Canada have set testing frequency for PrEP users to be once every three months [224]. This is standard follow up procedure and PrEP is only prescribed for three months only with no refills. A PrEP user needs to visit their physician and test negative for all STIs before they receive another three months prescription. Testing is usually subsidized by local governments or paid for by insurance companies (in the case of very specific tests). In this section, we examine several scenarios of testing frequency ranging from once every 2 months (more frequent than the current recommended frequency), twice per year, and once every 5 years. We run a 2-dimensional 101×101 grid sweep of the two parameters ρ and α_p. The parameter ρ ranges from 10^{-6} to 5×10^{-5}. The parameter α_p ranges from 0 to 20.

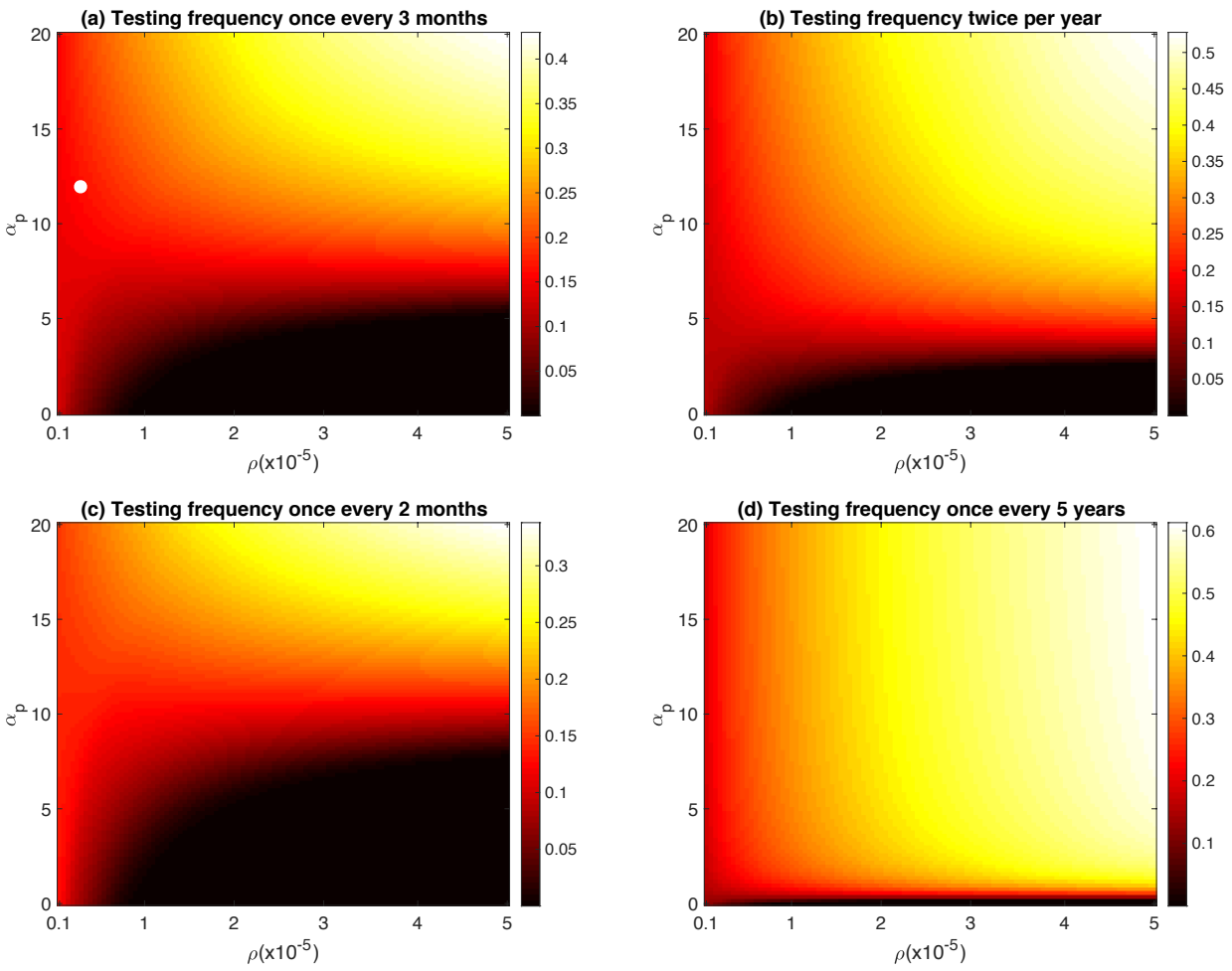

Figure 4.3: Gonorrhea prevalence heatmaps. PrEP recruitment rate (ρ) and gonorrhea transmission risk factor for PrEP users (α_p) are varied and all other parameters are held at baseline values. Different values of testing frequency for PrEP users (f_p) are considered. **(a)** Testing frequency once every three months (baseline value): $f_p = 1/90 \approx 0.0111$. The white dot locates baseline values for α_p and ρ. **(b)** Testing frequency twice every year: $f_p = 1/182 \approx 0.0055$. **(c)** Testing frequency once every two months: $f_p = 1/60 \approx 0.0167$. **(d)** Testing frequency once every 5 years: $f_p = 1/1825 \approx 0.0005$. Black regions represent regions of lower gonorrhea prevalence. Yellow regions represent regions of higher gonorrhea prevalence. Note the difference in vertical scale between the four subpanels.

The parameter planes illustrate that frequent testing is essential in order to maintain a lower prevalence of GC. GC infections can reach levels as high as 60% of the population when individuals on PrEP are tested only once every 5 years (Fig 4.3d) and 50% when tested twice every year (Fig 4.3b). Under both testing scenarios, black regions are very thin and therefore we would require extreme measures to control the propagation of the disease.

On the other hand, testing once every 2 months (Fig 4.3c) not only minimizes GC infections but allows for more flexibility in parameter combinations to maintain low GC prevalence. The black region in Fig 4.3c indicates that despite lower than necessary levels of condom use, we can still keep GC in control and prevent outbreaks at baseline PrEP recruitment, as long as risky behaviour does not increase too much under PrEP ($\alpha_p \lesssim 8$). However, more frequent testing may be cost prohibitive for ministries of health. Also, more frequent testing may reduce adherence since PrEP users would be required to visit their physician more often and do more blood work, in this case 6 times per year (versus 4 times per year under current recommendation).

The barrier between darker regions and lighter regions is nonlinear in these parameter planes. Moreover, the parameter planes show a region of rapid increase in GC prevalence as risky behaviour (α_p) increases from the pre-PrEP value to the baseline PrEP value of 12.8, for realistic testing frequencies. This shows that small increases in sexually risky behaviour may not change GC prevalence very much although a further increase could shift the system into a region where GC prevalence increases suddenly. Hence we expect that increases in GC prevalence under PrEP may be highly dependent on the population under consideration. Also, this emphasizes the importance of increasing the usage of preventive strategies such as condoms.

4.7 A 10–25 % decrease in risky behaviour on PrEP combined with increased testing frequency prevents gonorrhea prevalence from rising.

Figure 4.3 showed that reducing risk behaviour by 10—25% in individuals on PrEP in combination with an increase in testing frequency is sufficient to maintain GC prevalence at its pre-PrEP levels: the benefits of a reduction in risky behaviour act in synergy with an increase in the testing frequency. Our $\rho - f_p$ parameter planes (Fig 4.4) also reflect these observations. Here we constructed a 101×101 grid for ρ ranging from 10^{-6} to 5×10^{-5} and f_p ranging from 0.001 to 0.04 under four different scenarios for the value of α_p, representing the increase in risky behaviour after introduction of PrEP due to decreased condom usage, for instance. Recall that $\alpha_p = 1$ corresponds to no change in risky behaviour due to PrEP, while $\alpha_p > 1$ represents an increase in risky behaviour. $\alpha_p = 6.375$ represents an increase in condom use (or other preventive strategies) by 50% compared to the baseline value $\alpha_P = 12.8$, whereas $\alpha_p = 25.5$ represents a 50% decrease. $\alpha_p = 63.75$ represents a 5 times decrease in condom use.

For instance, GC prevalence decreases sharply for an intermediate range of values for the testing frequency f_p. Most importantly, the parameter planes show that a combination of decreasing risky behaviour through greater condom usage relatively to the baseline scenario, and changing testing frequency to once every two months (Fig 4.4b), can keep GC prevalence close to pre-PrEP levels. This is crucial since, as pointed out in the previous subsection, high frequency testing may be cost prohibitive and/or may incur low adherence rates. An interesting feature of Fig 4.4b is the switch of location of black regions from lower ρ and higher f_p values when α_p is greater than the baseline value to higher ρ and lower f_p values when α_p is lower than the baseline value (Figure 4.4a,b versus Figure 4.4c,d). This furthermore indicates that condom use can be very critical in determining optimal policies to reduce GC prevalence.

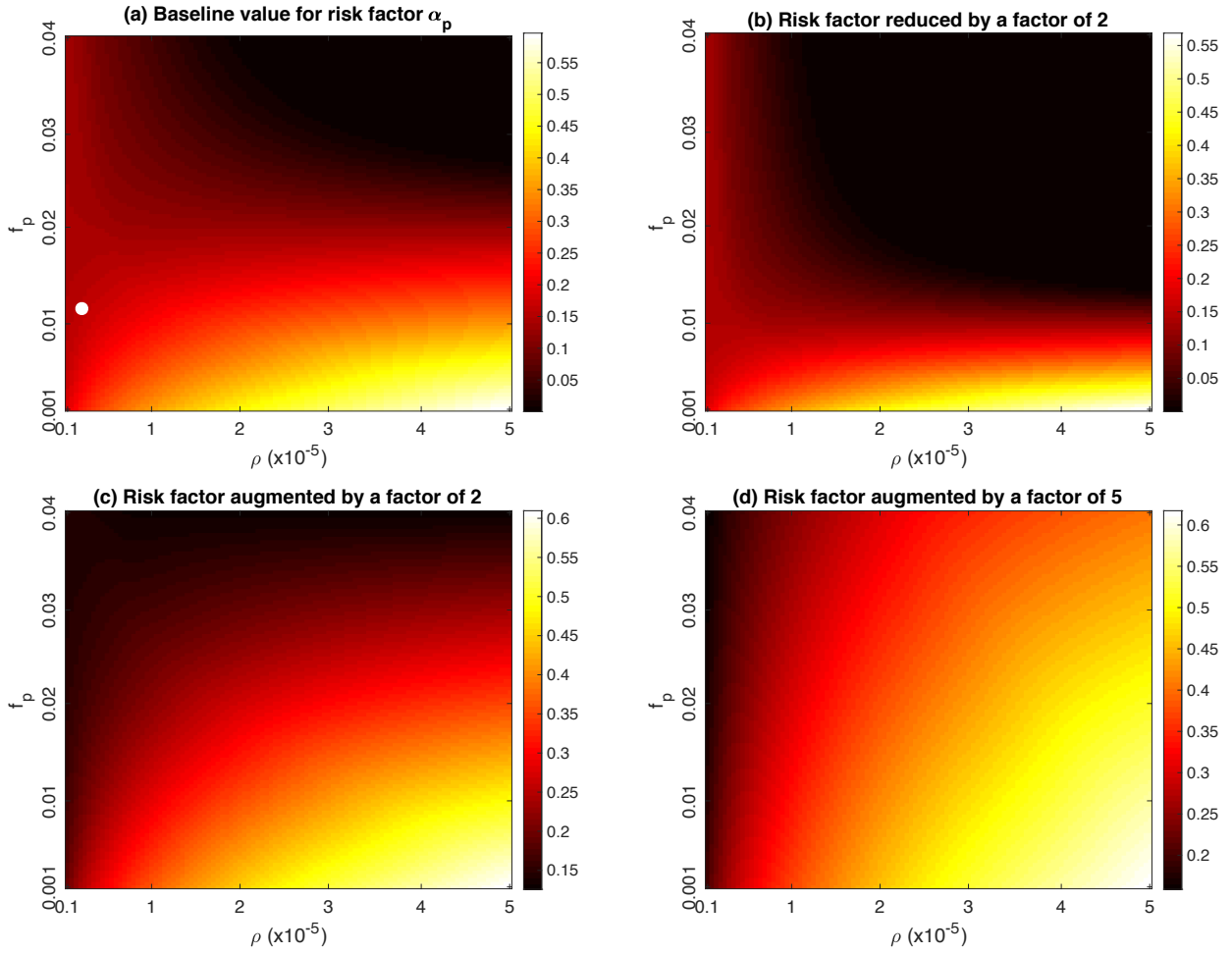

Figure 4.4: Gonorrhea prevalence heatmaps. PrEP recruitment rate (ρ) and testing frequency for PrEP users (f_p) are varied and all other parameters are held at baseline values. Different values of gonorrhea transmission risk factor for PrEP users (α_p) are considered. **(a)** gonorrhea transmission risk factor for PrEP users baseline value: $\alpha_p = 12.75$. The white dot locates baseline values for f_p and ρ. **(b)** gonorrhea transmission risk factor for PrEP users reduced by a factor of 2: $\alpha_p = 6.375$. **(c)** gonorrhea transmission risk factor for PrEP users augmented by a factor of 2: $\alpha_p = 25.5$. **(d)** gonorrhea transmission risk factor for PrEP users multiplied by 5: $\alpha_p = 63.75$. Black regions represent regions of lower gonorrhea prevalence. Yellow regions represent regions of higher gonorrhea prevalence. Note the difference in vertical scale between the four subpanels.

Contrariwise, very low rates of condom usage (high α_p, Fig 4.4c,d) result in very high prevalence of GC, unless the testing frequency is impractically high. Hence, condom use remains essential in the prevention of other transmitted STIs such as GC, despite increased STI testing frequency when individuals start PrEP.

4.8 A deeper look with time series analysis.

Time series indicate the temporal evolution of HIV and GC prevalence, showing that changes in prevalence unfold on different time scales depending on both the diseases and the intervention scenarios (Figs 4.5, 4.6). Upon the introduction of PrEP, HIV prevalence decreases exponentially from 4% to lower than 0.1% within 50 years, consistent with experience on the ground with PrEP programs (Fig 4.6a).

Exponential behaviour, as opposed to oscillatory behaviour, is also observed for GC. All simulations have resulted in a spike in GC followed by an exponential decrease to stable values (Fig 4.5,4.6). The values depend on the choice of social parameters. There are exceptions to this trend. When PrEP recruitment rate is five times greater than baseline value, GC prevalence increases steadily until it reaches a stable value of about 22% (Fig 4.5f). The baseline value for PrEP recruitment rate reflects the current trends in PrEP awareness. PrEP awareness is increasing with information being spread through social networks. Immediate decline in GC prevalence, despite current PrEP recruitment rate, is obtained when the efficacy of GC treatment is 100% (Fig 4.6f). The efficacy of treatment is related to early diagnosis and other biological factors. Interestingly, there is a situation under which we observe oscillatory behaviour in GC prevalence. If condom use is doubled for individuals who are treated for HIV, or if they get tested twice as often, GC prevalence oscillates (Fig 4.6d,e black curves).

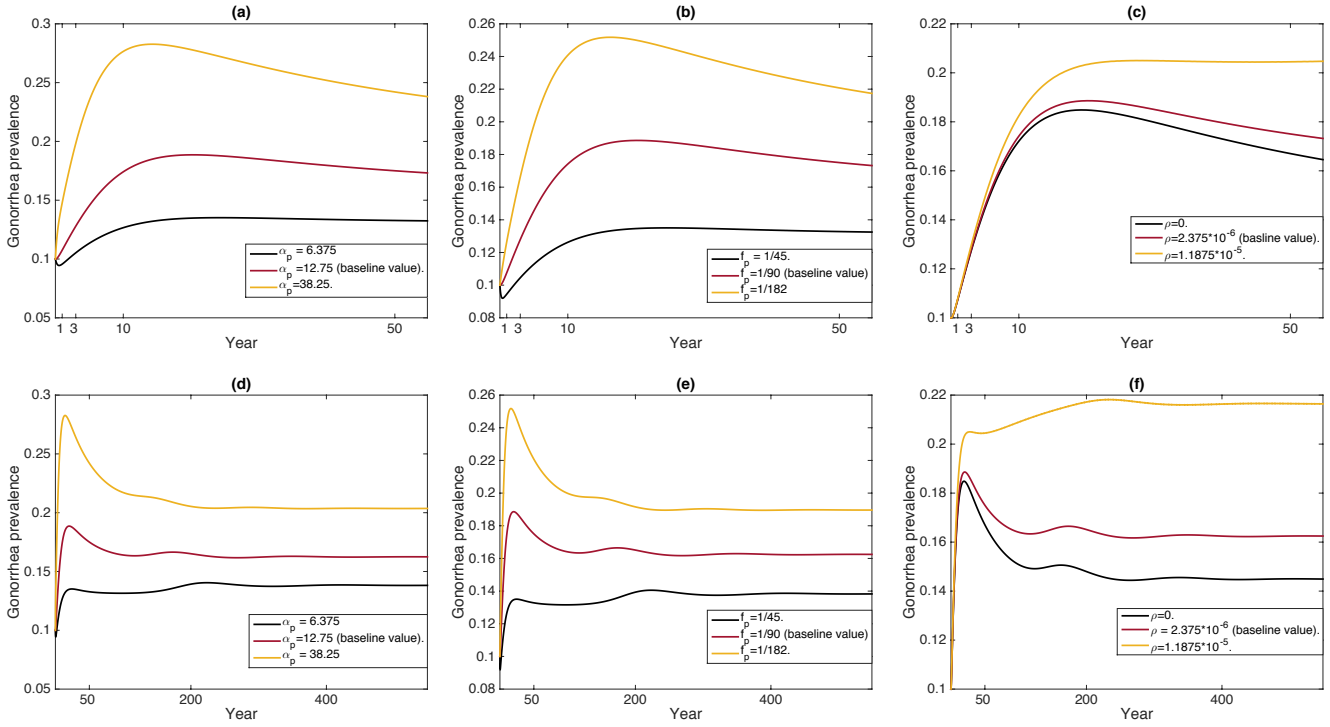

Figure 4.5: Time series of gonorrhea prevalence over different time scales. In each subfigure, all parameters but one are kept at baseline values. **(a,d)** gonorrhea transmission risk factor for PrEP users (α_p) is varied: baseline value in red (12.75), reduced by a factor of 2 in black (6.375), augmented by a factor of 3 in yellow (38.25). **(b,e)** Testing frequency for PrEP users (f_p) is varied: baseline value in red (1/90: once every three months), testing once every 1.5 months in black (1/45), testing twice per year in yellow (1/182). **(c,f)** PrEP recruitment rate (ρ) is varied: baseline value in red (2.375×10^{-6}), No PrEP recruitment in black (0), PrEP recruitment rate 5 times greater than baseline value in yellow (1.1875×10^{-5}).

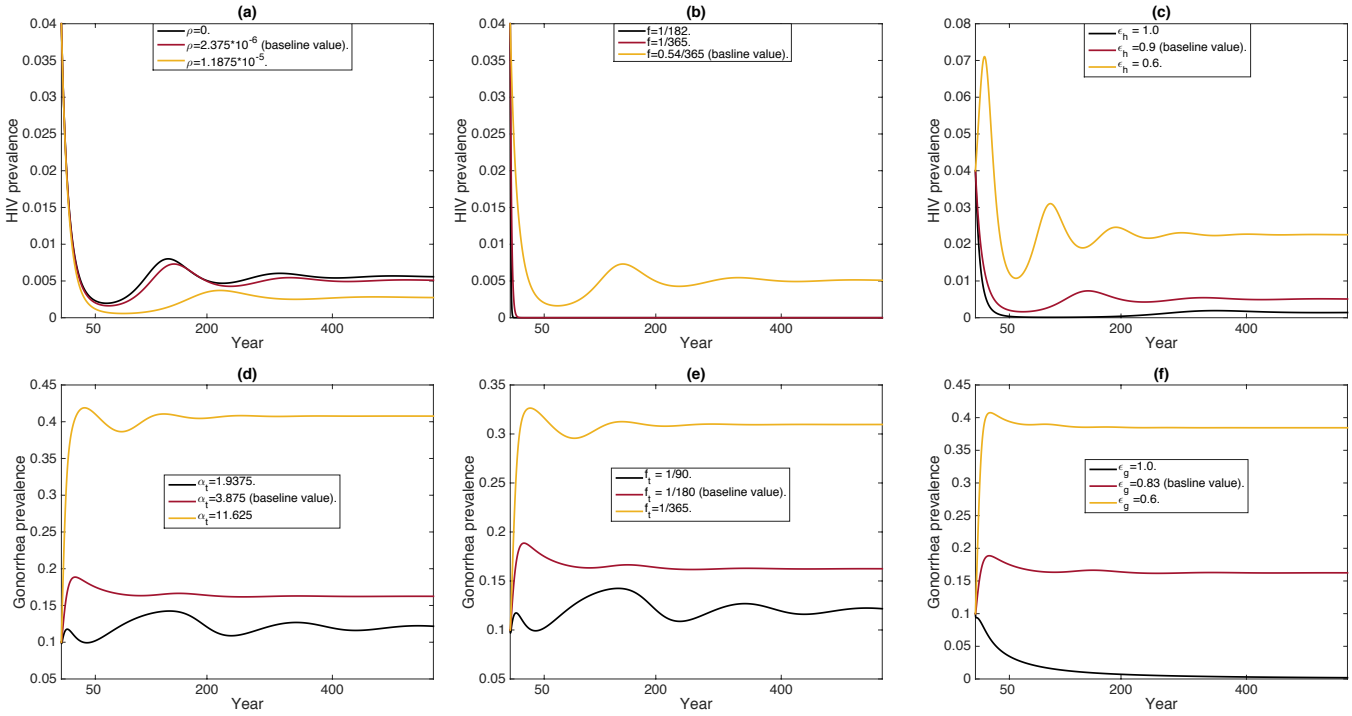

Figure 4.6: Time series of gonorrhea and HIV prevalence over long time scales. In the first row, we compute HIV prevalence. We vary **(a)** PrEP recruitment rate ρ (no PrEP recruitment $\rho = 0$, basline value PrEP recruitment rate and 5 times baseline value), **(b)** testing frequency for individuals in the susceptible class f (once every two years, once every year, twice per year), **(c)** efficacy of HIV treatment ϵ_h (90% effective:baseline value, 100% effective, 60% effective). In the second row, we compute gonorrhea prevalence. We vary **(d)** gonorrhea transmission risk factor for individuals who are treated for HIV ($\alpha_t = 3.875$ baseline value, twice lower than baseline value, three times higher than baseline value), **(e)** testing frequency for individuals who are treated for HIV f_t (twice per year, once per year, once every three months), **(f)** efficacy of gonorrhea treatment ϵ_g (83% effective: baseline value, 100% effective, 60% effective).

GC prevalence increases to a maximum within a decade and then it starts dropping to a stable value (Fig 4.5,4.6). The maximum increase depends on the combination of parameters. Highest levels of GC prevalence range between 20% and 25%. This represents an increase of up to 60% from current values. Those levels are observed if people on PrEP get tested less frequently, for example twice per year (Fig 4.5b,e) or if their condom use is reduced by a factor of 3 (Fig 4.5a,d). The interesting observation, however, is that the period of time until GC prevalence decreases is uniform for many parameter combinations. Even if people on PrEP get tested once every month and a half or they start using condoms more often, we still observe an initial spike in GC prevalence (black curves in Fig 4.5a,b).

There exist a value of PrEP recruitment rate somewhere between the baseline value and 5 times the baseline value where the qualitative behaviour of GC prevalence changes (Fig 4.5c,f). This indicates, that under current social behaviour, if PrEP recruitment increases, then there would be a 70% increase in GC prevalence (from 16% to 22%) at equilibrium value.

Testing frequency is essential to maintain lower levels of GC prevalence. Individuals on PrEP, as well as those who are treated for HIV, must get tested frequently otherwise GC prevalence rises (Fig 4.6e). While there are no testing policies and requirements for individuals treated for HIV, simulations show that when they get tested once every three months versus once per year, GC prevalence falls by 60%. This shows that GC prevalence is not only affected by individuals on PrEP but by other members of the community as well. The average testing frequency for gay and bisexual men is roughly once every two years in some populations, which is considered very low. PrEP is not the only way to prevent the transmission of HIV. Even though HIV is experiencing a decline [164, 50, 228], if members of the community are tested on average once per year (Fig 4.6b red curve), HIV will decline further.

4.9 Sensitivity Analysis

We perform a sensitivity analysis to study the effect of parameter ranges on one of the model outputs. We focus our attention on all GC infections as this is the main goal of this study. We begin with defining an interval for each parameter value centered roughly at its baseline value. We pick equidistant points in each interval and measure the proportion of GC infections at equilibrium. The results are presented in Fig 4.7.

Surprisingly, GC infections are not sensitive to PrEP as seen in Fig 4.7 (F). It could be that the values in the range of ρ are small enough to not create any sensitivity. Similarly, GC infections are not sensitive to testing frequency for PrEP users or levels of condom usage (Fig 4.7 (A,E)). We think that PrEP users are testing frequently enough (at the rate of once every three months). On the other hand, GC infections are highly sensitive to testing frequency to the general population.

There exists a threshold testing frequency f (about once every two months) after which, GC prevalence falls to zero at equilibrium, as seen in Fig 4.7 (C). This is a bifurcation point, and for any values of f less than roughly 0.018 (equivalent to once every 2 months), GC prevalence can be as high as 50%. A similar qualitative behaviour behaviour is observed in the transmission rate of GC Fig 4.7 (G).

Interestingly, we observe output sensitivity to the testing frequency of individuals who are treated for HIV. While this category represents a small proportion of the population (usually less than 15%), low enough testing frequency can increase GC prevalence above 50%.

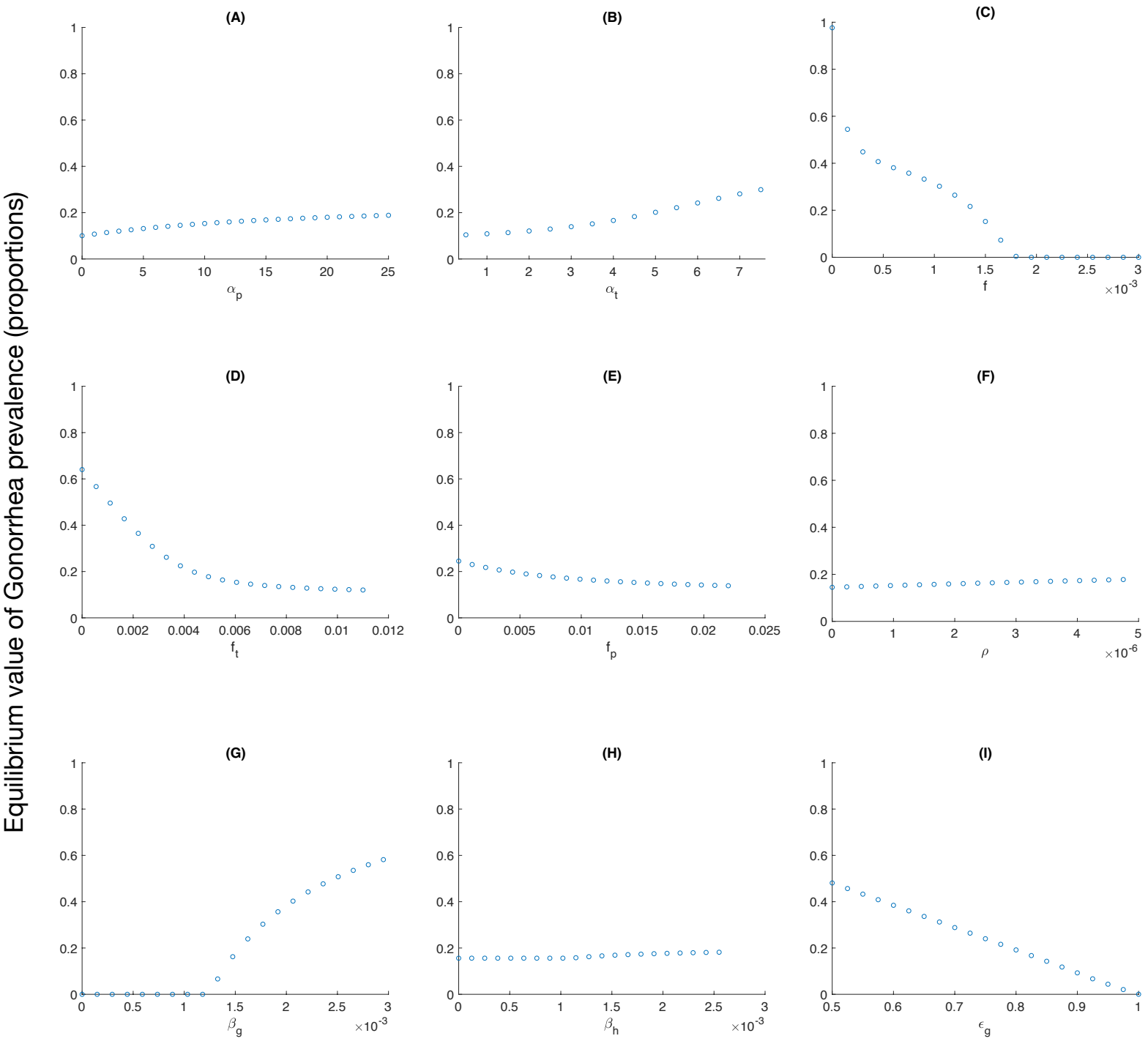

Figure 4.7: Sensitivity analysis for model parameters. For each parameter, an interval centered at the baseline value is considered and the equilibrium value of Gonorrhea infections is measured and plotted.

4.10 No drastic measures are needed to prevent a Gonorrhea outbreak

Here we developed and analyzed a compartmental model of HIV and GC transmission including allowances for behavioural changes upon the introduction of PrEP against HIV infection. We found that GC prevalence increases for a wide range of parameter assumptions, due to a likely increase in risky behaviour from the introduction of PrEP. Our results show that STI testing for individuals on PrEP once every three months is not enough to prevent an increase in GC prevalence, for our baseline assumptions about the impact of PrEP on risky behaviour. Moreover, increased STI testing frequency alone is not enough to prevent a rise in GC prevalence because the testing frequency would have to be increased to impractical levels in order to be effective. However, testing somewhat more frequently than every three months, in combination with sufficient condom usage by individuals on PrEP, would be successful in maintaining GC prevalence at pre-PrEP levels. We developed this model for GC, although the model assumptions are similar to those that would be made for other bacterial STIs such as Chlamydia or Syphilis. Hence, we expect qualitatively similar findings for all bacterial STIs.

Our model highlighted the importance of testing frequency. Testing frequency in many populations without mechanisms for recall (e.g. phone reminders about when it is time to get tested) can be as low as once every two years. Our model predictions show that massive reductions in prevalence are possible when moving from testing every two years to testing every year. This suggests it might be worthwhile to better incentivise frequency STI testing.

Increasing condom usage in the GbMSM community is a challenge, especially in the PrEP era [108, 231, 260, 157]. However, our model emphasises that condom usage rates would not have to change across the entire GbMSM community in order for benefits to accrue, in terms of stemming the rise of GC. The GbMSM population is heterogeneous with respect to both risk perception and willingness to change condom usage. For instance,

recent studies show that 9% of the GbMSM community consistently uses condoms, even in the PrEP era [157]. This suggests that a non-negligible GbMSM sub-population might respond to risk communication efforts to boost condom usage. Perhaps more importantly our model shows that all-or-none behaviour change is not required for benefits to accrue. In particular, Figure 4.3 shows that reductions in risk behaviour on the order of 10–25% in combination with an increase in testing frequency are enough to keep GC prevalence at its pre-PrEP levels, and that any reduction in risky behaviour has benefits that are compounded with an increase in the testing frequency. Hence, even a modest increase in condom usage could have benefits. This provides a useful target for public-health authorities to work toward.

Our findings about the importance of both condoms and STI testing to keep GC under control in the PrEP era do not replace other good advice. For instance, STI testing once every six months is recommended for individuals being treated for HIV infection every time they have a follow up with their physician on their viral loads and overall health. Other preventive strategies include having regular partners, asking sexual partners about their testing frequency and sexual habits, abstinence, adhering to treatment protocol when infected by an STI, and informing sexual partners when infected with an STI.

Our model made simplifying assumptions that could influence its predictions. For instance, GC and HIV, like many pathogens, are currently developing more drug resistance [3, 143, 52, 61, 195]. GC treatment efficacy is connected to early diagnosis and adherence to the medication [235]. Hence if treatment for GC becomes less effective due to drug resistance, GC prevalence in many populations will rise more than our model has predicted. Our model assumes a homogeneous population reaction to the introduction of PrEP, but we speculate that the quantitative predictions of a future version of the model accounting for a heterogeneous population might differ.

Similarly, both social dynamics and contact network structure can play a significant role in the spread of infectious diseases, including HIV and GC [233, 232, 90, 90, 159, 17, 26, 41, 146, 18, 73]. In future work, our study design could be refined by using network

simulations that account for social dynamics concerning HIV and GC transmission. The continued persistence of HIV in the gay and bisexual men's community, along with the resurgence of GC and other bacterial STIs, suggests a continued and urgent need for mathematical modelling studies that can help inform recommendations to result in better infection control.

Chapter 5

Toward a reduction in HIV prevalence in the GbMSM population of Toronto by 2050

5.1 Notification of submission

Submitted to the Canadian Journal of Public Health (CJPH) on the 14th of August 2020. Reviewers are assigned as of the 11th of September 2020.

- Model conceptualization: Joe Pharaon.
- Model analysis: Joe Pharaon.
- Manuscript write up: Joe Pharaon and Chris Bauch.
- Edits and Revisions: Joe Pharaon and Chris Bauch.

5.2 Abstract

BACKGROUND: The Human Immunodeficiency Virus (HIV) continues to infect the GbMSM population at disproportionate rates. Despite prophylactic and diagnostic tools, there continues to be a significant incidence of the disease. We develop testing and PrEP recruitment strategies to reduce HIV prevalence in the GbMSM population of Toronto by 2050.

METHODS: We build a system of stochastic differential equations with testing and PrEP recruitment interventions, that divides the population into two groups based on their sexual risk behaviour: low and high. We vary testing frequencies and PrEP recruitment rates over different risk groups and times of the year. We use MATLAB 2019a to calculate HIV prevalence in 2050, as well as average number of PrEP users and tests every year. We conclude with an optimal strategy that balances a low HIV prevalence with plausible testing and PrEP uptake rates.

RESULTS: Testing the entire GbMSM population once every year is essential to reduce HIV prevalence. Prevalence as low as 1.1 cases per 10,000 (95% confidence interval 1.0-1.3) can be achieved when the general population is tested four times per year and PrEP recruitment rate is 20% per year. Summer focused interventions, in some cases, present similar results to year long interventions. Optimal strategy is testing the entire population twice during the summer while maintaining PrEP recruitment at current rates.

INTERPRETATION: We advise heavy testing campaigns during the summer time. We also recommend incentives to individuals to increase guidelines set out by Public-Health Ontario for better compliance.

5.3 HIV in numbers

The Human Immunodeficiency Virus (HIV) has emerged in the 1980s as a pandemic affecting disproportionately the Gay and Bisexual Men who have Sex with Men (GbMSM) population [121, 87]. Since its discovery a few decades ago, there have been many advancements in the diagnosis, treatment, and prevention of the rapidly mutating virus. The Enzyme-Linked ImmunoSorbent Assay (ELISA) test was developed in 1985 [122]. The first treatment protocol was developed in 1987 [154]. Condoms have been, up until recently, the most effective way to protect individuals against HIV [182, 86]. In 2016, Pre-Exposure Prophylaxis (PrEP) was approved in Canada for preventive use [119], with studies showing that it can prevent HIV transmission by up to 99% [12]. Based on estimates from 2016 [167], the number of recorded HIV cases in Canada is 63110, with half of those GbMSM. It is estimated that roughly 14% of HIV cases are undiagnosed [167]. Once an individual is diagnosed, they immediately begin their Anti-Retroviral Therapy (ART) where they take a combination of pharmaceutical drugs to lower the concentration of the virus in their bodily fluids (such as blood, and semen) to undetectable levels [183, 117]. An individual achieving the undetectable status does not transmit HIV [76, 196].

Despite the efforts to decrease the burden of HIV on public health, the virus still remains a threat [167], with over half of new infections (incidence) in Canada in the GbMSM population. Several mathematical models have been developed in an attempt to understand the underlying complex dynamics between HIV transmission and sexual (or social) behaviour [159, 100, 101, 249, 58]. Preventative and diagnostic tools are available but the question remains on how to implement them and how to incentivise them [131, 179, 128]. A recent study [223] showed that PrEP uptake in Ontario is still lower than suggested by Canadian guidelines. Optimal implementation of PrEP is targeting high risk individuals which helps with reducing HIV prevalence [140]. However, PrEP alone is not enough to reduce HIV prevalence. For instance, it was shown that targeting low risk individuals can prevent new HIV infections based on testing frequency [252]. Risky sexual behaviour including, but not limited to, a decrease in condom usage, is more common during the

months of summer [55, 114], and previous models have not included seasonal testing as an option.

We are interested in addressing the effect of summer months interventions for different risk groups. We are thus looking for an effective strategy that would help significantly reduce HIV prevalence in the GbMSM population of Toronto by 2050. As such, we divide the GbMSM population of Toronto into two risk groups based on their sexual behaviour: low risk and high risk. Strategies combine different testing frequencies and different PrEP recruitment rates at different times of the year targeting a specific risk group. We then, estimate average testing rates and average PrEP uptake for each strategy considered. We conclude by finding an optimal strategy that quantifies trade-offs between season specific interventions and year long interventions, and trade-offs between risk group interventions versus population level interventions.

5.4 A Stochastic framework to predict HIV prevalence

We develop a system of stochastic differential equations that describes the mechanisms of HIV transmission, diagnosis and treatment, demographic processes, and PrEP uptake. The model diagram is shown below in Fig 5.1. The equations are given in 5.1 and parameter baseline values in Table 5.1.

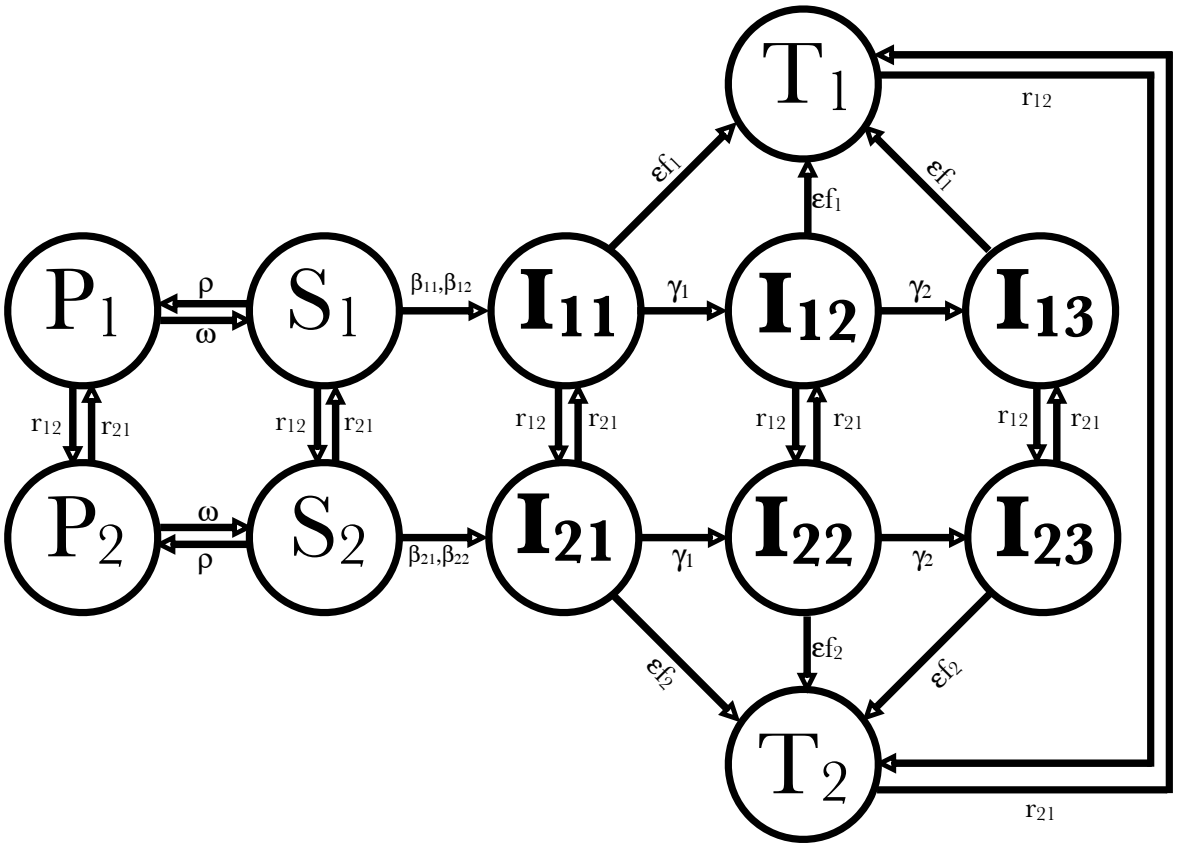

Figure 5.1: Diagram depicting the dynamics of the stochastic model presented in this paper. There are 12 continuous random variables. Arrows represent transition probabilities per time step.

Each individual either adopts a low risk sexual behaviour or a high risk sexual behaviour. The rate at which an individual transitions from low risk to high risk, peaks halfway through the month of June. The rate at which an individual transitions from high risk to low risk peaks in September. The equations for the transition rates are given below. In addition, every individual can be either susceptible to HIV, on PrEP and thus protected

from HIV, infected by HIV or treated for HIV. Furthermore, we divide infected individuals into three classes reflecting all three infection phases: acute phase, chronic phase, and clinical AIDS phase. The acute phase is the primary stage of infection and it lasts about four weeks [151]. The chronic phase is the second stage of HIV infection also known as the asymptomatic stage and lasts up to 10 years [198]. The clinical AIDS phase is the final stage of infection. An individual clinically enters this phase when their CD4+ T cell count drops below 200 per ml of blood. At this point, they become vulnerable to opportunistic infections that may result in severe illness, or death. Under no treatment, an individual can stay alive for up to three years [133]. In our model, we reduce the average period in this phase to two years under the assumption that during the last year, the individual gets severely sick and is practically no longer involved in the transmission dynamics. The system equations are given by:

$$
\begin{aligned}
\frac{d\mathcal{S}_1}{dt} =& \mu_1 + \psi_1\pi_S\phi(t) - \delta\mathcal{S}_1 - r_{12}(t)\mathcal{S}_1 - \rho\mathcal{S}_1 + \omega\mathcal{P}_1 - \mathcal{S}_1\sum_{j=1}^{3}\alpha_j\Big(\beta_{11}\frac{\mathcal{I}_{1j}}{\mathcal{N}_1} + \beta_{12}\frac{\mathcal{I}_{2j}}{\mathcal{N}_2}\Big) \\
&+ r_{21}(t)\mathcal{S}_2 + \sum_{k=1}^{12} B_{1k}\frac{d\mathcal{W}_{1k}}{dt}, \\
\frac{d\mathcal{P}_1}{dt} =& \psi_1\pi_P\phi(t) - \delta\mathcal{P}_1 - r_{12}(t)\mathcal{P}_1 + \rho\mathcal{S}_1 - \omega\mathcal{P}_1 + r_{21}(t)\mathcal{P}_2 + \sum_{k=1}^{12} B_{2k}\frac{d\mathcal{W}_{2k}}{dt} \\
\frac{d\mathcal{I}_{11}}{dt} =& \psi_1\pi_{I_1}\phi(t) - \delta_I(t)\mathcal{I}_{11} - r_{12}(t)\mathcal{I}_{11} - \gamma_1\mathcal{I}_{11} + \mathcal{S}_1\sum_{j=1}^{3}\alpha_j\Big(\beta_{11}\frac{\mathcal{I}_{1j}}{\mathcal{N}_1} + \beta_{12}\frac{\mathcal{I}_{2j}}{\mathcal{N}_2}\Big) \\
&+ r_{21}(t)\mathcal{I}_{21} - \epsilon f_1\mathcal{I}_{11} + \sum_{k=1}^{12} B_{3k}\frac{d\mathcal{W}_{3k}}{dt} \\
\frac{d\mathcal{I}_{12}}{dt} =& \psi_1\pi_{I_2}\phi(t) - \delta_I(t)\mathcal{I}_{12} - r_{12}(t)\mathcal{I}_{12} + \gamma_1\mathcal{I}_{11} - \gamma_2\mathcal{I}_{12} - \epsilon f_1\mathcal{I}_{12} + r_{21}(t)\mathcal{I}_{22} + \sum_{k=1}^{12} B_{4k}\frac{d\mathcal{W}_{4k}}{dt}, \\
\frac{d\mathcal{I}_{13}}{dt} =& \psi_1\pi_{I_3}\phi(t) - \delta_I(t)\mathcal{I}_{13} - r_{12}(t)\mathcal{I}_{13} + \gamma_2\mathcal{I}_{12} - \gamma_3\mathcal{I}_{13} - \epsilon f_1\mathcal{I}_{13} + r_{21}(t)\mathcal{I}_{23} + \sum_{k=1}^{12} B_{5k}\frac{d\mathcal{W}_{5k}}{dt},
\end{aligned}
\tag{5.1}
$$

$$
\begin{aligned}
\frac{d\mathcal{T}_1}{dt} =& \psi_1\pi_T\phi(t) - \delta\mathcal{T}_1 + \epsilon f_1 \sum_{j=1}^{3} \mathcal{I}_{1j} - r_{12}(t)\mathcal{T}_1 + r_{21}(t)\mathcal{T}_2 + \sum_{k=1}^{12} B_{6k}\frac{d\mathcal{W}_{6k}}{dt},\\
\frac{d\mathcal{S}_2}{dt} =& \mu_2 + \psi_2\pi_S\phi(t) - \delta\mathcal{S}_2 - r_{21}(t)\mathcal{S}_2 - \rho\mathcal{S}_2 + \omega\mathcal{P}_2 - \mathcal{S}_2\sum_{j=1}^{3}\alpha_j\left(\beta_{21}\frac{\mathcal{I}_{1j}}{\mathcal{N}_1} + \beta_{22}\frac{\mathcal{I}_{2j}}{\mathcal{N}_2}\right)\\
&+ r_{12}(t)\mathcal{S}_1 + \sum_{k=1}^{12} B_{7k}\frac{d\mathcal{W}_{7k}}{dt},\\
\frac{d\mathcal{P}_2}{dt} =& \psi_2\pi_P\phi(t) - \delta\mathcal{P}_2 - r_{21}(t)\mathcal{P}_2 + \rho\mathcal{S}_2 - \omega\mathcal{P}_2 + r_{12}(t)\mathcal{P}_1 + \sum_{k=1}^{12} B_{8k}\frac{d\mathcal{W}_{8k}}{dt}\\
\frac{d\mathcal{I}_{21}}{dt} =& \psi_2\pi_{I_1}\phi(t) - \delta_I(t)\mathcal{I}_{21} - r_{21}(t)\mathcal{I}_{21} - \gamma_1\mathcal{I}_{21} + \mathcal{S}_2\sum_{j=1}^{3}\alpha_j\left(\beta_{21}\frac{\mathcal{I}_{1j}}{\mathcal{N}_1} + \beta_{22}\frac{\mathcal{I}_{2j}}{\mathcal{N}_2}\right)\\
&+ r_{12}(t)\mathcal{I}_{11} - \epsilon f_2\mathcal{I}_{21} + \sum_{k=1}^{12} B_{9k}\frac{d\mathcal{W}_{9k}}{dt},\\
\frac{d\mathcal{I}_{22}}{dt} =& \psi_2\pi_{I_2}\phi(t) - \delta_I(t)\mathcal{I}_{22} - r_{21}(t)\mathcal{I}_{22} + \gamma_1\mathcal{I}_{21} - \gamma_2\mathcal{I}_{22} - \epsilon f_2\mathcal{I}_{22} + r_{12}(t)\mathcal{I}_{12} + \sum_{k=1}^{12} B_{10k}\frac{d\mathcal{W}_{10k}}{dt},\\
\frac{d\mathcal{I}_{23}}{dt} =& \psi_2\pi_{I_3}\phi(t) - \delta_I(t)\mathcal{I}_{23} - r_{21}(t)\mathcal{I}_{23} + \gamma_2\mathcal{I}_{22} - \gamma_3\mathcal{I}_{23} - \epsilon f_2\mathcal{I}_{23} + r_{12}(t)\mathcal{I}_{13} + \sum_{k=1}^{12} B_{11k}\frac{d\mathcal{W}_{11k}}{dt},\\
\frac{d\mathcal{T}_2}{dt} =& \psi_2\pi_T\phi(t) - \delta\mathcal{T}_2 + \epsilon f_2 \sum_{j=1}^{3} \mathcal{I}_{2j} - r_{21}(t)\mathcal{T}_2 + r_{12}(t)\mathcal{T}_1 + \sum_{k=1}^{8} B_{12k}\frac{d\mathcal{W}_{12k}}{dt},
\end{aligned}
$$

where $B = (B_{ik})$ is a 12×12 matrix defined as: $B = \sqrt{V}$ and V is the Covariance matrix [8]. $\mathcal{W}_{ik}$ are 144 Wiener processes. $\mathcal{S}_i(t)$ is the continuous random variable representing the number of susceptible individuals in risk group i. $\mathcal{P}_i(t)$ is the continuous random variable representing the number of individuals on PrEP in risk group i. $\mathcal{I}_{ij}(t)$ is the continuous random variable representing the number of infected individuals in risk group i in stage j of infection. $\mathcal{T}_i(t)$ is the continuous random variable representing the number of treated individuals in risk group i.

$\phi(t)$ is given by:

$$\phi(t) = \delta(\mathcal{S}_1(t)+\mathcal{S}_2(t)+\mathcal{P}_1(t)+\mathcal{P}_2(t)+\mathcal{T}_1(t)+\mathcal{T}_2(t))+\delta_I(t)(\mathcal{I}_{11}(t)+\mathcal{I}_{12}(t)+\mathcal{I}_{13}(t)+\mathcal{I}_{21}(t)+\mathcal{I}_{22}(t)+\mathcal{I}_{23}(t))$$
$$+\gamma_3(\mathcal{I}_{13}(t)+\mathcal{I}_{23}(t))$$

The transition rate from low risk to high risk is given by:

$$r_{12}(t) = \begin{cases} \frac{1}{365.25\times 2} & 0 \leq \text{mod}(t, 365.25) < 121 \\ -\frac{2}{1687455}t^2 + \frac{104}{241065}t - \frac{1712}{51135} & 121 \leq \text{mod}(t, 365.25) < 213 \\ \frac{1}{365.25\times 2} & 213 \leq \text{mod}(t, 365.25) < 365.25, \end{cases}$$

The transition rate from high risk to low risk is given by:

$$r_{21}(t) = \begin{cases} \frac{1}{365.25} & 0 \leq \text{mod}(t, 365.25) < 212 \\ -\frac{4}{468007}t^2 + \frac{1944}{468007}t - \frac{693212}{1404021} & 212 \leq \text{mod}(t, 365.25) < 274 \\ \frac{1}{365.25} & 274 \leq \text{mod}(t, 365.25) < 365.25, \end{cases}$$

Transition rates are plotted in appendix A.2.

The death rate for individuals in the infected classes changes over time, due to enhanced diagnosis and treatment since the beginning of the pandemic. It is given by:

$$\delta_I(t) = \begin{cases} \frac{1}{4*365.25} & 0 < t < 7 \text{ years} \\ \frac{1}{10*365.25} & 7 \text{ years} < t < 15 \text{ years} \\ \frac{1}{20*365.25} & 15 \text{ years} < t < 25 \text{ years} \\ \frac{1}{50*365.25} & t > 25 \text{ years} \end{cases}$$

The calibration process of model parameters is based on HIV incidence and prevalence data between 1980 and 2016 [167]. Fitting model parameters to data is depicted in Fig 5.2. In our model, transmission rates vary with respect to time and risk group. The difference in

rates was based on the number of sexual partnerships and levels of condom usage [96, 215]. Diagnosis and treatment are added to the model at the $t = 7$ year mark. The obtained calibrated value for low risk testing frequency is roughly 0.25 per year (equivalent to once

Parameter	Description	Value (per day)	Source
β_{11}	low-low HIV transmission rate	$0.000082/\sqrt{65}$	Calibrated
β_{12}	low-high HIV transmission rate	$\sqrt{65}(0.000082)$	Calibrated
β_{21}	high-low HIV transmission rate	$0.000082/\sqrt{65}$	Calibrated
β_{22}	high-high HIV transmission rate	$\sqrt{65}(0.000082)$	Calibrated
α_1	acute phase HIV transmission factor	26 (unitless)	[115]
α_2	chronic phase HIV transmission factor	1 (unitless)	[115]
α_3	AIDS phase HIV transmission factor	7 (unitless)	[115]
f_1	low risk testing frequency	0.25/365.25	Calibrated
f_2	high risk testing frequency	0.125/365.25	Calibrated
ϵ	efficacy of HIV treatment	0.91	[209]
ρ	PrEP recruitment rate	0.0075/365.25	Calibrated
ω	PrEP quitting rate	$1/(24 \times 30.5)$	Assumed
γ_1	acute-chronic transition rate	1/28	[151]
γ_2	chronic-AIDS transition rate	$1/(365.25 \times 10)$	[198]
γ_3	AIDS death rate	$1/(365.25 \times 2)$	[133]
δ	natural death rate	$1/(50 \times 365.25)$	[181]
π_S	proportion of migration to S classes	0.95 (unitless)	[30, 187]
π_P	proportion of migration to P classes	0.02 (unitless)	[30, 187, 234]
π_{I_1}	proportion of migration to I_{i1} classes	0.0000978 (unitless)	[30, 187]
π_{I_2}	proportion of migration to I_{i2} classes	0.0127518 (unitless)	[30, 187]
π_{I_3}	proportion of migration to I_{i3} classes	0.0025504 (unitless)	[30, 187]
π_T	proportion of migration to T classes	0.0146 (unitless)	[30, 187]
μ_1	pop. increase (low risk) due to pop. growth	1.926 (persons/day)	[44, 165, 1]
μ_2	pop. increase (high risk) due to pop. growth	0.214 (persons/day)	[44, 165, 1]
r_{12},r_{21}	transition rates	variable	*
$\mathcal{S}_1(0)$	Initial number of low risk susceptible	45280	[167, 166]
$\mathcal{S}_2(0)$	Initial number of high risk susceptible	10000	[167, 166]
$\mathcal{P}_i(0)$	Initial number of PrEP users	0	[167, 166]
$\mathcal{I}_{i1}(0)$	Initial number of low/high risk acute HIV+	10	[167, 166]
$\mathcal{I}_{i2}(0)$	Initial number of low/high risk chronic HIV+	50	[167, 166]
$\mathcal{I}_{i3}(0)$	Initial number of low/high risk HIV+ in AIDS	5	[167, 166]
$\mathcal{T}_i(0)$	Initial number of treated individuals	0	[167, 166]
ψ_1	proportion of low risk population	0.9	[194]
ψ_2	proportion of high risk population	0.1	[194]

Table 5.1: Baseline parameter values.

every four years) and the value was halved for high risk individuals. Note that the calibrated testing frequencies represent average values for the time period between 1987 and 2016. Finally, the calibration of PrEP recruitment rate is based on Global PrEP Tracker available on *www.PrEPwatch.org*. The value we obtain is 0.75% per year which agrees with previously computed estimates [160, 192]. Note that based on risk transition rates, we include a PrEP discontinuity rate where on average an individual discontinues PrEP within two years.

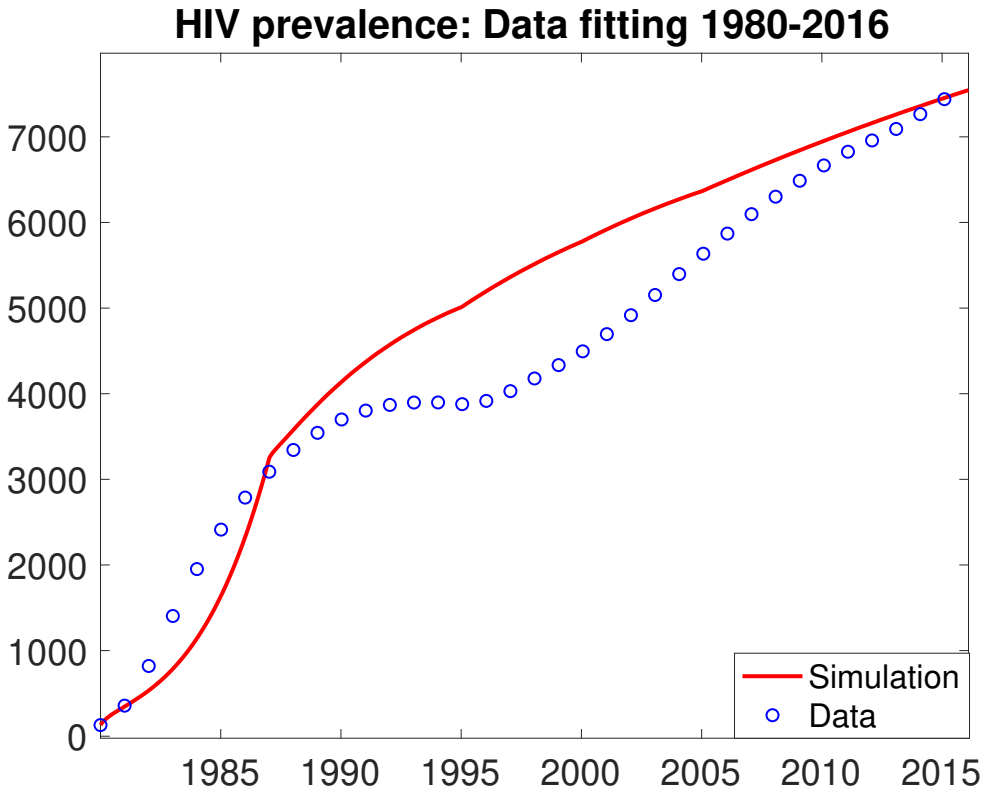

Figure 5.2: HIV prevalence: fitting of epidemiological parameters (transmission rates, testing frequencies, and PrEP recruitment rate) to data on HIV from 1980-2016 in Toronto. Data reflects both diagnosed and undiagnosed cases.

We consider strategies focusing only on individuals adopting a low risk sexual behaviour, strategies focusing only on individuals adopting a high risk sexual behaviour, and strategies that target both risk groups. Some strategies consider varying PrEP recruitment rates while keeping testing frequencies at baseline values. Other strategies consider varying testing frequencies while keeping PrEP recruitment rate at baseline value. Certain strategies combine variations to both interventions. Finally, to understand the potential effect of intervention during the summer season, we consider strategies with varying intervention rates depending on the time of the year. One set of strategies has uniform rates all year long. Another set of strategies has baseline rates outside of the summer months and increased rates during the summer months. One final set of strategies has high rates only during the summer months and no intervention during the rest of the year. Details on strategies can be found in the appendix.

For each strategy, we use MATLAB 2019a and measure the rate of undiagnosed HIV cases by 2050 (cases per 10000 individuals) with a 95% confidence interval based on the simulation of 50 sample paths. We also estimate the average number of tests administered on a yearly basis between 2020 and 2050, as well as the average number of individuals on PrEP every year. We construct a function that seeks to pick an optimal strategy where HIV infection rate is minimized subject to minimal testing and PrEP uptake rates.

5.5 Optimal Strategy for HIV Reduction is Testing Everyone Twice during the Summer

We report the results in number of undiagnosed cases per 10,000 individuals. Tables in the appendix also give a percentage of undiagnosed cases with their confidence intervals. The results are reported for the year 2050.

Frequent testing is essential to reduce HIV prevalence. Investigating all 106 strategies in total shows that merely increasing testing frequency leads to a lower HIV

prevalence than merely increasing PrEP recruitment rates (Fig 5.3,5.4). In addition, when a higher PrEP recruitment rate is considered, we do not observe a significant difference in HIV prevalence (Fig 5.3,5.5). Furthermore, we notice a notable decrease in prevalence when testing frequency increases from once every two years to once every year: 13.1 cases per 10,000 (12.1-14) to 5.4 cases per 10,000 (4.9-5.9), respectively (Fig 5.3C). Increasing population level testing frequency to four times every year (equivalent to testing frequency for PrEP users) produced the lowest prevalence of HIV: 1.2 cases per 10,000 (1.0-1.3) (Fig 5.3C).

Interventions should be implemented for both low risk individuals and high risk individuals for optimal results. According to our model, focusing interventions on high risk individuals only did not lead to a substantive decrease in HIV prevalence (Fig 5.3,5.5 B,E,H). If a strategy targets high risk individuals only, the lowest prevalence observed is 23.3 cases per 10,000 (22.5-25.0) when testing is performed at the rate of four times per year and PrEP recruitment rate is 20% all year round (Fig 5.5B). Targeting only low risk individuals produces a negligible increase in HIV prevalence compared to targeting both risk groups (Compare Fig 5.3,5.4,5.5 A,D,G to Fig 5.3,5.4,5.5 C,F,I).

Variability in outcomes is higher when increasing PrEP recruitment rate is the main focus. If testing frequency is kept at baseline value and PrEP recruitment rate is increased from 1% per year up to 20% per year, confidence intervals are wider (Fig 5.4). This suggests that there is a greater uncertainty when PrEP recruitment strategies are a priority. While a greater PrEP recruitment rate produces lower HIV prevalence (Fig 3C), it is not enough to bring down the number of undiagnosed HIV cases to minimal values. For instance, a PrEP recruitment rate of 20% per year all year long to both risk groups results in 35.7 cases per 10,000 (33.3-38.1). This happens with baseline testing frequencies, and once again, emphasizes the essential role of testing.

Seasonal focused interventions can help decrease HIV prevalence. Even though summer testing yields, in many cases, a lower amount of total tests, we still get a comparable HIV prevalence to year long uniform frequencies. This stems from the fact that

risky behaviour is increased during the summer time and thus there is a higher probability of diagnosing then and eliminating potential transmissions. For instance, if HIV testing is conducted during the summer only for the entire population, a prevalence as low as 3.8 cases per 10,000 (3.6-4.1) can be achieved when, on average, an individual is tested once at the beginning of the summer and once toward the end of the summer.

An optimal strategy is testing the entire population four times every year during the summer only while keeping PrEP at baseline values. In the search of an optimal strategy, we included criteria such as balancing a lower HIV prevalence with a not very high number of tests or PrEP users. Of course, if extremely frequent testing and an abnormally high PrEP recruitment rate are possible, this would certainly generate a minimal prevalence (1.1 cases per 10,000 (1.0-1.3)). However, it is not practical. As a first step, we eliminated all the strategies that resulted in more than 10 cases per 10,000. This reduced the number of strategies from 106 strategies to just 24. For each qualifying strategy, we normalized HIV prevalence, the average number of yearly tests administered, and the average number of yearly PrEP users. By doing so, we assign each variable an equal weight of 1/3. The strategy that resulted in the lowest value of our function is testing the entire population at the rate of four times every year during the summer months (see Table in the appendix). We also consider different weights to determine whether or not the same strategy is optimal. It turns out that doubling the weight of the average number of yearly tests administered, yielded the same optimal strategy. The same happened when we double the weight for the average number of yearly PrEP users. However, if we double the weight for HIV prevalence, the optimal strategy is testing twice every year, all year round, the entire population.

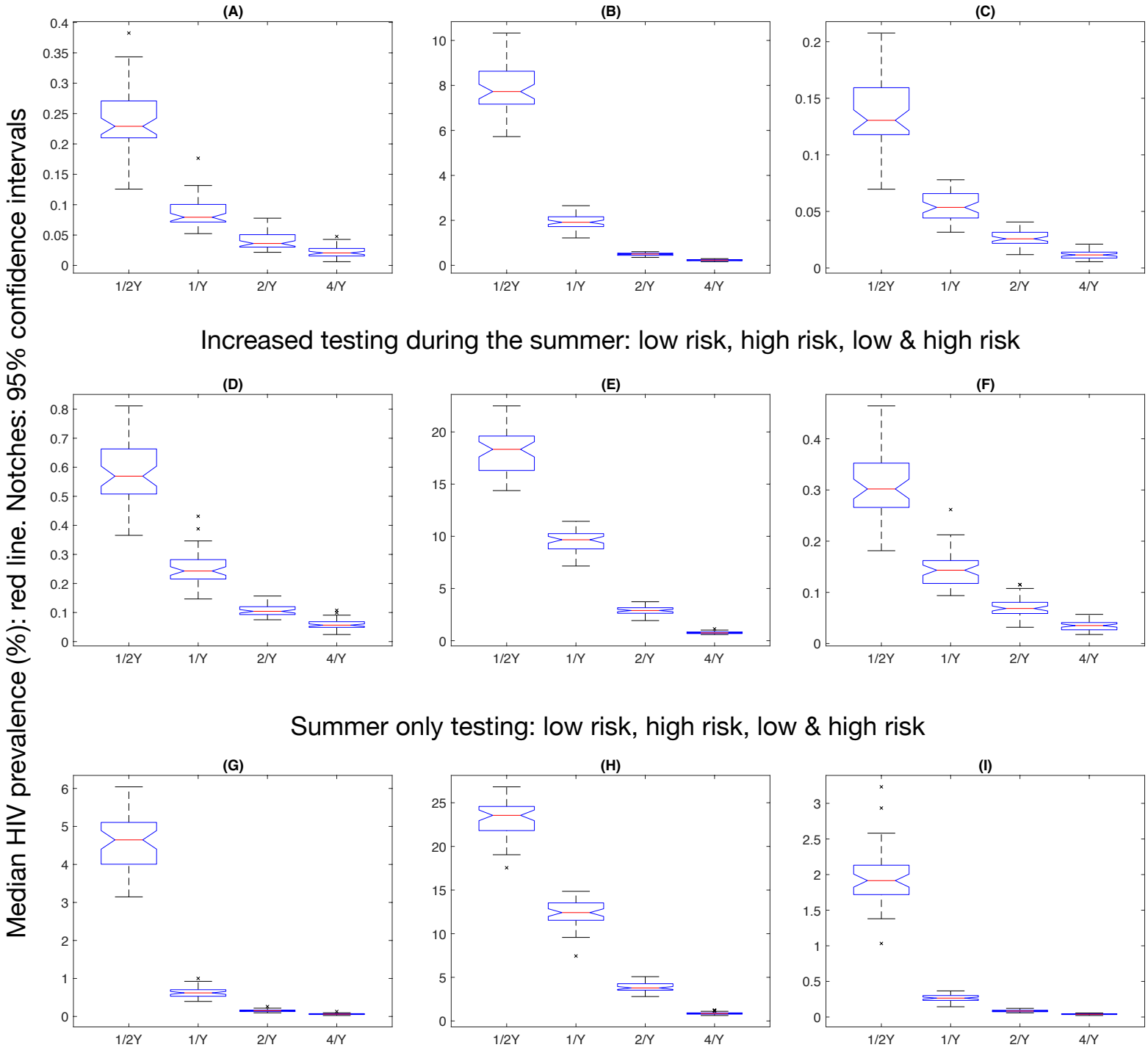

Figure 5.3: HIV prevalence (%) for different testing strategies. PrEP recruitment is at baseline value. Labels on the horizontal axes denote testing frequency. **(D-F)** Testing frequency is at baseline outside the summer months.

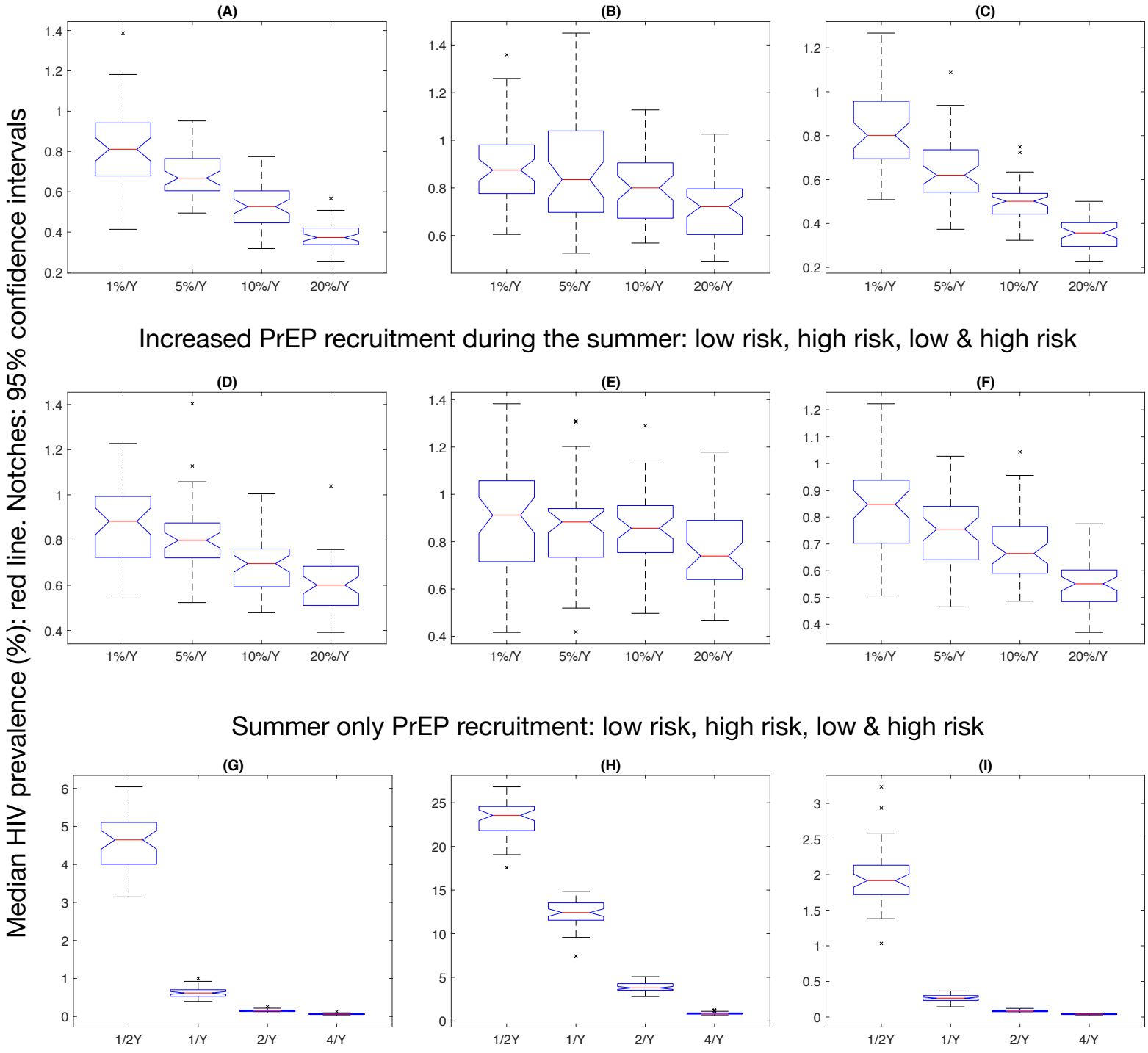

Figure 5.4: HIV prevalence (%) for different testing strategies. Testing frequency is at baseline value. Labels on the horizontal axes denote PrEP recruitment rates. **(D-F)** PrEP recruitment rate is at baseline value outside the summer months.

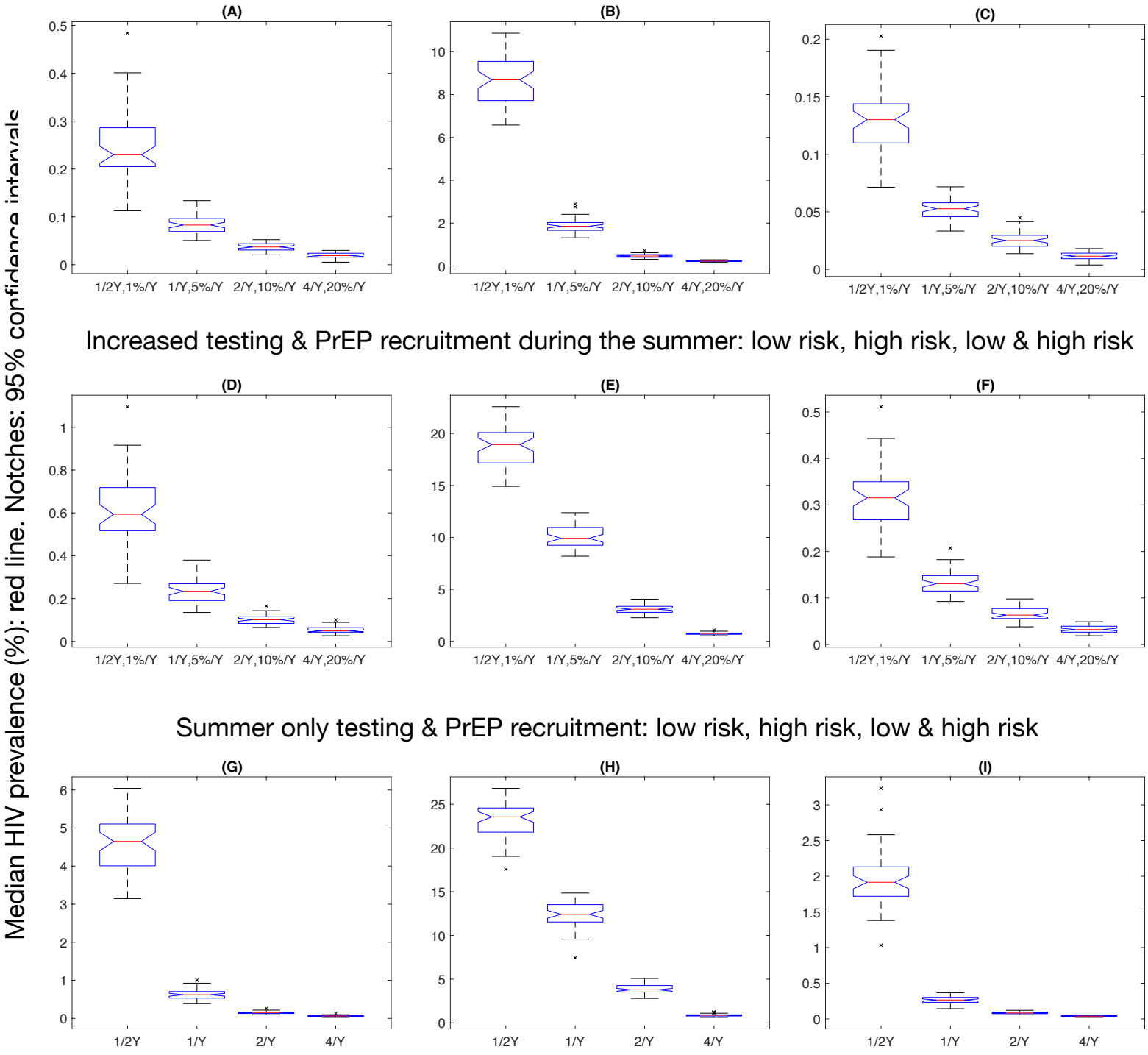

Figure 5.5: HIV prevalence (%) for different testing and PrEP recruitment strategies. Labels on the horizontal axes denote testing frequencies and PrEP recruitment rates, respectively. **(D-F)** PrEP recruitment rate and test frequency are at baseline value outside the summer months.

5.6 Sensitivity Analysis

We perform parameter sensitivity analysis to study the effect of a particular parameter on the output of the model. In our case, the output is the total number of HIV undiagnosed cases, measured as the sum of all the $\mathcal{I}$ classes. We start by fixing all parameters at baseline values and calculate the median of the total number of undiagnosed HIV cases by 2050 of 100 sample paths. We pick each parameter at baseline value and create an interval centered at its baseline value with the left end half the parameter's baseline value and its right end one and half of it. For example for the parameter a_3, the interval would be $(3.5, 10.5)$. We vary each parameter one at a time and record the output of the model in every case. The results are presented in a Tornado diagram in Fig 5.6.

Note that we didn't include parameters such that ϵ because it is multiplied by testing frequency in the model: a variation of f_1 (or f_2) can be viewed as a variation of ϵ. In most cases, output response to parameters was linear: output strictly increases (or decreases) with respect to an increase in parameter value. However, we did observe in particular that two parameters namely ω and β_{21} did not create a linear response. The reason could be either because we did not take enough sample paths, or that the response is truly non-linear. Both parameters in the figure are accompanied by an encircled negative sign. In most cases, the lowest value of a parameter produced the lowest output while the highest value produced the highest output. This, of course, depends on the biological interpretation of the parameter. For some parameters, on the other hand, the opposite was observed. For example, lower values of f_1 produced higher values of HIV cases. Those parameters are accompanied by a star, in the figure.

Testing frequency for low risk group produced the highest sensitivity to model output. Transmission rate between a susceptible individual and an infected individual both in the low risk group, produced the lowest sensitivity to model output. Out of all four transmission rates, β_{12} produced the highest sensitivity. This indicates that uncertainty in the transmission rate between a susceptible low risk individual and an infected high risk individual produces less reliable results. Model output is insensitive to PrEP recruitment

rate, possibly due to the fact of low levels of recruitment (interval right end is 1.5%).

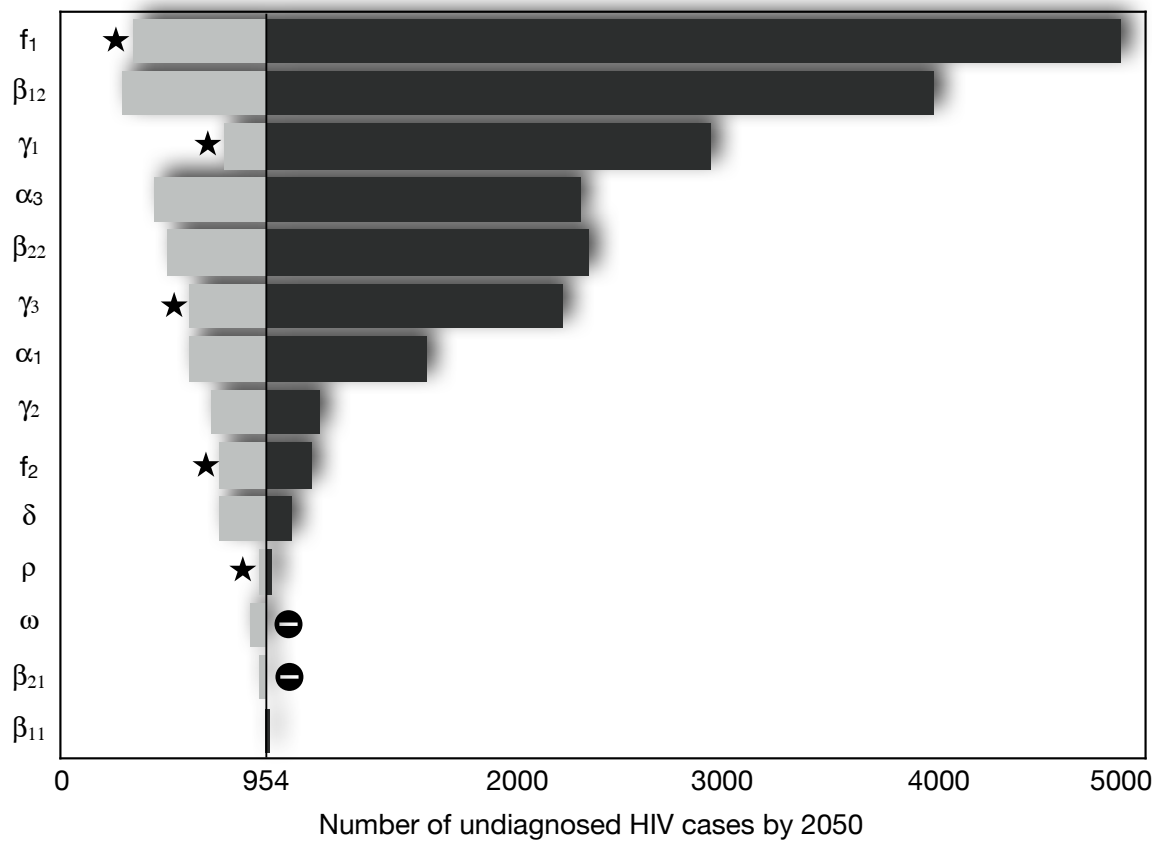

Figure 5.6: Sensitivity analysis for model parameters. 100 sample paths were produced for each parameter value. For each parameter, three values were considered one at a time: baseline value, half baseline value (lower end), one and a half baseline value (upper end).

5.7 Recommendations to Public Health Units in Ontario about the Reduction of HIV Prevalence

The reduction, and subsequently the elimination, of HIV in the GbMSM population can be challenging when interventions are not appropriately implemented. Understanding trends in risky behaviour is fundamental to tackling the situation. Our study shows that interventions conducted at increased rates during the summer months, can lead to a substantial decrease in HIV prevalence in Toronto. While more testing has shown to be more effective than simply increasing PrEP uptake (Fig 5.3,5.4), both measures combined together are essential for a successful reduction.

Based on our results, we recommend heavy testing campaigns for the summer months and we suggest that individuals get tested on average twice during the summer, regardless of their sexual risk level. Engaging the general population does not have to be challenging. The idea of universal testing, where an individual gets checked for HIV during a regular medical exam, is promising [67]. Making HIV self-testing an option would lead to higher testing frequency and thus a decline in transmission [124].

While PrEP uptake protects individuals against HIV, our studies show that a significant increase in PrEP recruitment doesn't have the same effect as a significant increase in frequent testing (Fig 5.3,5.4). We advise the continuation of PrEP awareness, and recommend the delivery of PrEP to high risk individuals [168]. This recommendation is based on how accessible high risk individuals are, compared to low risk individuals. We advise public health to develop programs to bring PrEP awareness to those individuals who get tested, who frequent bathhouses, and those who are involved in the night life. Incentivising testing and PrEP uptake can play an important role in increasing uptake rates. Offering financial incentives to club goers, such as a discounted admission fee, or a free drink upon showing a recent negative HIV test or a recent PrEP prescription is one way to go about it. Similarly, Public health can use platforms such as social apps to encourage interventions. Trends in using social apps to meet other individuals for sexual purposes keep increasing

[103]. Incentives to get tested can range from decreasing membership fee to mandatory testing for joining the network. We also recommend mandatory testing and PrEP uptake for individuals sexually engaging in public spaces such as bathhouses.

Compliance with public health guidelines can be problematic at times. Conducting surveys to discover what incentives individuals prefer can help increase testing rates and the uptake of PrEP, once those incentives are implemented. This study offers a perspective to the direction in which a cost-effectiveness analysis might take. Public health has budgetary limitations and as such a cost-effectiveness analysis would be informative to the implementation of an optimal strategy seeking to reduce HIV prevalence among GbMSM individuals, while meeting budgets.

There are several limitations to keep in mind. Our results present statistical uncertainties based on parameter values. In this sense, we acknowledge that exact quantitative outcomes might be hard to achieve. The presentation of only two risk groups does not reflect the reality of the situation. Human behaviour is very heterogeneous and it plays a big role in the spread of infectious diseases. However, approximations are necessary to paint a qualitative picture.

HIV has been persistent in GbMSM populations for over 40 years now. While interventions are helping with a decrease in transmission rates and contracting the virus, the virus is also building drug resistance [214, 34, 49]. It is a race to end the HIV epidemic in the GbMSM population and we have to act now.

Chapter 6

Conclusions

Societies' responses to emerging pathogens have always been critical in the control of their spread. In the absence of medical intervention, we have to rely on behavioural strategies that help mitigate or reduce risks of severe outbreaks. Currently, the global pandemic caused by the novel Coronavirus proves once again that the implementation of social strategies (such as social distancing, quarantining, and wearing face masks) is essential in the fight against an imminent public health threat [15, 152, 56]. Historically, this has always been the case. From the times of the bubonic plague in the 14th century [95], to last century's Spanish Influenza [229], to most recently in 2020, COVID-19.

Adding social components to the mathematical modelling of infectious diseases can help better guide public health response and give better predictions of outbreak probability and outbreak sizes. As we have learned in the second chapter of this thesis, the basic reproductive number is not necessarily the one and only reference to quantify the severity of an emergent virulent strain. Under certain (behavioural) conditions, a deadly outbreak can be prevented. This shows that complex systems such as those used in this thesis can offer insight that are, otherwise, not very obvious (or sometimes intuitive). Feedback loops created in nonlinear dynamics help inform experts about the effect of certain strategies and the success or failure of certain preventive measures.

Social behaviour that accompanies sexual partnership in the GbMSM population has always been important in the prevention of HIV transmission. From wearing condoms, to frequent testing, to uptaking PrEP, and to limiting the number of sexual partners; this combination of prophylactic measures aims to reduce the prevalence of HIV and other STIs (such as Gonorrhea) in the population. However, the disease is yet not eliminated. Other than the fact that no effective cure has yet been developed, the surveys and statistics we cited in chapters four and five show that compliance to public health guidelines is not optimal. Of course, this favours the continual transmission of the virus. The model we developed in chapter four informed us that drastic measures to increase condom usage is not necessary to avoid outbreaks in bacterial STIs so long the population is getting tested frequently. The same results were obtained in chapter five, even though we addressed a slightly different question and used a slightly different method. This is encouraging, because no matter the methodology, we came up to the same conclusion about the important of frequent STI testing. This is supported by conclusions from other studies [248, 71, 171]

Future work should focus on social behaviour and expand on the effect of social behaviour on the spread of disease. As we have seen throughout this thesis that social behaviour plays an essential role in determining the course of an emerging pathogen. This thesis doesn't consider within-host dynamics. By including this layer, we can certainly get a better understanding of an even more complex model, and the connection between inter-host and intra-host dynamics. We addressed our questions by building compartmental models but there are other useful tools such as network epidemiology for instance. Comparing outcomes from different methodologies can help strengthen the robustness (or lack thereof) of results.

The mathematical modelling of infectious diseases has helped understand complex dynamics of disease transmission in communities. The continual development and improvement of tools and techniques is important to enhance our assessments of real life situations, and to better inform public health about the efficacy of safety measures. The communication of scientific findings is also important. The messages should be delivered in a clear and concise way so that officials are able to successfully apply the findings in real life settings.

The public's role is important as well. Educating the public about the risks associated with neglecting guidelines helps with infection control and subsequently saves lives.

References

[1] Mancount sizes up the gaps. a sexual health survey of gay men in vancouver. 2010.

[2] Kamair Alaei, Christopher A Paynter, Shao-Chiu Juan, and Arash Alaei. Using Pre-Exposure Prophylaxis, losing condoms? Pre-Exposure Prophylaxis promotion may undermine safe sex. *Aids*, 30(18):2753–2756, 2016.

[3] Emilie Alirol, Teodora E Wi, Manju Bala, Maria Luiza Bazzo, Xiang-Sheng Chen, Carolyn Deal, Jo-Anne R Dillon, Ranmini Kularatne, Jutta Heim, Rob Hooft van Huijsduijnen, et al. Multidrug-resistant gonorrhea: A research and development roadmap to discover new medicines. *PLoS medicine*, 14(7):e1002366, 2017.

[4] Samuel Alizon. Transmission-recovery trade-offs to study parasite evolution. *The American Naturalist*, 172(3):E113–E121, 2008.

[5] Samuel Alizon and Christophe Fraser. Within-host and between-host evolutionary rates across the hiv-1 genome. *Retrovirology*, 10(1):49, 2013.

[6] Samuel Alizon, Amy Hurford, Nicole Mideo, and Minus Van Baalen. Virulence evolution and the trade-off hypothesis: history, current state of affairs and the future. *Journal of evolutionary biology*, 22(2):245–259, 2009.

[7] Samuel Alizon and Yannis Michalakis. Adaptive virulence evolution: the good old fitness-based approach. *Trends in ecology & evolution*, 30(5):248–254, 2015.

[8] Linda JS Allen. An introduction to stochastic epidemic models. In *Mathematical epidemiology*, pages 81–130. Springer, 2008.

[9] Linda JS Allen. *An introduction to stochastic processes with applications to biology*. CRC Press, 2010.

[10] Linda JS Allen, Fred Brauer, Pauline Van den Driessche, and Jianhong Wu. *Mathematical epidemiology*, volume 1945. Springer, 2008.

[11] Lawrence K Altman. New homosexual disorder worries health officials. *The New York Times*, 11:C1–6, 1982.

[12] Peter L Anderson, David V Glidden, Albert Liu, Susan Buchbinder, Javier R Lama, Juan Vicente Guanira, Vanessa McMahan, Lane R Bushman, Martín Casapía, Orlando Montoya-Herrera, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. *Science translational medicine*, 4(151):151ra125–151ra125, 2012.

[13] Roy M Anderson and RM May. Coevolution of hosts and parasites. *Parasitology*, 85(2):411–426, 1982.

[14] Julien Arino and P Van den Driessche. Disease spread in metapopulations. *Nonlinear dynamics and evolution equations*, 48:1–13, 2006.

[15] Hamada S Badr, Hongru Du, Maximilian Marshall, Ensheng Dong, Marietta M Squire, and Lauren M Gardner. Association between mobility patterns and covid-19 transmission in the usa: a mathematical modelling study. *The Lancet Infectious Diseases*, 2020.

[16] Franco Bagnoli, Pietro Lio, and Luca Sguanci. Risk perception in epidemic modeling. *Physical Review E*, 76(6):061904, 2007.

[17] C Bauch and DA Rand. A moment closure model for sexually transmitted disease transmission through a concurrent partnership network. *Proceedings of the Royal Society of London. Series B: Biological Sciences*, 267(1456):2019–2027, 2000.

[18] Chris T Bauch. Imitation dynamics predict vaccinating behaviour. *Proceedings of the Royal Society of London B: Biological Sciences*, 272(1573):1669–1675, 2005.

[19] Chris T Bauch and Samit Bhattacharyya. Evolutionary game theory and social learning can determine how vaccine scares unfold. *PLoS computational biology*, 8(4):e1002452, 2012.

[20] Chris T Bauch and David JD Earn. Vaccination and the theory of games. *Proceedings of the National Academy of Sciences of the United States of America*, 101(36):13391–13394, 2004.

[21] Chris T Bauch, Alison P Galvani, and David JD Earn. Group interest versus self-interest in smallpox vaccination policy. *Proceedings of the National Academy of Sciences*, 100(18):10564–10567, 2003.

[22] Chris T Bauch, Meng Li, Gretchen Chapman, and Alison P Galvani. Adherence to cervical screening in the era of human papillomavirus vaccination: how low is too low? *The Lancet Infectious Diseases*, 10(2):133–137, 2010.

[23] Chris T Bauch, James O Lloyd-Smith, Megan P Coffee, and Alison P Galvani. Dynamically modeling sars and other newly emerging respiratory illnesses: past, present, and future. *Epidemiology*, 16(6):791–801, 2005.

[24] Chris T Bauch and Richard McElreath. Disease dynamics and costly punishment can foster socially imposed monogamy. *Nature communications*, 7:11219, 2016.

[25] Chris T Bauch, Ram Sigdel, Joe Pharaon, and Madhur Anand. Early warning signals of regime shifts in coupled human–environment systems. *Proceedings of the National Academy of Sciences*, 113(51):14560–14567, 2016.

[26] CT Bauch. A versatile ODE approximation to a network model for the spread of sexually transmitted diseases. *Journal of mathematical biology*, 45(5):375–395, 2002.

[27] Steve E Bellan. The importance of age dependent mortality and the extrinsic incubation period in models of mosquito-borne disease transmission and control. *PLoS One*, 5(4):e10165, 2010.

[28] Kyle T Bernstein, Julia L Marcus, Giuliano Nieri, Susan S Philip, and Jeffrey D Klausner. Rectal gonorrhea and chlamydia reinfection is associated with increased risk of hiv seroconversion. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, 53(4):537–543, 2010.

[29] Allan Bérubé. The history of gay bathhouses. *Journal of Homosexuality*, 44(3-4):33–53, 2003.

[30] Chris Beyrer, Stefan D Baral, Frits Van Griensven, Steven M Goodreau, Suwat Chariyalertsak, Andrea L Wirtz, and Ron Brookmeyer. Global epidemiology of HIV infection in men who have sex with men. *the Lancet*, 380(9839):367–377, 2012.

[31] Derdei Bichara, Abderrahman Iggidr, and Gauthier Sallet. Global analysis of multi-strains sis, sir and msir epidemic models. *Journal of Applied Mathematics and Computing*, 44(1-2):273–292, 2014.

[32] Ottar N Bjørnstad, Bärbel F Finkenstädt, and Bryan T Grenfell. Dynamics of measles epidemics: estimating scaling of transmission rates using a time series sir model. *Ecological monographs*, 72(2):169–184, 2002.

[33] German Advisory Committee Blood et al. Human immunodeficiency virus (hiv). *Transfusion Medicine and Hemotherapy*, 43(3):203, 2016.

[34] Sally M Blower, AN Aschenbach, HB Gershengorn, and JO Kahn. Predicting the unpredictable: transmission of drug-resistant hiv. *Nature medicine*, 7(9):1016–1020, 2001.

[35] Annie-Claude Bourgeois, Michael Edmunds, Amnah Awan, Leigh Jonah, Olivia Varsaneux, and Winnie Siu. Can we eliminate hiv?: Hiv in canada—surveillance report, 2016. *Canada Communicable Disease Report*, 43(12):248, 2017.

[36] Fred Brauer, Carlos Castillo-Chavez, and Carlos Castillo-Chavez. *Mathematical models in population biology and epidemiology*, volume 40. Springer, 2001.

[37] Hans J Bremermann and John Pickering. A game-theoretical model of parasite virulence. *Journal of Theoretical Biology*, 100(3):411–426, 1983.

[38] M Brisson, NJ Gay, WJ Edmunds, and NJ Andrews. Exposure to varicella boosts immunity to herpes-zoster: implications for mass vaccination against chickenpox. *Vaccine*, 20(19-20):2500–2507, 2002.

[39] Gary L Buchschacher. Introduction to retroviruses and retroviral vectors, 2001.

[40] James J Bull. Virulence. *Evolution*, 48(5):1423–1437, 1994.

[41] Bruno Buonomo, Giuseppe Carbone, and Alberto d'Onofrio. Effect of seasonality on the dynamics of an imitation-based vaccination model with public-health intervention. *Mathematical Biosciences & Engineering*, 15(1):299–321, 2018.

[42] Thomas M Bury, Chris T Bauch, and Madhur Anand. Charting pathways to climate change mitigation in a coupled socio-climate model. *PLoS computational biology*, 15(6):e1007000, 2019.

[43] J Buyze, W Vanden Berghe, N Hens, and C Kenyon. Current levels of gonorrhoea screening in msm in belgium may have little effect on prevalence: a modelling study. *Epidemiology & Infection*, 146(3):333–338, 2018.

[44] Statistics Canada. Dwelling counts, for census metropolitan areas and census agglomerations, 2016 and 2011 censuses – 100 % data. 2016.

[45] Carlos Castillo-Chavez, K Cooke, W Huang, SA Levin, et al. Results on the dynamics for models for the sexual transmission of the human immuno-deficiency virus. 1989.

[46] Carlos Castillo-Chavez, Kenneth Cooke, Wenzhang Huang, and Simon A Levin. On the role of long incubation periods in the dynamics of acquired immunodeficiency syndrome (aids). *Journal of Mathematical Biology*, 27(4):373–398, 1989.

[47] W Cates Jr and H Hunter Handsfield. HIV counseling and testing: does it work? *American Journal of Public Health*, 78(12):1533–1534, 1988.

[48] Shi Chen, John Fricks, and Matthew J Ferrari. Tracking measles infection through non-linear state space models. *Journal of the Royal Statistical Society: Series C (Applied Statistics)*, 61(1):117–134, 2012.

[49] Margaret A Chesney, Michel Morin, and Lorraine Sherr. Adherence to hiv combination therapy. *Social science & medicine*, 50(11):1599–1605, 2000.

[50] Eric PF Chow, Nicholas A Medland, Ian Denham, Edwina J Wright, and Christopher K Fairley. Decline in new HIV diagnoses among MSM in melbourne. *The Lancet HIV*, 5(9):e479–e481, 2018.

[51] AA Chughtai, M Barnes, and CR Macintyre. Persistence of ebola virus in various body fluids during convalescence: evidence and implications for disease transmission and control. *Epidemiology & Infection*, 144(8):1652–1660, 2016.

[52] Tomas Cihlar and Marshall Fordyce. Current status and prospects of HIV treatment. *Current opinion in virology*, 18:50–56, 2016.

[53] John M Coffin, Stephen H Hughes, and Harold E Varmus. Course of infection with hiv and siv, 1997.

[54] John M Coffin, Stephen H Hughes, and Harold E Varmus. *Retroviral Virions and Genomes–Retroviruses*. Cold Spring Harbor Laboratory Press, 1997.

[55] Vincent J Cornelisse, Eric PF Chow, Marcus Y Chen, Catriona S Bradshaw, and Christopher K Fairley. Summer heat: a cross-sectional analysis of seasonal differences in sexual behaviour and sexually transmissible diseases in melbourne, australia. *Sexually transmitted infections*, 92(4):286–291, 2016.

[56] Benjamin J Cowling, Sheikh Taslim Ali, Tiffany WY Ng, Tim K Tsang, Julian CM Li, Min Whui Fong, Qiuyan Liao, Mike YW Kwan, So Lun Lee, Susan S Chiu, et al. Impact assessment of non-pharmaceutical interventions against coronavirus disease 2019 and influenza in hong kong: an observational study. *The Lancet Public Health*, 2020.

[57] Benjamin J Cowling, Dennis KM Ip, Vicky J Fang, Piyarat Suntarattiwong, Sonja J Olsen, Jens Levy, Timothy M Uyeki, Gabriel M Leung, JS Malik Peiris, Tawee Chotpitayasunondh, et al. Aerosol transmission is an important mode of influenza a virus spread. *Nature communications*, 4(1):1–6, 2013.

[58] Ide Cremin, Ramzi Alsallaq, Mark Dybul, Peter Piot, Geoffrey Garnett, and Timothy B Hallett. The new role of antiretrovirals in combination hiv prevention: a mathematical modelling analysis. *Aids*, 27(3):447–458, 2013.

[59] Clayton E Cressler, DAVID V McLEOD, Carly Rozins, Josée Van Den Hoogen, and Troy Day. The adaptive evolution of virulence: a review of theoretical predictions and empirical tests. *Parasitology*, 143(7):915–930, 2016.

[60] Alfred W Crosby. *America's forgotten pandemic: the influenza of 1918*. Cambridge University Press, 2003.

[61] Emma Cunningham, Yuen-Ting Chan, Adamma Aghaizu, David F Bibby, Gary Murphy, Jennifer Tosswill, Ross J Harris, Richard Myers, Nigel Field, Valerie Delpech, et al. Enhanced surveillance of HIV-1 drug resistance in recently infected MSM in the UK. *Journal of Antimicrobial Chemotherapy*, page dkw404, 2016.

[62] William W Darrow, Donald Barrett, Karla Jay, and Allen Young. The gay report on sexually transmitted diseases. *American Journal of Public Health*, 71(9):1004–1011, 1981.

[63] Troy Day. Parasite transmission modes and the evolution of virulence. *Evolution*, 55(12):2389–2400, 2001.

[64] Kevin M De Cock, Georgette Adjorlolo, Ehounou Ekpini, Toussaint Sibailly, Justin Kouadio, Matthieu Maran, Kari Brattegaard, Kathleen M Vetter, Ronan Doorly, and Helene D Gayle. Epidemiology and transmission of hiv-2: why there is no hiv-2 pandemic. *Jama*, 270(17):2083–2086, 1993.

[65] Jacobus C De Roode, Andrew J Yates, and Sonia Altizer. Virulence-transmission trade-offs and population divergence in virulence in a naturally occurring butterfly parasite. *Proceedings of the National Academy of Sciences*, 105(21):7489–7494, 2008.

[66] Ulf Dieckmann. Adaptive dynamics of pathogen-host interactions. 2002.

[67] Carl W Dieffenbach and Anthony S Fauci. Universal voluntary testing and treatment for prevention of hiv transmission. *Jama*, 301(22):2380–2382, 2009.

[68] Odo Diekmann, Johan Andre Peter Heesterbeek, and Johan AJ Metz. On the definition and the computation of the basic reproduction ratio r 0 in models for infectious diseases in heterogeneous populations. *Journal of mathematical biology*, 28(4):365–382, 1990.

[69] Klaus Dietz and JAP Heesterbeek. Daniel bernoulli's epidemiological model revisited. *Mathematical biosciences*, 180(1-2):1–21, 2002.

[70] Peng Ding and Tyler J VanderWeele. Sensitivity analysis without assumptions. *Epidemiology (Cambridge, Mass.)*, 27(3):368, 2016.

[71] Peter J Dodd, Geoff P Garnett, and Timothy B Hallett. Examining the promise of hiv elimination by 'test and treat'in hyper-endemic settings. *AIDS (London, England)*, 24(5):729, 2010.

[72] Mirela D'arc, Ahidjo Ayouba, Amandine Esteban, Gerald H Learn, Vanina Boué, Florian Liegeois, Lucie Etienne, Nikki Tagg, Fabian H Leendertz, Christophe Boesch, et al. Origin of the hiv-1 group o epidemic in western lowland gorillas. *Proceedings of the National Academy of Sciences*, 112(11):E1343–E1352, 2015.

[73] Ken TD Eames and Matt J Keeling. Modeling dynamic and network heterogeneities in the spread of sexually transmitted diseases. *Proceedings of the national academy of sciences*, 99(20):13330–13335, 2002.

[74] Lisa A Eaton, Seth C Kalichman, Devon Price, Stephanie Finneran, Aerielle Allen, and Jessica Maksut. Stigma and conspiracy beliefs related to Pre-Exposure Prophylaxis (PrEP) and interest in using PrEP among black and white men and transgender women who have sex with men. *AIDS and Behavior*, 21(5):1236–1246, 2017.

[75] Leah Edelstein-Keshet. *Mathematical models in biology*. SIAM, 2005.

[76] Robert W Eisinger, Carl W Dieffenbach, and Anthony S Fauci. Hiv viral load and transmissibility of hiv infection: undetectable equals untransmittable. *Jama*, 321(5):451–452, 2019.

[77] Yoichi Enatsu, Yukihiko Nakata, and Yoshiaki Muroya. Global stability of sir epidemic models with a wide class of nonlinear incidence rates and distributed delays. *Discrete & Continuous Dynamical Systems-B*, 15(1):61, 2011.

[78] Nuno R Faria, Andrew Rambaut, Marc A Suchard, Guy Baele, Trevor Bedford, Melissa J Ward, Andrew J Tatem, João D Sousa, Nimalan Arinaminpathy, Jacques Pépin, et al. The early spread and epidemic ignition of hiv-1 in human populations. *science*, 346(6205):56–61, 2014.

[79] Shannon M Fast, Sumiko Mekaru, John S Brownstein, Timothy A Postlethwaite, and Natasha Markuzon. The role of social mobilization in controlling ebola virus in lofa county, liberia. *PLoS currents*, 7, 2015.

[80] Zhilan Feng, Jorge Velasco-Hernandez, and Brenda Tapia-Santos. A mathematical model for coupling within-host and between-host dynamics in an environmentally-driven infectious disease. *Mathematical biosciences*, 241(1):49–55, 2013.

[81] Zhilan Feng, Jorge Velasco-Hernandez, Brenda Tapia-Santos, and Maria Conceição A Leite. A model for coupling within-host and between-host dynamics in an infectious disease. *Nonlinear Dynamics*, 68(3):401–411, 2012.

[82] Neil Ferguson. Capturing human behaviour. *Nature*, 446(7137):733–733, 2007.

[83] Neil M Ferguson, Matt J Keeling, W John Edmunds, Raymond Gani, Bryan T Grenfell, Roy M Anderson, and Steve Leach. Planning for smallpox outbreaks. *Nature*, 425(6959):681–685, 2003.

[84] Stephanie M Fingerhuth, Sebastian Bonhoeffer, Nicola Low, and Christian L Althaus. Antibiotic-resistant neisseria gonorrhoeae spread faster with more treatment, not more sexual partners. *PLoS pathogens*, 12(5):e1005611, 2016.

[85] Centre for Communicable Diseases, Infectious Disease Prevention Infection Control, and Public Health Agency of Canada Control Branch. Public Health agency of canada. M-Track: Enhanced surveillance of HIV, sexually transmitted and blood-borne infections, and associated risk behaviours among men who have sex with men in canada. phase 1 report. 2011.

[86] Centers for Disease Control, Prevention (CDC, et al. Update: barrier protection against hiv infection and other sexually transmitted diseases. *MMWR. Morbidity and mortality weekly report*, 42(30):589, 1993.

[87] Centers for Disease Control (CDC et al. Kaposi's sarcoma and pneumocystis pneumonia among homosexual men–new york city and california. *MMWR. Morbidity and mortality weekly report*, 30(25):305, 1981.

[88] Steven A Frank. Models of parasite virulence. *The Quarterly review of biology*, 71(1):37–78, 1996.

[89] Christophe Fraser, T Déirdre Hollingsworth, Ruth Chapman, Frank de Wolf, and William P Hanage. Variation in hiv-1 set-point viral load: epidemiological analysis and an evolutionary hypothesis. *Proceedings of the National Academy of Sciences*, 104(44):17441–17446, 2007.

[90] Feng Fu, Daniel I Rosenbloom, Long Wang, and Martin A Nowak. Imitation dynamics of vaccination behaviour on social networks. *Proceedings of the Royal Society B: Biological Sciences*, 278(1702):42–49, 2010.

[91] Sebastian Funk, Marcel Salathé, and Vincent AA Jansen. Modelling the influence of human behaviour on the spread of infectious diseases: a review. *Journal of the Royal Society Interface*, page rsif20100142, 2010.

[92] Feng Gao, Elizabeth Bailes, David L Robertson, Yalu Chen, Cynthia M Rodenburg, Scott F Michael, Larry B Cummins, Larry O Arthur, Martine Peeters, George M Shaw, et al. Origin of HIV-1 in the chimpanzee pan troglodytes troglodytes. *Nature*, 397(6718):436, 1999.

[93] Linda Gao and Herbert Hethcote. Simulations of rubella vaccination strategies in China. *Mathematical biosciences*, 202(2):371–385, 2006.

[94] Geoffrey P Garnett. Role of herd immunity in determining the effect of vaccines against sexually transmitted disease. *The Journal of infectious diseases*, 191(Supplement_1):S97–S106, 2005.

[95] Gian Franco Gensini, Magdi H Yacoub, and Andrea A Conti. The concept of quarantine in history: from plague to sars. *Journal of Infection*, 49(4):257–261, 2004.

[96] Sara Nelson Glick, Martina Morris, Betsy Foxman, Sevgi O Aral, Lisa E Manhart, King K Holmes, and Matthew R Golden. A comparison of sexual behavior patterns among men who have sex with men and heterosexual men and women. *Journal of acquired immune deficiency syndromes (1999)*, 60(1):83, 2012.

[97] William C Goedel, Kenneth H Mayer, Matthew J Mimiaga, and Dustin T Duncan. Considerable interest in Pre-Exposure Prophylaxis uptake among men who have sex with men recruited from a popular geosocial-networking smartphone application in London. *Global public health*, pages 1–10, 2017.

[98] Edward Goldstein, Virginia E Pitzer, Justin J O'Hagan, and Marc Lipsitch. Temporally varying relative risks for infectious diseases: implications for infectious disease control. *Epidemiology (Cambridge, Mass.)*, 28(1):136, 2017.

[99] Sarit A Golub, Corina Lelutiu-Weinberger, and Anthony Surace. Experimental investigation of implicit HIV and Pre-Exposure Prophylaxis stigma: Evidence for ancillary benefits of Pre-Exposure Prophylaxis use. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, 77(3):264–271, 2018.

[100] Steven M Goodreau, L Pedro Goicochea, and Jorge Sanchez. Sexual role and transmission of hiv type 1 among men who have sex with men, in peru. *The Journal of infectious diseases*, 191(Supplement_1):S147–S158, 2005.

[101] Reuben M Granich, Charles F Gilks, Christopher Dye, Kevin M De Cock, and Brian G Williams. Universal voluntary hiv testing with immediate antiretroviral therapy as a strategy for elimination of hiv transmission: a mathematical model. *The Lancet*, 373(9657):48–57, 2009.

[102] Thilo Gross, Carlos J Dommar D?Lima, and Bernd Blasius. Epidemic dynamics on an adaptive network. *Physical review letters*, 96(20):208701, 2006.

[103] Nicholas A Grosskopf, Michael T LeVasseur, and Debra B Glaser. Use of the internet and mobile-based "apps" for sex-seeking among men who have sex with men in new york city. *American journal of men's health*, 8(6):510–520, 2014.

[104] S Ha, L Pogany, J Seto, J Wu, and M Gale-Rowe. Sexually transmitted infections: What are Canadian primary care physicians prescribing for the treatment of Gonorrhea? *Canada Communicable Disease Report*, 43(2):33, 2017.

[105] Karl P Hadeler and Carlos Castillo-Chávez. A core group model for disease transmission. *Mathematical biosciences*, 128(1-2):41–55, 1995.

[106] Phillip L Hammack, Ilan H Meyer, Evan A Krueger, Marguerita Lightfoot, and David M Frost. HIV testing and Pre-Exposure Prophylaxis (PrEP) use, familiarity, and attitudes among gay and bisexual men in the United States: A national probability sample of three birth cohorts. *PloS one*, 13(9):e0202806, 2018.

[107] Andreas Handel and Pejman Rohani. Crossing the scale from within-host infection dynamics to between-host transmission fitness: a discussion of current assumptions and knowledge. *Phil. Trans. R. Soc. B*, 370(1675):20140302, 2015.

[108] Mallory Harrigan. Prep use among gbmsm: What does it mean for sti prevention? https://www.catie.ca/en/pif/spring-2019/prep-use-among-gbmsm-what-does-it-mean-sti-prevention. 2019.

[109] Kirsten A Henderson, Chris T Bauch, and Madhur Anand. Alternative stable states and the sustainability of forests, grasslands, and agriculture. *Proceedings of the National Academy of Sciences*, 113(51):14552–14559, 2016.

[110] Joshua T Herbeck, John E Mittler, Geoffrey S Gottlieb, Steven M Goodreau, James T Murphy, Anne Cori, Michael Pickles, and Christophe Fraser. Evolution of hiv virulence in response to widespread scale up of antiretroviral therapy: a modeling study. *Virus Evolution*, 2(2):vew028, 2016.

[111] Joshua T Herbeck, John E Mittler, Geoffrey S Gottlieb, and James I Mullins. An HIV epidemic model based on viral load dynamics: value in assessing empirical trends in HIV virulence and community viral load. *PLoS computational biology*, 10(6):e1003673, 2014.

[112] Herbert W Hethcote, Li Yi, and Jing Zhujun. Hopf bifurcation in models for pertussis epidemiology. *Mathematical and Computer Modelling*, 30(11-12):29–45, 1999.

[113] Josef Hofbauer and Karl Sigmund. *Evolutionary games and population dynamics*. Cambridge university press, 1998.

[114] J Carlo Hojilla, Kimberly A Koester, Stephanie E Cohen, Susan Buchbinder, Deawodi Ladzekpo, Tim Matheson, and Albert Y Liu. Sexual behavior, risk compensation, and hiv prevention strategies among participants in the san francisco prep demonstration project: a qualitative analysis of counseling notes. *AIDS and Behavior*, 20(7):1461–1469, 2016.

[115] T Déirdre Hollingsworth, Roy M Anderson, and Christophe Fraser. Hiv-1 transmission, by stage of infection. *The Journal of infectious diseases*, 198(5):687–693, 2008.

[116] DJ Hu, MA Kane, and David L Heymann. Transmission of hiv, hepatitis b virus, and other bloodborne pathogens in health care settings: a review of risk factors and guidelines for prevention. world health organization. *Bulletin of the World Health Organization*, 69(5):623, 1991.

[117] Jean-Baptiste Hubert, Marianne Burgard, Elisabeth Dussaix, Catherine Tamalet, Christiane Deveau, Jérôme Le Chenadec, Marie-Laure Chaix, Eric Marchadier, Jean-Louis Vildé, Jean-François Delfraissy, et al. Natural history of serum hiv-1 rna levels in 330 patients with a known date of infection. *Aids*, 14(2):123–131, 2000.

[118] M Hull and DHS Tan. Can we eliminate HIV?: Setting the stage for expanding HIV Pre-Exposure Prophylaxis use in Canada. *Canada Communicable Disease Report*, 43(12):272, 2017.

[119] Tan DHS. Hull M. Setting the stage for expanding hiv pre-exposure prophylaxis use in canada. *Can Commun Dis Rep*, 43(12):272–8, 2017.

[120] Christopher B Hurt, Joseph J Eron Jr, and Myron S Cohen. Pre-Exposure Prophylaxis and antiretroviral resistance: HIV prevention at a cost? *Clinical Infectious Diseases*, 53(12):1265–1270, 2011.

[121] KennethB Hymes, JeffreyB Greene, Aaron Marcus, DanielC William, Tony Cheung, NeilS Prose, Harold Ballard, and LindaJ Laubenstein. Kaposi's sarcoma in homosexual men—a report of eight cases. *The Lancet*, 318(8247):598–600, 1981.

[122] JE Johnson. Use of a commercial elisa test for the diagnosis of infection by the aids virus, hiv, in a patient population. *Diagnostic microbiology and infectious disease*, 6(3):267–271, 1987.

[123] Seth C Kalichman, Jennifer Pellowski, and Christina Turner. Prevalence of sexually transmitted co-infections in people living with HIV/AIDS: systematic review with implications for using HIV treatments for prevention. *Sexually transmitted infections*, 87(3):183–190, 2011.

[124] David A Katz, Matthew R Golden, James P Hughes, Carey Farquhar, and Joanne D Stekler. Hiv self-testing increases hiv testing frequency in high risk men who have sex with men: A randomized controlled trial. *Journal of acquired immune deficiency syndromes (1999)*, 78(5):505, 2018.

[125] Charlotte K Kent, Janice K Chaw, William Wong, Sally Liska, Steven Gibson, Gregory Hubbard, and Jeffrey D Klausner. Prevalence of rectal, urethral, and pharyngeal chlamydia and Gonorrhea detected in 2 clinical settings among men who have sex

with men: San Francisco, California, 2003. *Clinical Infectious Diseases*, 41(1):67–74, 2005.

[126] William O Kermack and Anderson G McKendrick. Contributions to the mathematical theory of epidemics. ii. the problem of endemicity. *Proceedings of the Royal Society of London. Series A, containing papers of a mathematical and physical character*, 138(834):55–83, 1932.

[127] William Ogilvy Kermack and Anderson G McKendrick. A contribution to the mathematical theory of epidemics. *Proceedings of the royal society of london. Series A, Containing papers of a mathematical and physical character*, 115(772):700–721, 1927.

[128] Rod Knight, Will Small, Kim Thomson, Mark Gilbert, and Jean Shoveller. Implementation challenges and opportunities for hiv treatment as prevention (tasp) among young men in vancouver, canada: a qualitative study. *BMC public health*, 16(1):1–10, 2016.

[129] Florence M Koechlin, Virginia A Fonner, Sarah L Dalglish, Kevin R O'Reilly, Rachel Baggaley, Robert M Grant, Michelle Rodolph, Ioannis Hodges-Mameletzis, and Caitlin E Kennedy. Values and preferences on the use of oral Pre-Exposure Prophylaxis (PrEP) for HIV prevention among multiple populations: a systematic review of the literature. *AIDS and Behavior*, 21(5):1325–1335, 2017.

[130] Noah Kojima, Dvora Joseph Davey, and Jeffrey D Klausner. Pre-Exposure Prophylaxis for HIV infection and new sexually transmitted infections among men who have sex with men. *Aids*, 30(14):2251–2252, 2016.

[131] Ann E Kurth, Connie Celum, Jared M Baeten, Sten H Vermund, and Judith N Wasserheit. Combination hiv prevention: significance, challenges, and opportunities. *Current Hiv/aids Reports*, 8(1):62–72, 2011.

[132] Joseph TF Lau, Xilin Yang, Ellie Pang, HY Tsui, Eric Wong, and Yun Kwok Wing. Sars-related perceptions in hong kong. *Emerging infectious diseases*, 11(3):417, 2005.

[133] Lisa M Lee, John M Karon, Richard Selik, Joyce J Neal, Patricia L Fleming, et al. Survival after aids diagnosis in adolescents and adults during the treatment era, united states, 1984-1997. *JAMA-Journal of the American Medical Association-International Edition*, 285(10):1308–1315, 2001.

[134] Thomas Leitner et al. Genetic subtypes of hiv-1. *Human retroviruses and AIDS*, 1996:28, 1996.

[135] Philippe Lemey, Oliver G Pybus, Bin Wang, Nitin K Saksena, Marco Salemi, and Anne-Mieke Vandamme. Tracing the origin and history of the hiv-2 epidemic. *Proceedings of the National Academy of Sciences*, 100(11):6588–6592, 2003.

[136] Richard E Lenski and Robert M May. The evolution of virulence in parasites and pathogens: reconciliation between two competing hypotheses. *Journal of theoretical biology*, 169(3):253–265, 1994.

[137] David E Lilienfeld, David E Lilienfeld, Paul D Stolley, Abraham M Lilienfeld, et al. *Foundations of epidemiology*. Oxford University Press, USA, 1994.

[138] Xiaodong Lin. On the uniqueness of endemic equilibria of an hiv/aids transmission model for a heterogeneous population. *Journal of mathematical biology*, 29(8):779–790, 1991.

[139] El Mehdi Lotfi, Marouane Mahrouf, Mehdi Maziane, Cristiana J Silva, Delfim FM Torres, and Noura Yousfi. A minimal HIV-AIDS infection model with general incidence rate and application to Morocco data. *arXiv preprint arXiv:1812.06965*, 2018.

[140] Derek R MacFadden, Darrell H Tan, and Sharmistha Mishra. Optimizing hiv pre-exposure prophylaxis implementation among men who have sex with men in a large urban centre: a dynamic modelling study. *Journal of the International AIDS Society*, 19(1):20791, 2016.

[141] Louis M Mansky. Retrovirus mutation rates and their role in genetic variation. *Journal of general Virology*, 79(6):1337–1345, 1998.

[142] Marsudi, Noor Hidayat, and Ratno Bagus Edy Wibowo. Sensitivity analysis of the parameters of an HIV/AIDS model with condom campaign and antiretroviral therapy. In *AIP Conference Proceedings*, volume 1913, page 020019. AIP Publishing, 2017.

[143] I Martin, P Sawatzky, V Allen, B Lefebvre, LMN Hoang, P Naidu, J Minion, P Van Caeseele, D Haldane, RR Gad, et al. Multidrug-resistant and extensively drug-resistant gonorrhea in Canada, 2012–2016. 2019.

[144] Eduardo Massad. Transmission rates and the evolution of hiv virulence. *Evolution*, 50(2):916–918, 1996.

[145] Naoki Masuda and Petter Holme. *Temporal network epidemiology*. Springer, 2017.

[146] Martial L Ndeffo Mbah, Jingzhou Liu, Chris T Bauch, Yonas I Tekel, Jan Medlock, Lauren Ancel Meyers, and Alison P Galvani. The impact of imitation on vaccination behavior in social contact networks. *PLoS computational biology*, 8(4):e1002469, 2012.

[147] Sheena McCormack, David T Dunn, Monica Desai, David I Dolling, Mitzy Gafos, Richard Gilson, Ann K Sullivan, Amanda Clarke, Iain Reeves, Gabriel Schembri, et al. Pre-Exposure Prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomized trial. *The Lancet*, 387(10013):53–60, 2016.

[148] Anthony J McMichael. Environmental and social influences on emerging infectious diseases: past, present and future. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, 359(1447):1049–1058, 2004.

[149] Lauren Ancel Meyers, Babak Pourbohloul, Mark EJ Newman, Danuta M Skowronski, and Robert C Brunham. Network theory and sars: predicting outbreak diversity. *Journal of theoretical biology*, 232(1):71–81, 2005.

[150] Nicole Mideo, Samuel Alizon, and Troy Day. Linking within-and between-host dynamics in the evolutionary epidemiology of infectious diseases. *Trends in ecology & evolution*, 23(9):511–517, 2008.

[151] William C Miller, Nora E Rosenberg, Sarah E Rutstein, and Kimberly A Powers. The role of acute and early hiv infection in the sexual transmission of hiv. *Current Opinion in HIV and AIDS*, 5(4):277, 2010.

[152] Evgenia Milman, Sherman A Lee, and Robert A Neimeyer. Social isolation and the mitigation of coronavirus anxiety: The mediating role of meaning. *Death Studies*, pages 1–13, 2020.

[153] Jason W Mitchell and Keith J Horvath. Factors associated with regular HIV testing among a sample of US MSM with HIV-negative main partners. *Journal of acquired immune deficiency syndromes (1999)*, 64(4):417, 2013.

[154] Hiroaki Mitsuya and Samuel Broder. Strategies for antiviral therapy in aids. *Nature*, 325(6107):773–778, 1987.

[155] AJ Mocroft, JD Lundgren, A d'Armino Monforte, B Ledergerber, SE Barton, S Vella, C Katlama, J Gerstoft, C Pedersen, and AN Phillips. Survival of aids patients according to type of aids-defining event. the aids in europe study group. *International journal of epidemiology*, 26(2):400–407, 1997.

[156] Hamish Mohammed, Holly Mitchell, Bersabeh Sile, Stephen Duffell, Anthony Nardone, and Gwenda Hughes. Increase in sexually transmitted infections among men who have sex with men, england, 2014. *Emerging infectious diseases*, 22(1):88, 2016.

[157] Michalina A Montano, Julia C Dombrowski, Lindley A Barbee, Matthew R Golden, and Christine M Khosropour. Changes in sexual behavior and sti diagnoses among msm using prep in seattle, wa. *Age*, 30(8):7, 2017.

[158] Jim Moore. The puzzling origins of aids: Although no one explanation has been universally accepted, four rival theories provide some important lesson. *American Scientist*, 92(6):540–547, 2004.

[159] Martina Morris and Mirjam Kretzschmar. Concurrent partnerships and the spread of HIV. *Aids*, 11(5):641–648, 1997.

[160] Terrance Mosley, Moliehi Khaketla, Heather L Armstrong, Zishan Cui, Paul Sereda, Nathan J Lachowsky, Mark W Hull, Gbolahan Olarewaju, Jody Jollimore, Joshua Edward, et al. Trends in awareness and use of HIV PrEP among gay, bisexual, and other men who have sex with men in Vancouver, Canada 2012–2016. *AIDS and Behavior*, pages 1–16, 2018.

[161] Andrés Moya, Edward C Holmes, and Fernando González-Candelas. The population genetics and evolutionary epidemiology of rna viruses. *Nature Reviews Microbiology*, 2(4):279–288, 2004.

[162] Carmen Lía Murall, Chris T Bauch, and Troy Day. Could the human papillomavirus vaccines drive virulence evolution? In *Proc. R. Soc. B*, volume 282, page 20141069. The Royal Society, 2015.

[163] Opendra Narayan and Janice E Clements. Biology and pathogenesis of lentiviruses. *Journal of General Virology*, 70(7):1617–1639, 1989.

[164] Nneka Nwokolo, Andrew Hill, Alan McOwan, and Anton Pozniak. Rapidly declining HIV infection in MSM in central london. *The lancet HIV*, 4(11):e482–e483, 2017.

[165] Public Health Agency of Canada. M-track: Enhanced surveillance of hiv, sexually transmitted and blood-borne infections and associated risk behaviours among men

who have sex with men in canada. phase 1 report. centre for communicable diseases and infection control, infectious disease prevention and control branch, public health agency of canada. 2011.

[166] Public Health Agency of Canada (through CATIE.ca). Hiv/aids epi updates: National hiv prevalence and incidence estimates for 2011. centre for communicable diseases and infection control, public health agency of canada. 2014.

[167] Public Health Agency of Canada (through CATIE.ca). Public health agency of canada. summary: Estimates of hiv incidence, prevalence and canada's progress on meeting the 90-90-90 hiv targets. *Public Health Agency of Canada*, 2016.

[168] Charles I Okwundu, Olalekan A Uthman, and Christy AN Okoromah. Antiretroviral pre-exposure prophylaxis (prep) for preventing hiv in high-risk individuals. *Cochrane database of systematic reviews*, (7), 2012.

[169] Dale O'Leary. The syndemic of aids and stds among msm. *The Linacre Quarterly*, 81(1):12–37, 2014.

[170] Tamer Oraby, Vivek Thampi, and Chris T Bauch. The influence of social norms on the dynamics of vaccinating behaviour for paediatric infectious diseases. *Proc. R. Soc. B*, 281(1780):20133172, 2014.

[171] A David Paltiel, Rochelle P Walensky, Bruce R Schackman, George R Seage III, Lauren M Mercincavage, Milton C Weinstein, and Kenneth A Freedberg. Expanded hiv screening in the united states: effect on clinical outcomes, hiv transmission, and costs. *Annals of internal medicine*, 145(11):797–806, 2006.

[172] Abhishek Pandey, Katherine E Atkins, Jan Medlock, Natasha Wenzel, Jeffrey P Townsend, James E Childs, Tolbert G Nyenswah, Martial L Ndeffo-Mbah, and Alison P Galvani. Strategies for containing ebola in west africa. *Science*, 346(6212):991–995, 2014.

[173] Abhishek Pandey and Alison P Galvani. The global burden of hiv and prospects for control. *The Lancet HIV*, 6(12):e809–e811, 2019.

[174] Sang Woo Park and Benjamin M Bolker. Effects of contact structure on the transient evolution of hiv virulence. *PLoS computational biology*, 13(3):e1005453, 2017.

[175] Preeti Pathela, Sarah L Braunstein, Susan Blank, and Julia A Schillinger. HIV incidence among men with and those without sexually transmitted rectal infections: estimates from matching against an HIV case registry. *Clinical infectious diseases*, 57(8):1203–1209, 2013.

[176] Rudy Patrick, David Forrest, Gabriel Cardenas, Jenevieve Opoku, Manya Magnus, II Gregory Phillips, Alan Greenberg, Lisa Metsch, Michael Kharfen, Marlene LaLota, et al. Awareness, willingness, and use of Pre-Exposure Prophylaxis among men who have sex with men in Washington, DC and Miami-Dade county, FL: national HIV behavioral surveillance, 2011 and 2014. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, 75:S375–S382, 2017.

[177] Lynn A Paxton, Tony Hope, and Harold W Jaffe. Pre-Exposure Prophylaxis for HIV infection: what if it works? *The lancet*, 370(9581):89–93, 2007.

[178] Jacques Pepin. *The origins of AIDS*. Cambridge University Press, 2011.

[179] Freddy Perez, Bertha Gomez, Giovanni Ravasi, and Massimo Ghidinelli. Progress and challenges in implementing hiv care and treatment policies in latin america following the treatment 2.0 initiative. *BMC public health*, 15(1):1260, 2015.

[180] Joe Pharaon and Chris Bauch. The influence of social behavior on competition between virulent pathogen strains. *bioRxiv*, page 293936, 2018.

[181] Joe Pharaon and Chris T Bauch. The impact of pre-exposure prophylaxis for human immunodeficiency virus on gonorrhea prevalence. *medRxiv*, page 19005207, 2019.

[182] Steven D Pinkerton and Paul R Abramson. Effectiveness of condoms in preventing HIV transmission. *Social science & medicine*, 44(9):1303–1312, 1997.

[183] Joseph A Politch, Kenneth H Mayer, Seth L Welles, William X O'BRIEN, Chong Xu, Frederick P Bowman, and Deborah J Anderson. Highly active antiretroviral therapy does not completely suppress hiv in semen of sexually active hiv-infected men who have sex with men. *AIDS (London, England)*, 26(12):1535, 2012.

[184] Elizabeth Pollom, Kristen K Dang, E Lake Potter, Robert J Gorelick, Christina L Burch, Kevin M Weeks, and Ronald Swanstrom. Comparison of siv and hiv-1 genomic rna structures reveals impact of sequence evolution on conserved and non-conserved structural motifs. *PLoS Pathog*, 9(4):e1003294, 2013.

[185] Jalal Poorolajal, Leila Molaeipoor, Minoo Mohraz, Hossein Mahjub, Maryam Taghizadeh Ardekani, Pegah Mirzapour, and Hanieh Golchehregan. Predictors of progression to aids and mortality post-HIV infection: a long-term retrospective cohort study. *AIDS care*, 27(10):1205–1212, 2015.

[186] Frank A Post, Motasim Badri, Robin Wood, and Gary Maartens. Aids in africa-survival according to aids-defining illness. *South African medical journal*, 91(7):583–586, 2001.

[187] Mapping PrEP. First ever data on prep users across the us aidsvu, 2018.

[188] Narat Punyacharoensin, William John Edmunds, Daniela De Angelis, Valerie Delpech, Graham Hart, Jonathan Elford, Alison Brown, Noel Gill, and Richard G White. Modelling the HIV epidemic among MSM in the United Kingdom: quantifying the contributions to HIV transmission to better inform prevention initiatives. *Aids*, 29(3):339–349, 2015.

[189] GH Rabbani and WB Greenough III. Food as a vehicle of transmission of cholera. *Journal of diarrhoeal diseases research*, pages 1–9, 1999.

[190] SM Ashrafur Rahman, Naveen K Vaidya, and Xingfu Zou. Impact of early treatment programs on HIV epidemics: An immunity-based mathematical model. *Mathematical biosciences*, 280:38–49, 2016.

[191] Andrew Rambaut, David L Robertson, Oliver G Pybus, Martine Peeters, and Edward C Holmes. Phylogeny and the origin of HIV-1. *Nature*, 410(6832):1047, 2001.

[192] Jayoti Rana, James Wilton, Shawn Fowler, Trevor A Hart, Ahmed M Bayoumi, and Darrell HS Tan. Trends in the awareness, acceptability, and usage of HIV Pre-Exposure Prophylaxis among at-risk men who have sex with men in Toronto. *Canadian Journal of Public Health*, pages 1–11, 2018.

[193] Andrew F Read, Susan J Baigent, Claire Powers, Lydia B Kgosana, Luke Blackwell, Lorraine P Smith, David A Kennedy, Stephen W Walkden-Brown, and Venugopal K Nair. Imperfect vaccination can enhance the transmission of highly virulent pathogens. *PLoS Biology*, 13(7):e1002198, 2015.

[194] Robert S Remis, Michel Alary, Juan Liu, Rupert Kaul, and Robert WH Palmer. Hiv transmission among men who have sex with men due to condom failure. *PloS one*, 9(9), 2014.

[195] Genevieve Rocheleau, Conrado Franco-Villalobos, Natalia Oliveira, Zabrina L Brumme, Melanie Rusch, Jeannie Shoveller, Chanson J Brumme, and P Richard Harrigan. Sociodemographic correlates of HIV drug resistance and access to drug resistance testing in British Columbia, Canada. *PloS one*, 12(9):e0184848, 2017.

[196] Alison J Rodger, Valentina Cambiano, Tina Bruun, Pietro Vernazza, Simon Collins, Olaf Degen, Giulio Maria Corbelli, Vicente Estrada, Anna Maria Geretti, Apostolos Beloukas, et al. Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study. *The Lancet*, 2019.

[197] Rachel A Royce, Arlene Sena, Willard Cates Jr, and Myron S Cohen. Sexual transmission of HIV. *New England Journal of Medicine*, 336(15):1072–1078, 1997.

[198] George W Rutherford, Alan R Lifson, Nancy A Hessol, William W Darrow, Paul M O'Malley, Susan P Buchbinder, J Lowell Barnhart, Torsten W Bodecker, Lyn Cannon, and Lynda S Doll. Course of hiv-i infection in a cohort of homosexual and bisexual men: an 11 year follow up study. *Bmj*, 301(6762):1183–1188, 1990.

[199] Andrea Saltelli, Marco Ratto, Stefano Tarantola, Francesca Campolongo, European Commission, et al. Sensitivity analysis practices: Strategies for model-based inference. *Reliability Engineering & System Safety*, 91(10-11):1109–1125, 2006.

[200] Dena L Schanzer. Trends in hiv/aids mortality in canada, 1987–1998. *Canadian journal of public health*, 94(2):135–139, 2003.

[201] Joshua T Schiffer, Bryan T Mayer, Youyi Fong, David A Swan, and Anna Wald. Herpes simplex virus-2 transmission probability estimates based on quantity of viral shedding. *Journal of The Royal Society Interface*, 11(95):20140160, 2014.

[202] Susan Scott and Christopher J Duncan. *Biology of plagues: evidence from historical populations*. Cambridge University Press, 2001.

[203] Swarnali Sharma and GP Samanta. Dynamical behaviour of an HIV/AIDS epidemic model. *Differential Equations and Dynamical Systems*, 22(4):369–395, 2014.

[204] O Sharomi, CN Podder, AB Gumel, EH Elbasha, and James Watmough. Role of incidence function in vaccine-induced backward bifurcation in some hiv models. *Mathematical Biosciences*, 210(2):436–463, 2007.

[205] Oluwaseun Sharomi, C Podder, Abba Gumel, and Baojun Song. Mathematical analysis of the transmission dynamics of HIV/TB coinfection in the presence of treatment. *Mathematical Biosciences and Engineering*, 5(1):145, 2008.

[206] Paul M Sharp and Beatrice H Hahn. Origins of hiv and the aids pandemic. *Cold Spring Harbor perspectives in medicine*, 1(1):a006841, 2011.

[207] Leah B Shaw and Ira B Schwartz. Fluctuating epidemics on adaptive networks. *Physical Review E*, 77(6):066101, 2008.

[208] Boris Shulgin, Lewi Stone, and Zvia Agur. Pulse vaccination strategy in the sir epidemic model. *Bulletin of mathematical biology*, 60(6):1123–1148, 1998.

[209] Paul A Shuper, Narges Joharchi, Hyacinth Irving, David Fletcher, Colin Kovacs, Mona Loutfy, Sharon L Walmsley, David KH Wong, and Jürgen Rehm. Differential predictors of art adherence among HIV-monoinfected versus HIV/HCV-coinfected individuals. *AIDS care*, 28(8):954–962, 2016.

[210] Cristiana J Silva and Delfim FM Torres. A SICA compartmental model in epidemiology with application to HIV/AIDS in Cape Verde. *Ecological complexity*, 30:70–75, 2017.

[211] Harold J Simon et al. Attenuated infection. the germ theory in contemporary perspective. *Attenuated Infection. The Germ Theory in Contemporary Perspective.*, 1960.

[212] Jane M Simoni, Cynthia R Pearson, David W Pantalone, Gary Marks, and Nicole Crepaz. Efficacy of interventions in improving highly active antiretroviral therapy adherence and hiv-1 rna viral load: a meta-analytic review of randomized controlled trials. *Journal of acquired immune deficiency syndromes (1999)*, 43(0 1):S23, 2006.

[213] Ameeta E Singh, Jennifer Gratrix, Irene Martin, Dara S Friedman, Linda Hoang, Richard Lester, Gila Metz, Gina Ogilvie, Ron Read, and Tom Wong. Gonorrhea treatment failures with oral and injectable expanded spectrum Cephalosporin monotherapy vs dual therapy at 4 Canadian sexually transmitted infection clinics, 2010–2013. *Sexually transmitted diseases*, 42(6):331–336, 2015.

[214] Davey M Smith, Joseph K Wong, George K Hightower, Caroline C Ignacio, Kersten K Koelsch, Christos J Petropoulos, Douglas D Richman, and Susan J Little. Hiv drug resistance acquired through superinfection. *Aids*, 19(12):1251–1256, 2005.

[215] Dawn K Smith, Jeffrey H Herbst, Xinjiang Zhang, and Charles E Rose. Condom effectiveness for HIV prevention by consistency of use among men who have sex with men in the United States. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, 68(3):337–344, 2015.

[216] Miriam Smith. Social movements and equality seeking: the case of gay liberation in Canada. *Canadian Journal of Political Science/Revue canadienne de science politique*, 31(2):285–309, 1998.

[217] Robert J Smith? and Sally M Blower. Could disease-modifying HIV vaccines cause population-level perversity? *The Lancet infectious diseases*, 4(10):636–639, 2004.

[218] Christoph D Spinner, Christoph Boesecke, Alexander Zink, Heiko Jessen, Hans-Jürgen Stellbrink, Jürgen Kurt Rockstroh, and Stefan Esser. HIV Pre-Exposure Prophylaxis (PrEP): a review of current knowledge of oral systemic HIV PrEP in humans. *Infection*, 44(2):151–158, 2016.

[219] Benjamin B Strauss, George J Greene, Gregory Phillips, Ramona Bhatia, Krystal Madkins, Jeffrey T Parsons, and Brian Mustanski. Exploring patterns of awareness and use of HIV Pre-Exposure Prophylaxis among young men who have sex with men. *AIDS and Behavior*, 21(5):1288–1298, 2017.

[220] Zhimin Su, Caiting Dong, Ping Li, Hongxia Deng, Yuhan Gong, Shiyong Zhong, Min Wu, Yuhua Ruan, Guangming Qin, Wen Yang, et al. A mathematical modeling study of the HIV epidemics at two rural townships in the Liangshan prefecture of the Sichuan province of China. *Infectious Disease Modelling*, 1(1):3–10, 2016.

[221] NH Swellengrebel et al. The efficient parasite. *Science*, 92(2395):465–469, 1940.

[222] Trussler T., Banks P., Marchand R., Robert W., Gustafson R., Hogg R., Gilbert M., and the ManCount Survey Team. Mancount sizes-up the gaps: a sexual health survey of gay men in Vancouver. Vancouver coastal health: Vancouver. 2010.

[223] Darrell HS Tan, Thomas M Dashwood, James Wilton, Abigail Kroch, Tara Gomes, and Diana Martins. Trends in hiv pre-exposure prophylaxis uptake in ontario, canada, and impact of policy changes: a population-based analysis of projected pharmacy data (2015–2018). *Canadian Journal of Public Health*, pages 1–8, 2020.

[224] Darrell HS Tan, Mark W Hull, Deborah Yoong, Cécile Tremblay, Patrick O'byrne, Réjean Thomas, Julie Kille, Jean-Guy Baril, Joseph Cox, Pierre Giguere, et al. Canadian guideline on HIV pre-exposure prophylaxis and nonoccupational postexposure prophylaxis. *Canadian Medical Association Journal*, 189(47):E1448–E1458, 2017.

[225] John Tapsall. Antibiotic resistance in Neisseria Gonorrhoeae is diminishing available treatment options for Gonorrhea: some possible remedies. *Expert review of anti-infective therapy*, 4(4):619–628, 2006.

[226] Raymond A Tetteh, Barbara A Yankey, Edmund T Nartey, Margaret Lartey, Hubert GM Leufkens, and Alexander NO Dodoo. Pre-Exposure Prophylaxis for HIV prevention: safety concerns. *Drug safety*, 40(4):273–283, 2017.

[227] Stephen R Thomas and Joseph S Elkinton. Pathogenicity and virulence. *Journal of invertebrate pathology*, 85(3):146–151, 2004.

[228] K Tomas, P Dhami, C Houston, S Ogunnaike-Cooke, and C Rank. Good news on HIV: HIV in Canada: 2009 to 2014. *Canada Communicable Disease Report*, 41(12):292, 2015.

[229] Nancy Tomes. "destroyer and teacher": Managing the masses during the 1918–1919 influenza pandemic. *Public Health Reports*, 125(3_suppl):48–62, 2010.

[230] S Towers and G Chowell. Impact of weekday social contact patterns on the modeling of influenza transmission, and determination of the influenza latent period. *Journal of theoretical biology*, 312:87–95, 2012.

[231] Michael W Traeger, Sophia E Schroeder, Edwina J Wright, Margaret E Hellard, Vincent J Cornelisse, Joseph S Doyle, and Mark A Stoové. Effects of pre-exposure prophylaxis for the prevention of human immunodeficiency virus infection on sexual risk behavior in men who have sex with men: a systematic review and meta-analysis. *Clinical Infectious Diseases*, 67(5):676–686, 2018.

[232] Stephen Tully, Monica Cojocaru, and Chris T Bauch. Sexual behavior, risk perception, and HIV transmission can respond to HIV antiviral drugs and vaccines through multiple pathways. *Scientific reports*, 5:15411, 2015.

[233] Stephen Tully, Monica-Gabriela Cojocaru, and Chris T Bauch. Multiplayer games and HIV transmission via casual encounters. *Mathematical Biosciences & Engineering*, 14(2):359–376, 2017.

[234] UNAIDS. Men who have sex with men, size estimate. 2018.

[235] Magnus Unemo, Daniel Golparian, and David W Eyre. Antimicrobial resistance in Neisseria Gonorrhoeae and treatment of Gonorrhea. In *Neisseria Gonorrhoeae*, pages 37–58. Springer, 2019.

[236] Ana Vallari, Pierre Bodelle, Charlotte Ngansop, Florence Makamche, Nicaise Ndembi, Dora Mbanya, Lazare Kaptué, Lutz G Gürtler, Carole P McArthur, Sushil G Devare, et al. Four new hiv-1 group n isolates from cameroon: Prevalence continues to be low. *AIDS research and human retroviruses*, 26(1):109–115, 2010.

[237] Jay J Van Bavel, Katherine Baicker, Paulo S Boggio, Valerio Capraro, Aleksandra Cichocka, Mina Cikara, Molly J Crockett, Alia J Crum, Karen M Douglas, James N Druckman, et al. Using social and behavioural science to support covid-19 pandemic response. *Nature Human Behaviour*, pages 1–12, 2020.

[238] Pauline Van den Driessche and James Watmough. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical biosciences*, 180(1-2):29–48, 2002.

[239] Anna Van Laarhoven, Elske Hoornenborg, Roel Achterbergh, Henry De Vries, Maria Prins, and Maarten Schim Van Der Loeff. O09. 3 changes in sexual risk behaviour among daily PrEP users after 6 months of use in the Amsterdam prep project, 2017.

[240] Gregory T Vanley, Robert Huberman, and Robert B Lufkin. Atypical pneumocystis carinii pneumonia in homosexual men with unusual immunodeficiency. *American Journal of Roentgenology*, 138(6):1037–1041, 1982.

[241] Pietro L Vernazza, Joseph J Eron, Susan A Fiscus, and Myron S Cohen. Sexual transmission of hiv: infectiousness and prevention. *Aids*, 13(2):155–166, 1999.

[242] Erik M Volz, James S Koopman, Melissa J Ward, Andrew Leigh Brown, and Simon DW Frost. Simple epidemiological dynamics explain phylogenetic clustering of HIV from patients with recent infection. *PLoS computational biology*, 8(6):e1002552, 2012.

[243] Sabine Vygen, Aurélie Fischer, Laure Meurice, Ibrahim Mounchetrou Njoya, Marina Gregoris, Bakhao Ndiaye, Adrien Ghenassia, Isabelle Poujol, Jean Paul Stahl, Denise Antona, et al. Waning immunity against mumps in vaccinated young adults, france 2013. *Eurosurveillance*, 21(10):30156, 2016.

[244] Zixin Wang, Joseph TF Lau, Yuan Fang, Mary Ip, and Danielle L Gross. Prevalence of actual uptake and willingness to use Pre-Exposure Prophylaxis to prevent HIV acquisition among men who have sex with men in Hong Kong, China. *PloS one*, 13(2):e0191671, 2018.

[245] Susan C Weller. A meta-analysis of condom effectiveness in reducing sexually transmitted HIV. *Social science & medicine*, 36(12):1635–1644, 1993.

[246] Annemarie MJ Wensing, David A Van De Vijver, Gioacchino Angarano, Birgitta Åsjö, Claudia Balotta, Enzo Boeri, Ricardo Camacho, Maire-Laure Chaix, Dominique Costagliola, Andrea De Luca, et al. Prevalence of drug-resistant HIV-1 variants in untreated individuals in europe: implications for clinical management. *The Journal of infectious diseases*, 192(6):958–966, 2005.

[247] Brian G Williams, James O Lloyd-Smith, Eleanor Gouws, Catherine Hankins, Wayne M Getz, John Hargrove, Isabelle De Zoysa, Christopher Dye, and Bertran Auvert. The potential impact of male circumcision on HIV in Sub-Saharan Africa. *PLoS medicine*, 3(7):e262, 2006.

[248] David P Wilson, Alexander Hoare, David G Regan, and Matthew G Law. Importance of promoting hiv testing for preventing secondary transmissions: modelling the australian hiv epidemic among men who have sex with men. *Sexual health*, 6(1):19–33, 2009.

[249] David P Wilson, David G Regan, Kelly-Jean Heymer, Fengyi Jin, Garrett P Prestage, and Andrew E Grulich. Serosorting may increase the risk of hiv acquisition among men who have sex with men. *Sexually transmitted diseases*, 37(1):13–17, 2010.

[250] J Wilton, J Liu, A Sullivan, B Rachlis, A Marchand-Austin, M Giles, et al. Ontario hiv epidemiology and surveillance initiative. trends in hiv care cascade engagement among diagnosed people living with hiv in ontario, canada: A retrospective, population-based cohort study. *PLoS One*, 14(1):e0210096, 2019.

[251] Jacqui Wise. Pre-exposure prophylaxis may increase risky behaviour when introduced, study finds, 2018.

[252] Ngai Sze Wong, Tsz Ho Kwan, Owen TY Tsang, Man Po Lee, Wing Cheong Yam, Wilson Lam, Wai Shing Leung, Jacky MC Chan, Kai Man Ho, and Shui Shan Lee. Pre-exposure prophylaxis (prep) for msm in low hiv incidence places: should high risk individuals be targeted? *Scientific reports*, 8(1):1–9, 2018.

[253] Kimberly A Workowski and Gail A Bolan. Sexually transmitted diseases treatment guidelines, 2015. *MMWR. Recommendations and reports: Morbidity and mortality weekly report. Recommendations and reports*, 64(RR-03):1, 2015.

[254] Michael Worobey, Marlea Gemmel, Dirk E Teuwen, Tamara Haselkorn, Kevin Kunstman, Michael Bunce, Jean-Jacques Muyembe, Jean-Marie M Kabongo, Raphaël M Kalengayi, Eric Van Marck, et al. Direct evidence of extensive diversity of hiv-1 in kinshasa by 1960. *Nature*, 455(7213):661–664, 2008.

[255] Michael Worobey, Thomas D Watts, Richard A McKay, Marc A Suchard, Timothy Granade, Dirk E Teuwen, Beryl A Koblin, Walid Heneine, Philippe Lemey, and Harold W Jaffe. 1970s and 'patient 0'hiv-1 genomes illuminate early hiv/aids history in north america. *Nature*, 539(7627):98–101, 2016.

[256] Jianyong Wu, Radhika Dhingra, Manoj Gambhir, and Justin V Remais. Sensitivity analysis of infectious disease models: methods, advances and their application. *Journal of The Royal Society Interface*, 10(86):20121018, 2013.

[257] Yanni Xiao, Sanyi Tang, Yicang Zhou, Robert J Smith, Jianhong Wu, and Ning Wang. Predicting the HIV/AIDS epidemic and measuring the effect of mobility in mainland China. *Journal of theoretical biology*, 317:271–285, 2013.

[258] Ashley York. Undetectable equals untransmittable, 2019.

[259] Tunde T Yusuf and Francis Benyah. Optimal strategy for controlling the spread of HIV/AIDS disease: a case study of south africa. *Journal of biological dynamics*, 6(2):475–494, 2012.

[260] I Zablotska, S Vaccher, M Bloch, et al. No hiv infections despite high-risk behaviour and sti incidence among gay/bisexual men taking daily pre-exposure prophylaxis (prep): the prelude demonstration project. In *Program and abstracts of the 9th IAS Conference on HIV Science, Paris, France*, 2017.

[261] Damián H Zanette and Sebastián Risau-Gusmán. Infection spreading in a population with evolving contacts. *Journal of biological physics*, 34(1-2):135–148, 2008.

[262] Lei Zhang, David G Regan, Eric PF Chow, Manoj Gambhir, Vincent Cornelisse, Andrew Grulich, Jason Ong, David A Lewis, Jane Hocking, and Christopher K Fairley. Neisseria gonorrhoeae transmission among men who have sex with men: an anatomical site-specific mathematical model evaluating the potential preventive impact of mouthwash. *Sexually transmitted diseases*, 44(10):586–592, 2017.

[263] Tuofu Zhu, Bette T Korber, Andre J Nahmias, Edward Hooper, Paul M Sharp, and David D Ho. An african hiv-1 sequence from 1959 and implications for the origin of the epidemic. *Nature*, 391(6667):594–597, 1998.

APPENDICES

Appendix A

Tables and Codes

A.1 Sample MATLAB code for heat-maps in chapter 4

```
options2 = odeset('NonNegative',[1 2 3 4 5 6 7 8]);
global mu delta eg f bh eh ft ap bg at

mu=1/20075.0;
delta=1/20075.0;
bh=0.001275;
eg=0.83;
f=0.54/365;
eh=0.9;
ft=1/180.0;
ap=12.75;
bg=0.001475;
at=3.875;
```

```
fp=0.001:0.00039:0.04;
rho=0.000001:0.00000049:0.00005;
A=zeros(length(fp),length(rho));

for i=1:length(rho)
    for j=1:length(fp)
        [t,y]=ode45(@(t,Y)HIVGCPREP_HeatMap_fprho(t,Y,rho(i),fp(j)),[0 100000],[0.7
0.08 0.02 0.06 0.03 0.01 0.09 0.01],options2);
        A(j,i)=y(end,3)+y(end,4)+y(end,6)+y(end,8);
    end
end

colormap('hot')
imagesc(A)
set(gca,'YDir','normal')
set(gca,'FontSize',16)
set(gca,'YTickLabelRotation',90)
ax=gca;
ax.XTick=[1 20 40 60 81 101];
ax.XTickLabel={'0.1','1','2','3','4','5'};
ax.YTick=[1 24 50 75 101];
ax.YTickLabel={'0.001','0.01','0.02','0.03','0.04'};
xlabel('\rho (x10^{-5})')
ylabel('f_p')
colorbar
```

A.2 Transition rates for Chapter 5

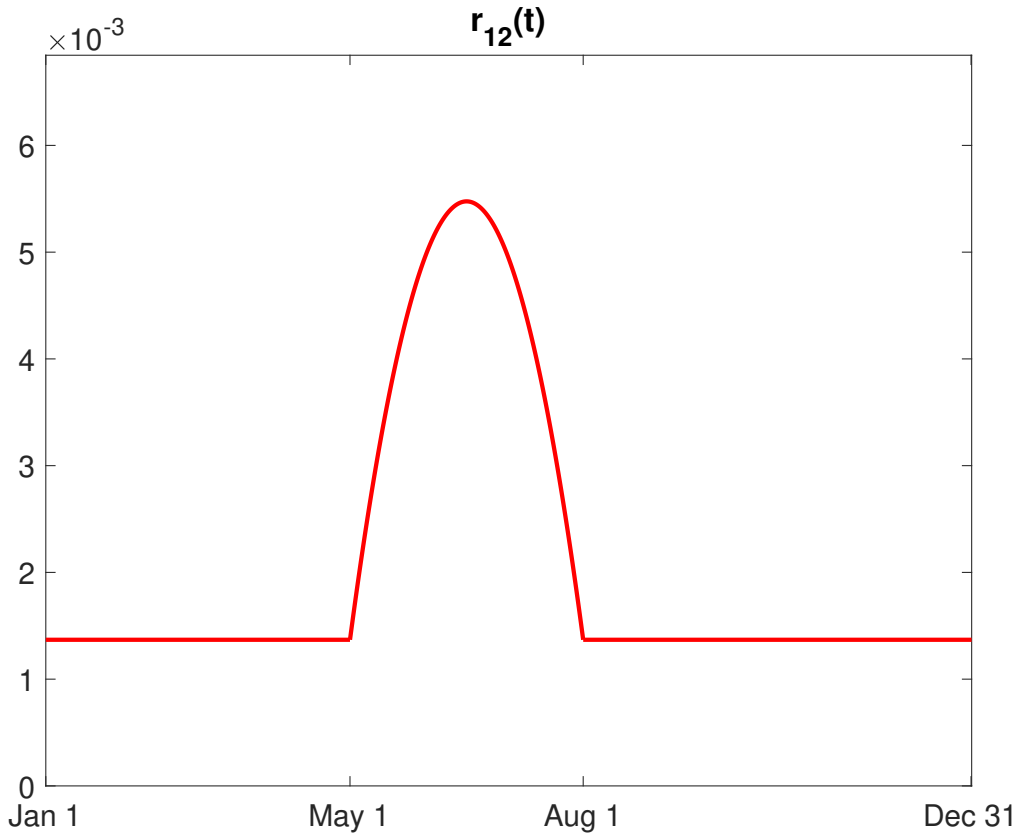

Figure A.1: Transition rate from low risk to high risk

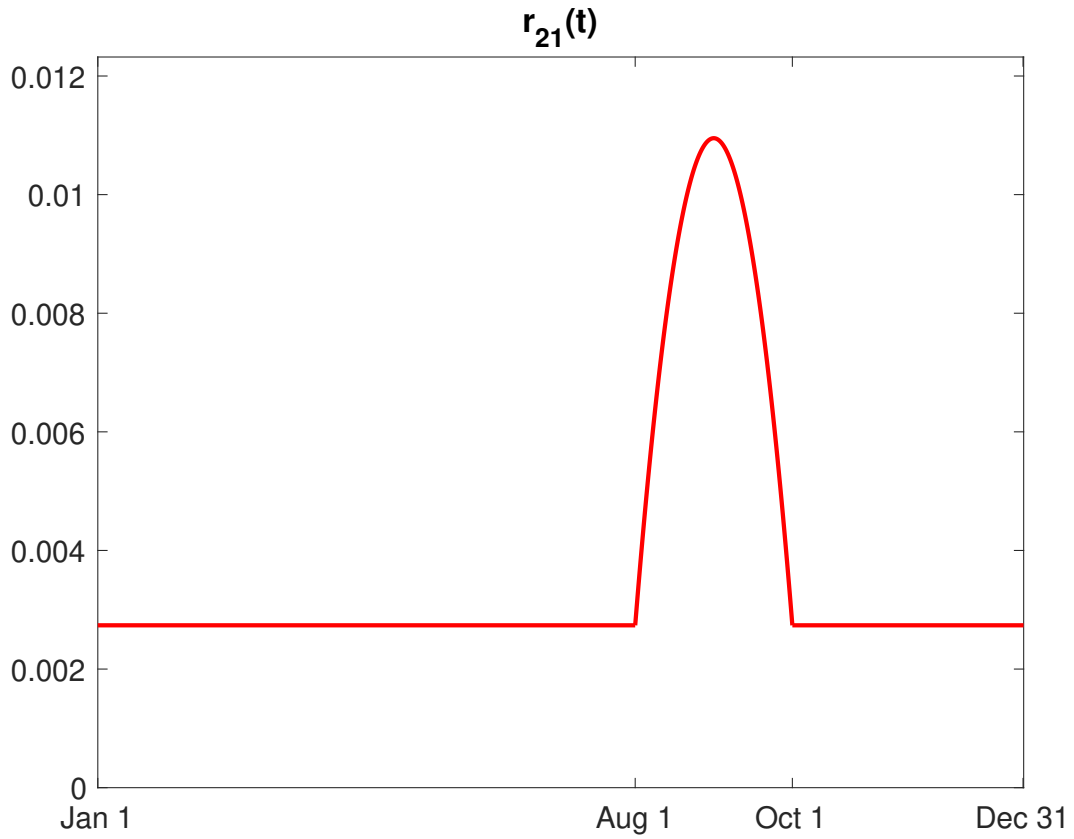

Figure A.2: Transition rate from high risk to low risk

A.3 Tables for Chapter 5

Table 2: HIV Prevalence (%) with Average Number of Yearly Tests and PrEP Users for Different Testing Strategies (PrEP recruitment is at baseline)

Testing strategy	HIV prevalence	95% CI	Cases/10K	Avg(S_1+I_1)/Y	Avg(S_1+I_1)/S	Avg(S_2+I_2)/Y	Avg(S_2+I_2)/S	#Tests/Y	Avg(P_1)/Y	Avg(P_1)/S	Avg(P_2)/Y	Avg(P_2)/S	#PrEP/Y
Once every 2 years LR	0.229	(0.216-0.243)	23	77638	76333	11345	12650	38819	1169	1150	171	190	1340
Once every year LR	0.079	(0.073-0.086)	8	78684	77362	11503	12825	78684	1180	1160	174	194	1354
Twice every year LR	0.036	(0.032-0.041)	4	78908	77582	11535	12861	157816	1179	1159	172	192	1351
four times every year LR	0.021	(0.018-0.023)	3	79238	77907	11586	12918	316952	1180	1160	173	193	1353
Once every 2 years HR	7.728	(7.403-8.053)	773	79601	78263	11528	12866	5764	1156	1137	170	189	1326
Once every year HR	1.916	(1.819-2.013)	192	79446	78110	11533	12868	11533	1176	1157	170	190	1346
Twice every year HR	0.503	(0.482-0.523)	51	80168	78821	11659	13006	23318	1196	1176	175	195	1371
four times every year HR	0.231	(0.220-0.241)	24	79536	78199	11585	12922	46340	1182	1162	172	192	1354
Once every 2 years LHR	0.131	(0.121-0.140)	14	78807	77482	11516	12840	45162	1173	1153	171	191	1344
Once every year LHR	0.054	(0.049-0.059)	6	78595	77274	11471	12792	90066	1178	1158	172	192	1350
Twice every year LHR	0.026	(0.024-0.028)	3	79396	78062	11608	12943	182008	1185	1165	173	193	1358
four times every year LHR	0.012	(0.010-0.013)	2	79133	77803	11559	12889	362768	1185	1165	173	193	1358
Step once every 2 years LR	0.569	(0.535-0.604)	57	78297	76981	11461	12777	25880	1171	1152	170	190	1341
Step once every year LR	0.243	(0.228-0.258)	25	78185	76871	11445	12759	38655	1162	1142	169	188	1331
Step twice every year LR	0.104	(0.098-0.110)	11	78142	76829	11437	12750	64243	1166	1147	170	190	1336
Step four times every year LR	0.057	(0.052-0.061)	6	79162	77832	11588	12919	116970	1182	1162	171	191	1353
Step once every 2 years HR	18.333	(17.602-19.065)	1834	79626	78287	11504	12842	3099	1129	1110	164	183	1293
Step once every year HR	9.67	(9.345-9.995)	967	78308	76992	11328	12644	5159	1138	1119	166	185	1304
Step twice every year HR	2.891	(2.773-3.009)	290	78812	77487	11423	12747	9450	1155	1136	168	187	1323
Step four times every year HR	0.745	(0.711-0.779)	75	78586	77625	11427	12748	17950	1173	1154	171	191	1344
Step once every 2 years LHR	0.302	(0.283-0.321)	31	78641	77319	11495	12817	29088	1170	1151	170	190	1340
Step once every year LHR	0.143	(0.133-0.153)	15	78877	77551	11522	12847	44239	1177	1157	172	192	1349
Step twice every year LHR	0.069	(0.064-0.073)	7	78826	77501	11508	12833	74320	1181	1161	172	192	1353
Step four times every year LHR	0.035	(0.032-0.038)	4	79024	77696	11537	12865	134881	1186	1166	173	193	1359
Hub once every 2 years LR	4.646	(4.402-4.891)	465	76559	75272	11212	12498	12546	1121	1102	162	181	1283
Hub once every year LR	0.62	(0.582-0.659)	62	77715	76409	11363	12669	25470	1155	1136	169	188	1324
Hub twice every year LR	0.153	(0.145-0.162)	16	77996	76685	11409	12720	51124	1167	1147	170	190	1337
Hub four times every year LR	0.062	(0.056-0.067)	7	79388	78054	11615	12949	104072	1191	1171	174	194	1365
Hub once every 2 years HR	23.558	(22.944-24.172)	2356	79870	78528	11552	12895	2150	1121	1102	164	182	1285
Hub once every year HR	12.416	(11.975-12.858)	1242	78508	77189	11349	12668	4223	1119	1100	164	183	1283
Hub twice every year HR	3.783	(3.618-3.947)	379	78954	77627	11444	12770	8514	1159	1140	169	188	1328
Hub four times every year HR	0.861	(0.829-0.893)	87	79652	78313	11581	12920	17227	1193	1172	175	195	1368
Hub once every 2 years LHR	1.915	(1.824-2.007)	192	77656	76351	11341	12646	14833	1152	1133	168	188	1320
Hub once every year LHR	0.265	(0.250-0.280)	27	79049	77720	11556	12885	30202	1181	1161	172	192	1353
Hub twice every year LHR	0.084	(0.079-0.088)	9	79782	78441	11660	13001	60962	1189	1169	174	194	1363
Hub four times every year LHR	0.038	(0.036-0.041)	4	79468	78133	11612	12947	121440	1184	1165	173	193	1357

Table 3: HIV Prevalence (%) with Average Number of Yearly Tests and PrEP Users for Different PrEP Recruitment Strategies (Testing frequencies are at baseline)

PrEP recruitment strategy	HIV prevalence	95% CI	Cases/10K	Avg(S_1+I_1)/Y	Avg(S_1+I_1)/S	Avg(S_2+I_2)/Y	Avg(S_2+I_2)/S	#Tests/Y	Avg(P_1)/	Avg(P_1)/S	Avg(P_2)/Y	Avg(P_2)/S	#PrEP/Y
1%/Y recruitment LR	0.811	(0.752-0.869)	81	78437	77118	11516	12835	21049	1388	1365	148	172	1536
5%/Y recruitment LR	0.688	(0.633-0.704)	69	72880	71655	10890	12115	19582	5962	5861	626	726	6588
10%/Y recruitment LR	0.527	(0.492-0.562)	53	68524	67372	10475	11627	18441	11121	10934	1159	1345	12280
20%/Y recruitment LR	0.373	(0.355-0.391)	38	60707	59687	9697	10717	16389	19629	19299	2051	2381	21680
1%/Y recruitment HR	0.875	(0.829-0.920)	88	78834	77509	11471	12796	21143	256	252	90	95	346
5%/Y recruitment HR	0.835	(0.759-0.911)	84	78888	77562	11268	12594	21131	765	752	376	389	1141
10%/Y recruitment HR	0.800	(0.749-0.852)	80	78129	76816	10914	12227	20897	1374	1351	714	737	2088
20%/Y recruitment HR	0.721	(0.678-0.764)	72	77839	76531	10403	11711	20761	2487	2445	1340	1381	3827
1%/Y recruitment LHR	0.801	(0.743-0.859)	80	77918	76608	11380	12690	20902	1503	1478	219	245	1722
5%/Y recruitment LHR	0.620	(0.577-0.663)	62	72918	71692	10651	11876	19561	6579	6468	963	1073	7542
10%/Y recruitment LHR	0.501	(0.480-0.522)	51	67520	66385	9868	11003	18114	12094	11891	1770	1973	13864
20%/Y recruitment LHR	0.357	(0.333-0.381)	36	58754	57766	8577	9564	15761	20969	20616	3067	3420	24036
Step 1%/Y recruitment LR	0.883	(0.823-0.943)	89	78095	76783	11459	12772	20957	1171	1151	126	146	1297
Step 5%/Y recruitment LR	0.799	(0.765-0.833)	80	76386	75103	11282	12566	20507	2757	2711	287	333	3044
Step 10%/Y recruitment LR	0.695	(0.658-0.733)	70	74336	73087	11065	12314	19968	4671	4592	488	567	5159
Step 20%/Y recruitment LR	0.601	(0.563-0.639)	61	72220	71006	10919	12133	19420	8380	8239	867	1008	9247
Step 1%/Y recruitment HR	0.912	(0.836-0.988)	92	78965	77637	11508	12835	21180	240	236	79	83	319
Step 5%/Y recruitment HR	0.883	(0.838-0.929)	89	79232	77901	11452	12784	21240	448	440	183	191	631
Step 10%/Y recruitment HR	0.857	(0.813-0.901)	86	78675	77353	11293	12615	21081	700	688	309	321	1009
Step 20%/Y recruitment HR	0.739	(0.684-0.795)	74	78953	77626	11175	12502	21136	1199	1179	560	580	1759
Step 1%/Y recruitment LHR	0.848	(0.795-0.900)	85	77964	76654	11396	12707	20916	1278	1256	187	209	1465
Step 5%/Y recruitment LHR	0.755	(0.711-0.799)	76	76116	74836	11132	12411	20421	3065	3013	449	501	3514
Step 10%/Y recruitment LHR	0.644	(0.625-0.703)	65	74276	73028	10854	12103	19926	5217	5129	764	852	5981
Step 20%/Y recruitment LHR	0.552	(0.525-0.578)	56	69706	68534	10174	11345	18699	9080	8927	1332	1485	10412
Hub 1%/Y recruitment LR	0.867	(0.818-0.916)	87	78162	76849	11436	12750	20970	534	525	59	68	593
Hub 5%/Y recruitment LR	0.774	(0.728-0.819)	78	76587	75300	11289	12577	20558	2162	2125	227	263	2389
Hub 10%/Y recruitment LR	0.711	(0.668-0.755)	72	75044	73783	11145	12406	20155	4105	4036	428	497	4533
Hub 20%/Y recruitment LR	0.616	(0.590-0.643)	62	71717	70511	10808	12013	19281	7734	7604	798	928	8532
Hub 1%/Y recruitment HR	0.860	(0.805-0.914)	86	79231	77900	11565	12896	21254	179	176	45	48	224
Hub 5%/Y recruitment HR	0.895	(0.838-0.952)	90	78846	77521	11440	12765	21142	390	383	148	155	538
Hub 10%/Y recruitment HR	0.824	(0.766-0.881)	83	78448	77130	11278	12596	21022	645	634	276	287	921
Hub 20%/Y recruitment HR	0.797	(0.739-0.855)	80	78315	76999	11076	12392	20964	1132	1113	522	541	1654
Hub 1%/Y recruitment LHR	0.895	(0.854-0.937)	90	79489	78153	11616	12952	21325	605	595	88	98	693
Hub 5%/Y recruitment LHR	0.799	(0.750-0.848)	80	76340	75057	11156	12439	20480	2408	2367	352	392	2760
Hub 10%/Y recruitment LHR	0.681	(0.643-0.719)	69	74874	73616	10937	12196	20086	4587	4510	672	749	5259
Hub 20%/Y recruitment LHR	0.566	(0.529-0.604)	57	71631	70427	10473	11676	19217	8701	8555	1280	1426	9981

Table 4: HIV Prevalence (%) with Average Number of Yearly Tests and PrEP Users for Combined Testing & PrEP Recruitment Strategies

Testing & PrEP recruitment strategy	HIV prevalence	95% CI	Cases/10K	Avg(S_1+I_1)/Y	Avg(S_1+I_1)/S	Avg(S_2+I_2)/Y	Avg(S_2+I_2)/S	#Tests/Y	Avg(P_1)/Y	Avg(P_1)/S	Avg(P_2)/Y	Avg(P_2)/S	#PrEP/Y
1/2Y Testing, 1%/Y PrEP LR	0.230	(0.212-0.248)	23	77810	76503	11428	12736	38905	1375	1352	146	169	1521
1/Y Testing, 5%/Y PrEP LR	0.083	(0.077-0.089)	9	74181	72935	11109	12356	74181	6113	6011	640	743	6753
2/Y Testing, 10%/Y PrEP LR	0.037	(0.034-0.040)	4	69334	68169	10609	11774	138668	11345	11154	1186	1377	12531
4/Y Testing, 20%/Y PrEP LR	0.019	(0.017-0.021)	2	61028	60002	9768	10794	244112	19923	19589	2078	2413	22001
1/2Y Testing, 1%/Y PrEP HR	8.686	(8.281-9.092)	869	79512	78175	11444	12781	5722	257	252	89	93	346
1/Y Testing, 5%/Y PrEP HR	1.853	(1.772-1.934)	186	80317	78967	11403	12753	11403	779	766	382	395	1161
2/Y Testing, 10%/Y PrEP HR	0.464	(0.436-0.491)	47	78901	77575	10961	12287	21922	1376	1353	717	740	2093
4/Y Testing, 20%/Y PrEP HR	0.233	(0.225-0.240)	24	78467	77148	10441	11759	41764	2514	2472	1354	1397	3868
1/2Y Testing, 1%/Y PrEP LHR	0.130	(0.123-0.138)	13	79182	77852	11568	12898	45375	1536	1510	225	251	1761
1/Y Testing, 5%/Y PrEP LHR	0.053	(0.050-0.055)	6	74103	72857	10831	12076	84934	6753	6639	988	1102	7741
2/Y Testing, 10%/Y PrEP LHR	0.025	(0.023-0.027)	3	67643	66506	9873	11010	155032	12208	12003	1789	1994	13997
4/Y Testing, 20%/Y PrEP LHR	0.011	(0.010-0.013)	2	59010	58018	8620	9611	270520	21201	20845	3112	3469	24313
Step 1/2Y Testing, 1%/Y PrEP LR	0.594	(0.549-0.638)	60	78539	77219	11549	12869	25960	1185	1165	128	148	1313
Step 1/Y Testing, 5%/Y PrEP LR	0.234	(0.217-0.252)	24	76887	75595	11353	12645	38013	2810	2762	295	342	3105
Step 2/Y Testing, 10%/Y PrEP LR	0.101	(0.094-0.108)	11	75192	73928	11211	12474	61818	4756	4676	495	575	5251
Step 4/Y Testing, 20%/Y PrEP LR	0.049	(0.044-0.054)	5	72145	70932	10919	12131	106601	8445	8303	876	1018	9321
Step 1/2Y Testing, 1%/Y PrEP HR	18.927	(18.279-19.575)	1893	80204	78856	11546	12894	3112	244	240	78	82	322
Step 1/Y Testing, 5%/Y PrEP HR	9.912	(9.530-10.293)	992	79383	78049	11374	12708	5184	439	432	178	186	617
Step 2/Y Testing, 10%/Y PrEP HR	3.082	(2.953-3.212)	309	80402	79051	11465	12816	9500	713	701	315	327	1028
Step 4/Y Testing, 20%/Y PrEP HR	0.749	(0.722-0.777)	75	79496	78160	11181	12517	17622	1204	1184	561	581	1765
Step 1/2Y Testing, 1%/Y PrEP LHR	0.315	(0.297-0.334)	32	79033	77704	11549	12877	29232	1304	1282	191	213	1495
Step 1/Y Testing, 5%/Y PrEP LHR	0.131	(0.123-0.138)	14	77015	75720	11267	12562	43203	3129	3076	458	511	3587
Step 2/Y Testing, 10%/Y PrEP LHR	0.063	(0.058-0.068)	7	75362	74096	11004	12271	71056	5320	5231	781	870	6101
Step 4/Y Testing, 20%/Y PrEP LHR	0.032	(0.029-0.035)	4	70933	69740	10364	11557	121082	9292	9136	1362	1519	10654
Hub 1/2Y Testing, 1%/Y PrEP LR	4.993	(4.750-5.236)	500	77679	76374	11403	12708	12729	534	525	61	70	595
Hub 1/Y Testing, 5%/Y PrEP LR	0.572	(0.539-0.605)	58	77069	75774	11366	12661	25258	2173	2137	229	265	2402
Hub 2/Y Testing, 10%/Y PrEP LR	0.141	(0.130-0.151)	15	75795	74521	11259	12532	49681	4181	4110	434	504	4615
Hub 4/Y Testing, 20%/Y PrEP LR	0.065	(0.061-0.069)	7	71424	70223	10777	11978	93631	7763	7632	801	932	8564
Hub 1/2Y Testing, 1%/Y PrEP HR	24.178	(23.442-24.913)	2418	80813	79455	11668	13027	2172	193	189	45	48	238
Hub 1/Y Testing, 5%/Y PrEP HR	12.918	(12.601-13.235)	1292	79066	77737	11342	12671	4224	382	375	142	148	524
Hub 2/Y Testing, 10%/Y PrEP HR	3.751	(3.542-3.960)	376	79706	78366	11373	12713	8476	642	631	274	284	916
Hub 4/Y Testing, 20%/Y PrEP HR	0.826	(0.780-0.872)	83	79314	77981	11183	12516	16688	1148	1129	528	547	1676
Hub 1/2Y Testing, 1%/Y PrEP LHR	2.000	(1.877-2.123)	200	77987	76676	11389	12699	14896	591	581	87	97	678
Hub 1/Y Testing, 5%/Y PrEP LHR	0.270	(0.254-0.286)	27	77403	76102	11300	12601	29568	2451	2410	359	400	2810
Hub 2/Y Testing, 10%/Y PrEP LHR	0.086	(0.080-0.092)	9	75408	74141	11016	12284	57617	4655	4577	683	761	5338
Hub 4/Y Testing, 20%/Y PrEP LHR	0.036	(0.033-0.038)	4	72403	71186	10571	11788	110632	8842	8694	1299	1447	10141

Table 5: The search for the optimal strategy (Only strategies that resulted in less than 10 cases per 10,000 individuals are considered)

Strategy	HIV (Cases/10K)	Avg tests	Avg PrEP	Mean HIV	Mean Avg Tests	Mean Avg PrEP	StDev HIV	StDev Tests	StDev PrEP	Equal weights	Prevalence Weighted higher	Tests Weighted higher	PrEP weighted higher
Testing once every year LR	8	78684	1354	5.208	138708.542	6405.375	2.284	81688.313	6637.508	-0.091	0.237	-0.252	-0.259
Testing twice every year LR	4	157816	1351	5.208	138708.542	6405.375	2.284	81688.313	6637.508	-0.352	-0.396	-0.206	-0.454
Testing four times every year LR	3	316952	1353	5.208	138708.542	6405.375	2.284	81688.313	6637.508	0.151	-0.128	0.659	-0.077
Testing once every year LHR	6	90066	1350	5.208	138708.542	6405.375	2.284	81688.313	6637.508	-0.337	-0.166	-0.401	-0.443
Testing twice every year LHR	3	182008	1358	5.208	138708.542	6405.375	2.284	81688.313	6637.508	-0.399	-0.541	-0.167	-0.489
Testing four times every year LHR	2	362768	1358	5.208	138708.542	6405.375	2.284	81688.313	6637.508	0.193	-0.207	0.83	-0.046
Testing step 4 times every year LR	6	116970	1353	5.208	138708.542	6405.375	2.284	81688.313	6637.508	-0.227	-0.083	-0.237	-0.36
Testing step twice every year LHR	7	74320	1353	5.208	138708.542	6405.375	2.284	81688.313	6637.508	-0.255	0.005	-0.388	-0.382
Testing step four times every year LHR	4	134881	1359	5.208	138708.542	6405.375	2.284	81688.313	6637.508	-0.445	-0.466	-0.346	-0.524
Testing hub four times every year LR	7	104072	1365	5.208	138708.542	6405.375	2.284	81688.313	6637.508	-0.133	0.096	-0.206	-0.29
Testing hub twice every year LHR	9	60962	1363	5.208	138708.542	6405.375	2.284	81688.313	6637.508	-0.017	0.402	-0.251	-0.203
Testing hub four times every year LHR	4	121440	1357	5.208	138708.542	6405.375	2.284	81688.313	6637.508	-0.5	-0.507	-0.428	-0.565
1/Y Testing, 5%/Y PrEP LR	9	74181	6753	5.208	138708.542	6405.375	2.284	81688.313	6637.508	0.308	0.646	0.033	0.244
2/Y Testing, 10%/Y PrEP LR	4	138668	12531	5.208	138708.542	6405.375	2.284	81688.313	6637.508	0.131	-0.034	0.098	0.329
4/Y Testing, 20%/Y PrEP LR	2	244112	22001	5.208	138708.542	6405.375	2.284	81688.313	6637.508	0.745	0.208	0.881	1.146
1/Y Testing, 5%/Y PrEP LHR	6	84934	7741	5.208	138708.542	6405.375	2.284	81688.313	6637.508	-0.037	0.059	-0.192	0.023
2/Y Testing, 10%/Y PrEP LHR	3	155032	13997	5.208	138708.542	6405.375	2.284	81688.313	6637.508	0.126	-0.147	0.144	0.38
4/Y Testing, 20%/Y PrEP LHR	2	270520	24313	5.208	138708.542	6405.375	2.284	81688.313	6637.508	0.969	0.376	1.13	1.401
Step 4/Y Testing, 20%/Y PrEP LR	5	106601	9321	5.208	138708.542	6405.375	2.284	81688.313	6637.508	-0.015	-0.034	-0.109	0.099
Step 2/Y Testing, 10%/Y PrEP LHR	7	71056	6101	5.208	138708.542	6405.375	2.284	81688.313	6637.508	-0.03	0.174	-0.229	-0.034
Step 4/Y Testing, 20%/Y PrEP LHR	4	121082	10654	5.208	138708.542	6405.375	2.284	81688.313	6637.508	-0.035	-0.158	-0.08	0.134
Hub 4/Y Testing, 20%/Y PrEP LR	7	93631	8564	5.208	138708.542	6405.375	2.284	81688.313	6637.508	0.186	0.336	0.002	0.221
Hub 2/Y Testing, 10%/Y PrEP LHR	9	57617	5338	5.208	138708.542	6405.375	2.284	81688.313	6637.508	0.169	0.542	-0.121	0.086
Hub 4/Y Testing, 20%/Y PrEP LHR	4	110632	10141	5.208	138708.542	6405.375	2.284	81688.313	6637.508	-0.103	-0.21	-0.163	0.063
MEAN	5.208	138708.542	6405.375							-0.5	-0.541	-0.428	-0.565
STANDARD DEVIATION	2.284	81688.313	6637.508										