Treat your partners right: Implication of sexual contact networks in partner management for sexually transmitted infections

A THESIS
SUBMITTED TO THE FACULTY OF THE
UNIVERSITY OF MINNESOTA
BY

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IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

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June, 2020

Acknowledgements

The six-year journey to a PhD has been challenging and wonderful at the same time. I could not complete this journey and my dissertation without tremendous support from so many people.

First and foremost, I am indebted to my awesome adviser, Dr. Eva A. Enns, who kindled my interest in infectious disease modeling and network modeling. Eva has always been confident in my capability when I have doubted myself and been patient with me when I tried to experiment with different methods or learn different techniques. From Eva, I learned so much about being a critical researcher and being a kind, passionate, thoughtful, and effective instructor and mentor. Eva, if I ever have a chance to become a better researcher or mentor in the future, it is because you set up a great example.

I want to thank my co-adviser, Dr. Karen M. Kuntz, from whom I learned the fundamentals of decision science. Karen has always been very helpful and supportive of the research quest and ideas that I have. She always provided me with valuable and insightful feedback that helped me focus on the big picture of the studies. I am grateful and fortunate to have my committee members, Dr. Ankur Mani and Dr. Rebecca Wurtz. Thank you for being supportive of my dissertation idea since the first day I presented the research proposal to you. This dissertation would have been impossible without your knowledge, insight, and assistance.

My PhD journey would have been more difficult without the support of my partner, Dan, who has been faithful, supportive, and patient with me throughout the journey. I am thankful to have him by my side. A special thanks to my friend Shane. I would have not started the PhD journey without his encouragement. Moreover, I am very lucky to have develop friendships with Peiyin Hung, Vee Thao, and Yang Liu throughout the past six years. I will always cherish the moments that we shared research insights and dreams with each other. Furthermore, I wish to thank Maureen Andrew and Sarah Trachet for their constant support of the PhD program. Because of them, the PhD journey has been easier, smoother, and less stressful. Most importantly, I want to thank my parents, 玉妹 and 瑞益, for their unconditional love and unlimited tolerance of me. Thank you for allowing me to go on my own adventure and seek my passion.

Dedication

To my parents, Yu-Mei Kao and Ruei-Yi Chen

獻給我的父母，高玉妹和陳瑞益

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Chapter 1
Introduction

Reported cases of sexually transmitted infections (STIs) have continued to increase among the heterosexual population and men who have sex with men (MSM) in the last five years.[1] To better inform STI control strategies, the factors that influence the disease dynamics of STIs can be important to incorporate in developing infectious disease modeling for cost-effectiveness analysis. The spread of STIs depends on the macrostructure (e.g., random, clustered, scale-free) and the microstructure of the contact networks (e.g., relationship dynamics), and the sexual behaviors (e.g., condom use) commonly adopted in the population.[2–14] The macrostructure of the contact networks govern the general contact pattern in the population. For example, a scale-free network that has a small number of highly connected individuals (hubs) tends to facilitate infection in the population.[4,15,16] A network with community structure can slow infection propagating through contacts.[5,17] The microstructure (e.g., concurrent partnerships versus sequential partnerships) in the contact networks can be formed via relationship dynamics, which captures how quickly individuals form and end partnerships. Infection is more likely to spread through long concurrent partnerships than through short one-night stands or sequential partnerships.[8,9,11] Furthermore, protective and risky sexual behaviors could emerge interchangeably due to

the change of risk of infection in the population, resulting in a feedback loop between sexual behaviors and STI prevalence.[12–14]

Mathematical models have shown that the macrostructure and the microstructure of contact networks influence the spread of STIs. However, very few studies have evaluated how these structures influence the effectiveness and efficiency of STI control strategies.[8,9,18–21] To address these questions, we employed partner management strategies in treatable bacterial STIs as an example to demonstrate the importance of these structures in determining the optimal disease control strategies. In addition, while studies have demonstrated the interaction between sexual behaviors and disease dynamics in STIs, studies have not investigated the interaction in a more realistic decision-making process behind partner selection and protective behaviors.[12–14] We used the game theoretical framework to explore the interaction.

Partner management strategies aim to test or treat the sex partners of the STI patients.[22] These strategies alter the probability of transmission between partners; therefore, they are sensitive to the contact patterns. The most resource-intensive partner management strategy in STIs in general is contact tracing, which usually requires public health officials to intervene. Public health officials will elicit the names of the sex contacts of an index patient in a period of time (e.g., the past 6 months). Public health officials will then contact and inform each sex contact about the risk of exposure to an STI, and encourage the contact to seek testing.[22] This process is difficult to implement for disease with a high volume of incidence (e.g., chlamydia and gonorrhea). Contact tracing is reserved for severe STIs such as HIV and syphilis.[22] However, due to the involvement of the public health officials, contact tracing is more likely to bring the sex contacts to seek testing. Among less severe

STIs, the common practice of partner management is partner notification (PN). Under PN, index patients voluntarily notify their sex contacts about the risk of STI. Because index patients might choose not to notify the contacts and contacts might not seek testing, the treatment rate among the sex contacts could be low, resulting in reinfection among index patients. Expedited partner therapy (EPT) aims to increase partner treatment rate and reduce reinfection among the index patients.[22–25] Under EPT, index patients are permitted to directly deliver medications to sex contacts without requiring the clinic visits among the contacts. However, sex contacts are unlikely to seek testing to confirm the infection is clear after the EPT treatment. As a result, EPT might miss the chance to identify an undiagnosed patient and might result in overtreatment if the contact is uninfected. Therefore, EPT is only allowed for less severe STIs such as chlamydia and gonorrhea and is not recommended for populations at increased risk such as MSM.[22]

Although studies have compared the effectiveness and cost-effectiveness among partner management strategies, these studies did not consider the influence of the macrostructure or microstructure of contact networks on the relative efficiency between partner management strategies.[26,27] Regarding the macrostructure, given the same resource constraint and the same average sexual behaviors, the optimal partner management strategy might vary with the contact pattern in the population. In a network with scale-free properties, PN might be favored over contact tracing because contact tracing, solely relying on the public health officials, could be too slow to test and treat a high volume of infections. In comparison, in a network with community structure, EPT might outperform PN because individuals are less connected through hubs. Treating partners with EPT is unlikely to miss

the chance of testing or treating highly connected individuals, and can reduce reinfection between partners.

The microstructure formed by relationship dynamics, low partner turnover and high concurrent partnerships versus high partner turnover and low concurrent partnerships, could result in different recommendation of the partner management strategy. Therefore, collecting data that can characterize the relationship dynamics in a population can be essential to inform the decision on partner management strategy. Studies have suggested important parameters that can determine relationship dynamics, including cumulative number of sex partners, relationship duration, gap length between the end of last relationship and the onset of the subsequent relationship, and concurrency (i.e., the proportion of population who had concurrent partners).[9,10,28,29] However, studies have not yet determined how the additional data on relationship dynamics might improve decision making, and how valuable the information is to collect.

Finally, the sexual contact network and relationship dynamics in the population are shaped by the threat of disease infection, including STIs and HIV, in sexual activities. In particular, in a population like MSM, which is at increased risk of HIV infection, individuals might adopt risk reduction methods to reduce the risk of HIV acquisition/transmission. These risk reduction methods, known as "serosorting", include selecting partners who have the same HIV status (i.e., pure serosorting), and use condoms with partners of different or unknown HIV status (i.e., condom serosorting).[30] Risk reduction behaviors commonly adopted in the population can potentially influence the effectiveness of disease control strategies. For instance, in populations with high levels of serosorting (i.e., HIV-negative men tend to have HIV-negative partners) PN is unlikely to

detect new HIV infections in the sexual partners of newly diagnosed bacterial STI patients who are HIV-negative.

In this dissertation, we evaluated how these factors influence or interact with the dynamics of STI and the policy implication resulting from these factors. In Chapter 2, we used four stylized network structures, random, community-structured, scale-free, and empirical networks to demonstrate that the network structure in a population matters in determining the cost-effective partner management strategy in bacterial STIs. In Chapter 3, we determined how valuable the information about relationship dynamics, including relationship duration and concurrency, is by using the decision analytical framework. We evaluated how the cost-effective partner management strategy changed as additional information was considered in the mathematical model. In Chapter 4, we explored how disclosure behaviors, partner selection, and condom use behaviors were shaped by the interactions between HIV-positive and HIV-negative individuals using an evolutionary game theoretical framework. We then projected how behaviors vary with different HIV prevalence. In Chapter 5, we concluded the dissertation.

Chapter 2
Follow the sex: influence of network structure on STI control

"Kao, Szu-Yu Zoe MA; Enns, Eva A. MS, PhD Follow the Sex, Sexually Transmitted Diseases: February 2020 - Volume 47 - Issue 2 - p 71-79
doi: 10.1097/OLQ.0000000000001100"

2.1 Introduction

It is well-established that contact network structure influences infectious disease dynamics.[4–7,15–17,31,32] For example, for the same disease parameters and average behaviors, an outbreak is more likely to spread in a random network than a clustered network with community structure.[5,17,32] Similarly, networks that have scale-free properties can maintain an infectious disease even with very low transmissibility due to the presence of highly connected individuals that serve as hubs in the population.[4,15,16] Despite the rich literature describing the relationship between network structure and infectious disease dynamics, only a small number of studies have compared the effectiveness and efficiency of infectious disease interventions over different types of network structures.[7,18,19] None have investigated how network structures interact with the relative efficiency among multiple disease interventions.

Partner management strategies for sexually transmitted infections (STIs) are a class of interventions that may have a particularly strong dependence on the population's sexual contact network structure. For example, contact tracing involves tracing through chains of sexual contacts to find undiagnosed cases; thus, both the effectiveness and the resources required to conduct contact tracing are directly depending on the underlying contact network structure. Past studies have shown that contact tracing is more effective in controlling a disease outbreak in clustered networks than in random networks.[7,19,20] It has also been demonstrated that in order to detect the same proportion of infections, contact tracing requires more resources in scale-free networks than in random networks.[18]

Regardless of the underlying network structure, any real-world implementation of contact tracing is resource-intensive, as it must be undertaken centrally by public health staff to maintain continuity and confidentiality as individuals within chains are identified and contacted. A less resource-intensive partner management strategy is partner notification (PN), which relies on the index patient to voluntarily notify sex partners of potential STI exposure and encourage partners to seek testing. PN is typically employed in cases of chlamydia and gonorrhea infections, while contact tracing is reserved for the most serious STIs, like HIV and syphilis.[22] While being less costly, PN also tends to be less effective than contact tracing; individuals may not feel comfortable notifying partners directly and any notification that does occur might not be as impactful as official communication from a health department.[33] Thus, empirical studies find that few partners ultimately seek testing under PN, resulting in, among other things, a high risk of re-infection of the index case.[23,24,34] To increase partner treatment rates, expedited partner therapy (EPT) was developed to allow the index patients to deliver antibiotic regimens

directly to their partners without requiring medical evaluation.[22] Studies of EPT find that it both increases the timeliness of treatment as well as increases the proportion of partners notified, as the index case is empowered to deliver a solution (namely, antibiotic treatment) alongside the difficult news of a potential STI exposure.[35] However, treated partners are unlikely to seek testing to confirm whether they were in fact infected, precluding opportunities to identify infections among an infected partners' partners or any further down the transmission chain.

Prior studies comparing the effectiveness and efficiency of PN and EPT did not consider the impact of network structure.[26,27] However, the structure of a sexual contact network may have a particular influence on the relative efficiency and effectiveness of these partner management strategies because these strategies intervene upon transmission pathways that are wholly determined by the network. In this paper, we examine how the cost, effectiveness, and efficiency of partner management strategies for a treatable STI changes with different assumptions about the network structure, keeping the population's average sexual behavior the same. We use this example as a case study in evaluating the impact that network structure may have on the effectiveness and efficiency of interventions for the control and treatment of infectious disease.

2.2 Methods

2.2.1 Overview

We simulated outbreaks of a hypothetical, treatable chlamydia/gonorrhea-like STI in a closed, same-sex population, parameterized to reflect the sexual behaviors of MSM. STI

introduction was modeled using a constant external force of infection (EFOI). STI spread within the population was modeled as occurring through a dynamic sexual contact network following a Susceptible-Infected-Susceptible (*SIS*) disease model, simulated in bi-weekly time steps. We evaluated the costs and disease impacts of four different partner management strategies (none, PN, EPT, and contact tracing) over a two-year time horizon in four different types of sexual network structures (random, community-structured, scale-free, empirical). We conducted a cost-effectiveness analysis (CEA) to determine if and how the efficiency of partner management strategies varies across different network structures. Model parameters were estimated from the literature (Table 2.1). The simulation model was implemented in Python 3.7.3.[36]

2.2.2 Simulating sexual contact networks

We simulated 5,000 individuals interacting with each other through a sexual contact network. The sexual contact network follows four different network structures: random, community-structured, scale-free, and empirical. These network structures were assumed to represent the 5-year cumulative sexual contact network, which reflects all sexual partnerships that were active over 5 years. Each 5-year sexual contact network consisted of a three-year burn in period for the relationship dynamics to stabilize, followed by a two-year time horizon for simulating disease spread through sexual contact networks and implementing interventions. Each network was generated to have the same average degree of 20 sex partners over 5 years (or equivalently 4 partners per year). This is consistent with the mean estimated from the distribution of the number of sex partners in the previous 12 months reported by MSM in the 2013 Seattle Pride survey, by assuming a maximum of 30

sex partners in a year.[37] Sexual contact networks were generated using standard network generation techniques (described below).

2.2.2.1 Cumulative network generation

We followed the configuration model to generate a network using the degree distribution characterized by different network structures.[38] Following the configuration model, we first sampled a degree sequence (a sequence of the number of sex partners of each individual) from a degree distribution assumed by a network structure of interest with a mean degree of 20. We then sequentially matched individual to other individuals until all sexual partnerships had been paired without duplication.

In a simple random network, any pair of individuals can form a relationship with the same probability. This assumption implies that the degree distribution of a random network follows a Poisson distribution.[3,6] Thus, we generated a random network by sampling a degree sequence from a Poisson distribution with mean 20. However, in many sexual contact networks, assotativity is often observed, where individuals are not equally likely to form connections with anyone, but rather with individuals who have similar attributes (e.g., race, age, socioeconomic status).[39–42] We approximated assortativity using community-structured networks to allow different probability of relationship formation according to the community to which an individual belongs. We created five communities with equal population size and assumed that 99% of an individuals' sex partners (an average of 19.8) were from the same community.[5,43,44] We chose 99% to induce high levels of assortativity to demonstrate how the effectiveness of interventions in community-structured networks might differ from the random networks in the extreme. Community-

structured networks were formed by sampling from two different Poisson distributions to generate two degree sequences for the population, one reflecting within community partnerships and the other reflecting inter-community partnerships.

However, both random and community-structured networks do not account for individuals with high levels of sexual activity observed in some population. We therefore considered scale-free networks as a stylized way to capture highly connected hubs in the population.[45,46] We generated scale-free networks by sampling degree sequences from a power-law distribution with a mean of 20.[2,15] Finally, we also considered an empirical network which had a degree distribution reconstruction from the distribution of sex partners in the past 12 months reported by MSM in 2013 Seattle Pride survey.[1] In the report, participant's responses were categorized (e.g., 2-4 partners), as summarized in Table 2.1. In sampling from this distribution, the value of each range was sampled uniformly within the range. For the final category (10+ partners), we assumed a maximum of 30 partners in the past 12 months. For empirical network, we constructed a 5-year cumulative degree sequence through repeated sampling of the distribution of annual sex partners.

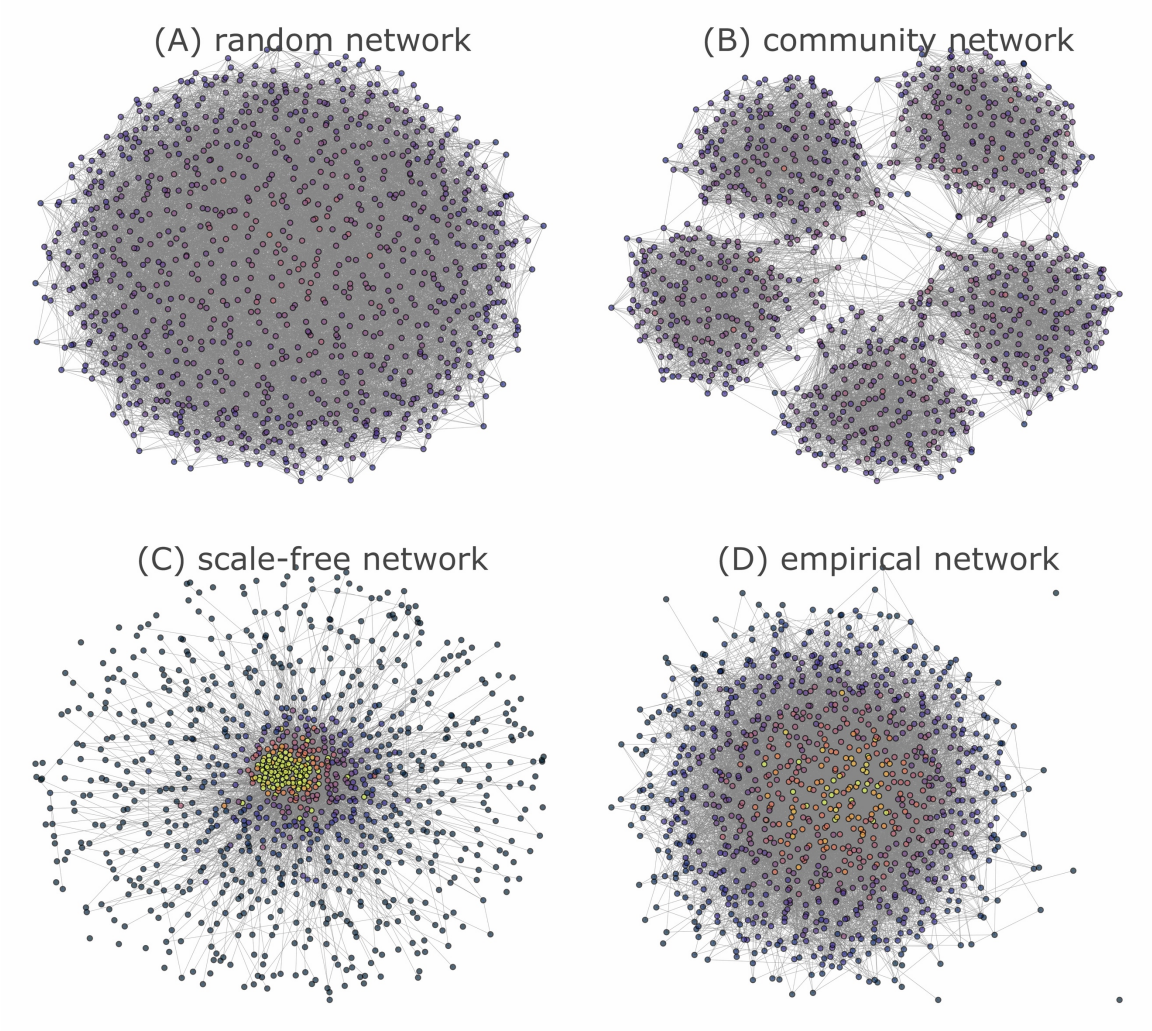

Figure 2.1. Cumulative sexual contact networks of a sample of 1,000 individuals in the population in the last year (26 cycles) of simulation for four different types of network structure: (A) random, (B) community, (C) scale-free, and (D) empirical. Each node represents an individual in the population and each line indicates a sexual relationship in the last year of a simulation.

2.2.2.2 Network dynamics

At any given simulation cycle, partnerships in a network were either active or inactive, determine by their assigned time of onset and duration. We first assigned each partnership's duration to a relationship. The marginal distribution of duration followed the casual partnership durations among a sample of young MSM.[47] While individuals with more sex partners might be less likely to have long-term relationships, sexual behavior studies often only report the marginal means of the degree and duration without measuring correlation between the two.[47,48] To induce some reasonable degree of correlation between number of partners and partnership duration, we assumed a -0.1 correlation between a given relationship's duration and the total number of other sex partners over 5 years among the two members of the relationship. We used the copula method to construct a joint distribution of degree and duration to maintain their own marginal distribution.[49] We then assigned the onset of each relationship by uniformly sampling from the range [-duration, time horizon] to allow left-censored relationships. STI transmission could only occur through active sexual partnerships. Active pairs of sex partners were assumed to engage in sex at an average rate of 1.04 sex acts per cycle.[47] Partnerships in the last year of the simulation are shown in Figure 2.1 for each of the four simulated sexual network structures. The simulated network dynamics and measures are presented in Figure 2.2.

2.2.3 Disease dynamics

We simulated the spread of the hypothetical STI through each of the random, community-structured, scale-free, and empirical networks following the *SIS* framework. A susceptible individual (*S*) could be infected through sex with an infected sex partner in an active

relationship, or through external sexual contacts. The population was assumed to have a 0% prevalence of infection at the start of the simulation, with infection being introduced externally at a constant EFOI. We considered two EFOI scenarios: 0.5 (low level) and 5 (high level) persons infected per cycle. The probability of disease transmission per sex act was assumed to be 13.5% based on chlamydia transmission probability estimated in model-based studies.[50,51] Transmission could be reduced by 60% with condom use[52], which was assumed in 44% of sex acts.[53] An infected individual (*I*) could spontaneously recover back to the susceptible state at a rate of 1/6 months.[54,55]

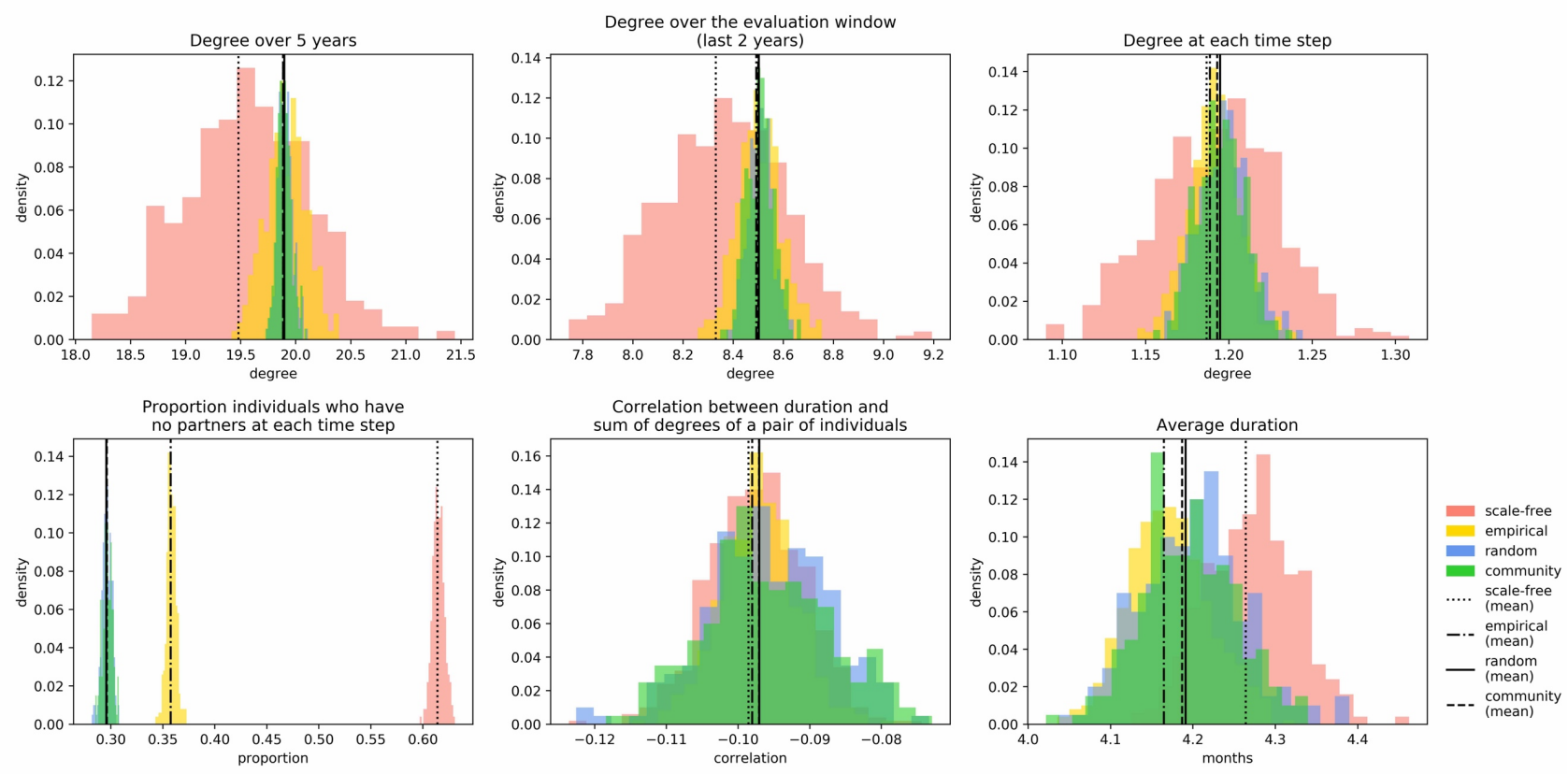

Figure 2.2. The distribution of the simulated network measures and duration of relationships from 1,000 simulated networks, including the cumulative degree distribution over 5 years, cumulative degree distribution over the last 2 years, the instantaneous degree distribution at each cycle, the proportion of individuals who have no sex partners (isolates) at each cycle, the correlation between duration and the sum of cumulative degree of a pair of individuals, and the average duration of relationships.

An infected individual could be identified and treated through routine annual screening or via partner management (e.g., PN, EPT, and contact tracing). As a simplification, we assumed that all infections were asymptomatic, consistent with the high proportion of asymptomatic chlamydial infections in men.[56,57] Thus, in the simulation, individuals did not seek treatment in response to symptoms. We allowed routine screening to be correlated with the number of sex partner of individuals in the past 12 months. Routine screening was implemented by randomly sampling a full screening schedule (i.e., who gets screened when) at the beginning of the two-year time horizon. We sampled 30% of the population to be screened every 26 cycles based on the proportion of MSM who reported chlamydia/gonorrhea testing in the past 12 months in Seattle/King county.[58] The probability of individuals being screened was proportional to their number of partners in the past 12 months to reflect a positive correlation in screening and sexual risk behavior. To inform the number of screening per year among the 30% of MSM, we used PrEP coverage in King County (24.3% of MSM) as a proxy for the number of people undergoing STI screening multiple times per year.[59] We assumed that 24.3% of MSM were screened 2-4 times a year, whereas the rest of 5.7% of MSM who were selected to undergo screening were only screened once a year.[60] Among the 30% of MSM who were screened, whether a man would get 1 screening test or ≥ 2 screening tests depended on the number of partners in a year. Due to partner management activities, individuals could undergo more screening tests (due to PN or contact tracing) or rounds of treatment (due to EPT), but not more than once every month. We did not model treatment failure.

2.2.4 Partner management strategies

We considered four partner management strategies: routine screening alone (no partner management), PN, EPT, and contact tracing. All partner management strategies were implemented on top of routine screening. Each partner management strategy was associated with two compliance parameters. Patient compliance reflects how likely a patient might contact or deliver medicine to each sex partner. Partner compliance indicates how likely a partner seeks testing or takes the medicine. Patient and partner compliance under each partner management strategy was taken from a randomized control trial that evaluated the effectiveness of EPT and PN among men who had urethritis due to infection with chlamydia or gonorrhea.[23] Under PN, 49% of partners were notified and 71% of notified partners sought testing. Under EPT, 70% of partners were delivered treatment and 79% of them completed the treatment course. We assumed the trial results applied to current partners, but that for past partners, patient compliance would decay with the time since partnership termination following an exponential function $e^{-\frac{[t-T_{ij}^{end}]}{2}}$, where t denotes the current cycle and T_{ij}^{end} reflects the end cycle of a relationship between individual i and j. This probability drops to 0.3% for PN and 0.4% for EPT, respectively, for a relationship that ended five months prior. We assumed that index patients would only reach out to partners from the past 6 months.

In the absence of quantitative assessments, we assumed that contact tracing has the same patient and partner compliance levels equal to the maximum of that of EPT or PN, consistent with a general consensus that contact tracing has the highest compliance of any partner management approach.[22,25] In the base case, index patients reported 70% of their

partners to public health staff and 79% of partners contacted by public health staff seeking testing under contact tracing. This is consistent with a general consensus that contact tracing is more effective than PN.[22,25] However, these assumptions were varied in sensitivity analysis. Contact tracing was simulated by maintaining a roster of partner names; each cycle, names of partners of new index cases were added, while names of contacted partners were removed. We assumed that in any given cycle, a maximum of 14 partners could be contacted, reflecting agency capacity constraints. Partners were prioritized for tracing by the number of times they had been named by index cases.[21,22]

2.2.5 Costs and health outcomes

Costs were incurred for STI testing, treatment, and contact tracing.[21,61] Primary health outcomes included incidence, prevalence, average number of infections per person, average duration of infection, and total infected person-months, in the population over the two-year time horizon.

Table 2.1. The description, values, sources of the parameters used in the simulation model.

Parameter	Description	Base case value / unit	Sensitivity analysis	Source
N	Population size	5000		Assumed
Network structure				
d_0	0 sex partners in the past 12 months	16%		[37]
d_1	1 sex partners in the past 12 months	36%		[37]
$d_{2\text{-}4}$	2-4 sex partners in the past 12 months	26%		[37]
$d_{5\text{-}9}$	5-9 sex partners in the past 12 months	12%		[37]
d_{10+}	≥10 sex partners in the past 12 months	10%		[37]
d	Average number of sex partners in 5 years	20		[37]
c	Number of communities in community network	5		Assumed
Nc	Population size in each community	1000		Assumed
a	Proportion of sexual contacts in the same community in the community network	0.99		Assumed
Relationship dynamics				
$freq$	Average number of sex acts per cycle	1.04		[47]
η	Correlation between duration and number of sex partners	-0.1		Assumed
σ_0	% of relationships with duration ≤ 1 month	55.8%		[47]
σ_6	% of relationships with duration > 1 and ≤ 6 months	21.6%		[47]
σ_{12}	% of relationships with duration > 6 and ≤ 12 months	7.3%		[47]
σ_{24}	% of relationships with duration > 12 and ≤ 24 months	7.4%		[47]
σ_{36}	% of relationships with duration > 24 and ≤ 36 months	2.3%		[47]
Disease dynamics				
$init$	Initial prevalence	0%		Assumed
$Seeds$	Rate of external force of infection per month	10 individuals	1 individual	Assumed
β	Probability of infection per sex act	0.135		[50,51]

δ	Probability of condom use per sex act	0.44		[53]
ε	Condom effectiveness	0.6		[52]
τ^I	Average duration of infection (I)	6 months		[54,55]
γ	Proportion of population screened per year	30%		[58]
γ^{2+}	Proportion of population who were screened 2-4 times a year	24.3%		[59]
γ^1	Proportion of population who were screened 1 time a year	5.7%		calculated
Patient compliance				
ρ^N	Probability of contacting partners (Null)	0		Assumed
ρ^P	Probability of contacting partners (partner notification: PN)	0.49		[23]
ρ^E	Probability of contacting partners (expedited partner therapy: EPT)	0.7		[23]
ρ^T	Probability of contacting partners (contact tracing)	0.7		[23]
Partner compliance				
ϕ^N	Probability of partners getting tested (null strategy)	0		Assumed
ϕ^P	Probability of partners getting tested (partner notification: PN)	0.71		[23]
ϕ^E	Probability of partners getting treated (expedited partner therapy: EPT)	0.79		[23]
ϕ^T	Probability of partners getting tested (contact tracing)	0.79		[23]
Max^T	Maximum number of partners allowed to be notified by public health officials in contact tracing in a cycle (two weeks)	14 individuals		Assumed
Cost				
C(medicine)	Cost of medicine	$58		[61]
C(personnel)	Cost of investigation by public health officials in contact tracing	$120		[21]
C(Test)	Cost of STD testing	$101.5		[61]
Other				
r	Annual discount rate	3%		[62]

2.2.6 Model simulation and cost-effectiveness analysis

We performed 10,000 simulations for each partner management scenario for each type of network structure to obtain stable estimates of costs and health outcomes. At the beginning of each simulation, we initiated a disease-free population and simulated relationship dynamics for three years to allow the sexual contact network to stabilize. After the three-year burn-in period, we introduced infection into the disease-free population through the EFOI and simulated spread for two years. Partner management strategies were also implemented and evaluated over the two-year time horizon.

We conducted a cost-effectiveness analysis (CEA) of partner management strategies using the base case partner compliance parameter in each of four network structures (base case analysis). For a given network structure, we first calculated the costs and total infected person-months (effectiveness) accrued over the two-year time horizon, averaged over the 10,000 simulations, for each partner strategy. For the purposes of the CEA, costs and effectiveness were discounted annually at 3%.[62] Strongly and weakly dominated strategies (strategies that avert fewer infected person-months at a higher cost) were identified and eliminated. Among non-dominated strategies, we calculated the incremental cost-effectiveness ratio (ICER), as the incremental cost per additional infected person-months averted of switching to a strategy from its next least costly counterpart strategy.

2.2.7 Sensitivity analysis

We varied patient compliance parameters in sensitivity analysis to evaluate how cost-effectiveness analysis results changed across the different network structures and EFOI scenarios. We considered all combinations of partner compliance of PN and EPT ranging from 10% to 100%. Simulations were conducted for all combinations in 10% increments. A generalized additive meta-model was used to extrapolate cost and effectiveness outcomes on a finer scale.[63,64] For all simulations, partner compliance under contact tracing was assumed to be the maximum compliance of the PN or EPT strategy. For each combination of PN and EPT partner compliance values, the optimal partner management strategy was defined as the strategy averting the greatest number of infected person-months with an ICER less than a willingness-to-pay (WTP) threshold. In this context, the WTP represents the monetary value of health gains from averting a month of infection with the hypothetical STI. A greater WTP would reflect an STI with greater sequalae. Given the hypothetical nature of our analysis, we present two-way sensitivity analysis results with different WTP thresholds as an illustration of how the optimal decision might change.

2.3 Results

2.3.1 Base case analysis

The projected prevalence (last cycle), incidence, average duration of infection, and total infected person-months for a given partner management strategy varied with network structures in both EFOI scenarios (Table 2.2, Table 2.3, Table A.1, Table A.2). Under routine screening alone, community-structured networks had the lowest burden of disease

(prevalence, incidence, and infected person-months), while scale-free networks had the highest. However, scale-free networks yielded the shortest average duration of infection. The correlation between the average number of infections and the number of sex partners was the highest in scale-free networks (~0.5) compared to the correlation in the other network structures (0.1-0.3). In routine screening alone, although the number of screening tests was the same in different network structures, the number of sex partners (in the past 6 months) of the index cases varied widely, being smallest in community-structured networks and highest in scale-free networks. This has implications for the resource requirements of partner management strategies. The prevalence in the partners of index cases was higher than the population prevalence in all network structures, and was the highest in community-structured networks.

Table 2.2. The mean and standard deviation (sd) of the disease incidence, disease prevalence, average number of infections and total infected person-months in the two-year time horizon for the base case analysis at a high external force of infection (EFOI). The values were calculated using 10,000 simulations.

Strategy		**Prevalence**	**Incidence**	**Total infected person-months**	**Average duration of infection (month)**
Random networks					
Screening	mean	5.9%	924	3,271	3.54
	sd	0.7%	100	393	0.11
PN	mean	5.1%	856	2,925	3.42
	sd	0.6%	89	337	0.11
EPT	mean	4.9%	841	2,843	3.38
	sd	0.6%	88	332	0.11
Tracing	mean	4.6%	825	2,763	3.35
	sd	0.6%	86	321	0.11
Community-structured networks					
Screening	mean	3.4%	629	2,328	3.70
	sd	0.4%	60	254	0.14
PN	mean	3.0%	594	2,095	3.53
	sd	0.4%	55	225	0.14
EPT	mean	3.0%	587	2,042	3.48
	sd	0.4%	54	216	0.14
Tracing	mean	2.7%	574	1,967	3.42
	sd	0.4%	53	207	0.14
Scale-free networks					
Screening	mean	15.2%	4,117	9,663	2.35
	sd	1.0%	256	705	0.05
PN	mean	10.2%	3,566	6,727	1.89
	sd	0.9%	238	465	0.04
EPT	mean	11.2%	3,599	6,729	1.87
	sd	0.9%	242	476	0.04
Tracing	mean	14.6%	4,066	9,334	2.29
	sd	1.0%	263	710	0.05
Empirical networks					
Screening	mean	7.7%	1,226	3,989	3.25
	sd	1.0%	149	521	0.09
PN	mean	5.9%	1,060	3,271	3.08
	sd	0.8%	123	407	0.10
EPT	mean	5.7%	1,031	3,137	3.04

	sd	0.8%	118	385	0.10
Tracing	mean	5.7%	1,042	3,186	3.05
	sd	0.9%	129	435	0.10

Partner management strategies reduced disease burden and improved health outcomes because these strategies increased the number of individuals screened/tested/treated (Table 2.2, Table 2.3, Table A.1, Table A.2). Generally, the strategy that was most effective at reducing disease burden was the one that treated the most infected partners of index cases. In random and community-structured networks, contact tracing was the most effective strategy, resulting in the greatest reduction in prevalence, incidence, average duration of infection, and total infected person-months. In empirical networks, contact tracing was the most effective strategy at a low EFOI (Table A.2), but EPT was most effective at a high EFOI, even though it resulted in slightly fewer infected partners being treated than contact tracing (Table 2.3). However, in empirical networks, the percent of infected partners being treated in contact tracing reduced from 55% (higher than that of EPT) at a low EFOI to 37% (lower than that of EPT). In scale-free networks, PN was the most effective strategy. In contrast to the other network structures, contact tracing treated the fewest sex partners in scale-free networks because it reached its capacity constraint.

Table 2.3. The mean and standard deviation (sd) of outcomes related to partner management strategies in the two-year time horizon for the base case analysis at a high external force of infection (EFOI). The values were calculated using 10,000 simulations.

Strategy		**# of individuals screened or tested**	**# of index cases**	**Total # of partners in the past 6 months among the index case**	**Average # of partners in the past 6 months of the index case**	**% partners infected**	**# of partners reached**	**# of partners tested / treated under partner management**	**# of infected partners who were treated**
Random networks									
Screening	mean	6,340	158	563	3.56	18.9%			
	sd	41	22	80	0.51	1.7%			
PN	mean	6,451	183	737	4.03	17.6%	196	111	40
	sd	46	26	112	0.61	1.5%	33	20	9
EPT	mean	6,340	158	563	3.56	18.9%	207	138	48
	sd	41	22	80	0.51	1.7%	32	22	9
Tracing	mean	6,530	199	798	4.01	16.9%	302	200	64
	sd	53	28	121	0.61	1.4%	47	35	13
Community-structured networks									
Screening	mean	6,340	117	405	3.45	22.8%			
	sd	40	17	57	0.49	2.3%			
PN	mean	6,422	140	543	3.89	21.5%	145	83	33
	sd	43	20	83	0.59	2.0%	26	16	8
EPT	mean	6,340	117	405	3.45	22.8%	150	101	39
	sd	40	17	57	0.49	2.3%	24	17	8
Tracing	mean	6,480	154	597	3.88	20.1%	229	146	54
	sd	48	23	94	0.61	1.8%	39	28	12
Scale-free networks									

Screening	mean	6,340	2,061	8,781	4.26	13.5%			
	sd	40	135	458	0.22	0.8%			
PN	mean	8,348	2,212	13,574	6.14	15.1%	4,755	2,008	680
	sd	201	164	1,078	0.49	0.9%	409	203	83
EPT	mean	6,340	2,061	8,781	4.26	13.5%	4,338	2,066	584
	sd	40	135	458	0.22	0.8%	261	174	63
Tracing	mean	6,544	2,093	12,280	5.87	19.8%	616	313	154
	sd	41	140	676	0.32	1.1%	0	11	12
Empirical networks									
Screening	mean	6,340	273	1,277	4.67	14.8%			
	sd	40	41	182	0.66	1.2%			
PN	mean	6,571	305	1,685	5.53	14.3%	428	231	76
	sd	56	45	257	0.84	1.1%	70	39	16
EPT	mean	6,340	273	1,277	4.67	14.8%	447	277	84
	sd	40	41	182	0.66	1.2%	67	43	16
Tracing	mean	6,636	308	1,708	5.54	14.4%	479	321	90
	sd	47	40	241	0.78	1.1%	39	29	12

Compared to the other network structures, scale-free networks had the highest costs and greatest number of infected person-months under any partner management strategy due to the higher burden of infection (Table 2.4, Table A.3). Regardless of the EFOI scenarios or WTP threshold, EPT was never dominated and its efficiency relative to screening alone (in terms of ICER) was very similar between EFOI scenarios in any given network structure. For the other strategies, PN was strongly dominated in all network structures except for scale-free networks; contact tracing was strongly dominated in scale-free networks under both EFOI scenarios and in empirical networks under the high EFOI scenario. In scale-free networks, the efficiency of PN relative to EPT increased from a low EFOI to a high EFOI. Similarly, in random and community-structures networks, the relative efficiency of contact tracing to EPT increased from a low EFOI to a high EFOI. In empirical networks, contact tracing was the next efficient strategy relative to EPT at a low EFOI but became strongly dominated at a high EFOI.

Table 2.4. Cost-effectiveness analysis of various partner management strategies in each network structure at a high external force of infection (EFOI) in base case analysis. The mean and standard deviation (sd) of total cost and total infected person-months were calculated using the 10,000 simulations.

Strategy		**Total infected person-months**	**Cost**	**Incremental benefit**	**Incremental cost**	**ICER**
Random networks						
Screening	mean	3,271	632,129			
	sd	393	4,212			
EPT	mean	2,843	638,818	428	6,689	16
	sd	332	4,613			
PN	mean	2,925	644,378			Strongly
	sd	337	5,269			dominated
Tracing	mean	2,763	687,840	80	49,021	612
	sd	321	10,878			
Community-structure networks						
Screening	mean	2,328	629,871			
	sd	254	4,070			
EPT	mean	2,042	634,827	286	4,957	17
	sd	216	4,291			
PN	mean	2,095	639,189			Strongly
	sd	225	4,771			dominated
Tracing	mean	1,967	672,056	75	37,229	494
	sd	207	9,179			
Scale-free networks						
Screening	mean	9,663	738,947			
	sd	705	8,665			
EPT	mean	6,729	829,720	2,934	90,774	31
	sd	476	15,451			
Tracing	mean	9,334	832,038			Strongly
	sd	710	8,950			dominated
PN	mean	6,727	943,756	2	114,036	47,916
	sd	465	28,439			
Empirical networks						
Screening	mean	3,989	638,599			
	sd	521	4,575			
EPT	mean	3,137	651,241	852	12,642	15
	sd	385	5,643			
PN	mean	3,271	662,946			Strongly
	sd	407	7,346			dominated
Tracing	mean	3,186	724,750			Strongly
	sd	435	9,539			dominated

2.3.2 Sensitivity analysis

The optimal strategy at different combinations of PN and EPT partner compliance levels under a high EFOI is shown for a low WTP of $100 (Figure 2.3) and high WTP of $600 (Figure 2.4) per infected person-months averted. At a low WTP, the optimal strategy followed a similar pattern across partner compliance levels across the different network structures (Figure 2.3). The optimal strategy was one of either EPT or PN; EPT was optimal even if its partner compliance was slightly lower than PN. Contact tracing was not optimal in any of the four network structures at a low WTP. A high WTP did not substantially change the pattern of the optimal strategy in empirical networks (Figure 2.4). However, in scale-free networks, at a high WTP, PN was the optimal strategy for a larger share of partner compliance values (Figure 2.4). Contact tracing was never optimal in both empirical and scale-free networks. In random and community-structured networks, at a high WTP, contact tracing was optimal for moderate-to-high levels of partner compliance, with partner compliance values for which PN was optimal being largely diminished (Figure 2.4).

Regarding the optimal strategies at a low EFOI, we observed a similar pattern in random, community-structured, and scale-free networks (Figure A.1, Figure A.2) compared to the patterns at a high EFOI. At a high WTP, contact tracing was optimal for a larger share of partner compliance values in random and community-structured than under a high EFOI (Figure A.2). In empirical networks, while the pattern of optimal strategies at a low WTP was similar to the pattern observed in the high EFOI scenario, at a high WTP

contact tracing was optimal for a large portion of partner compliance values in contrast to never being optimal under a high EFOI (Figure A.1, Figure A.2).

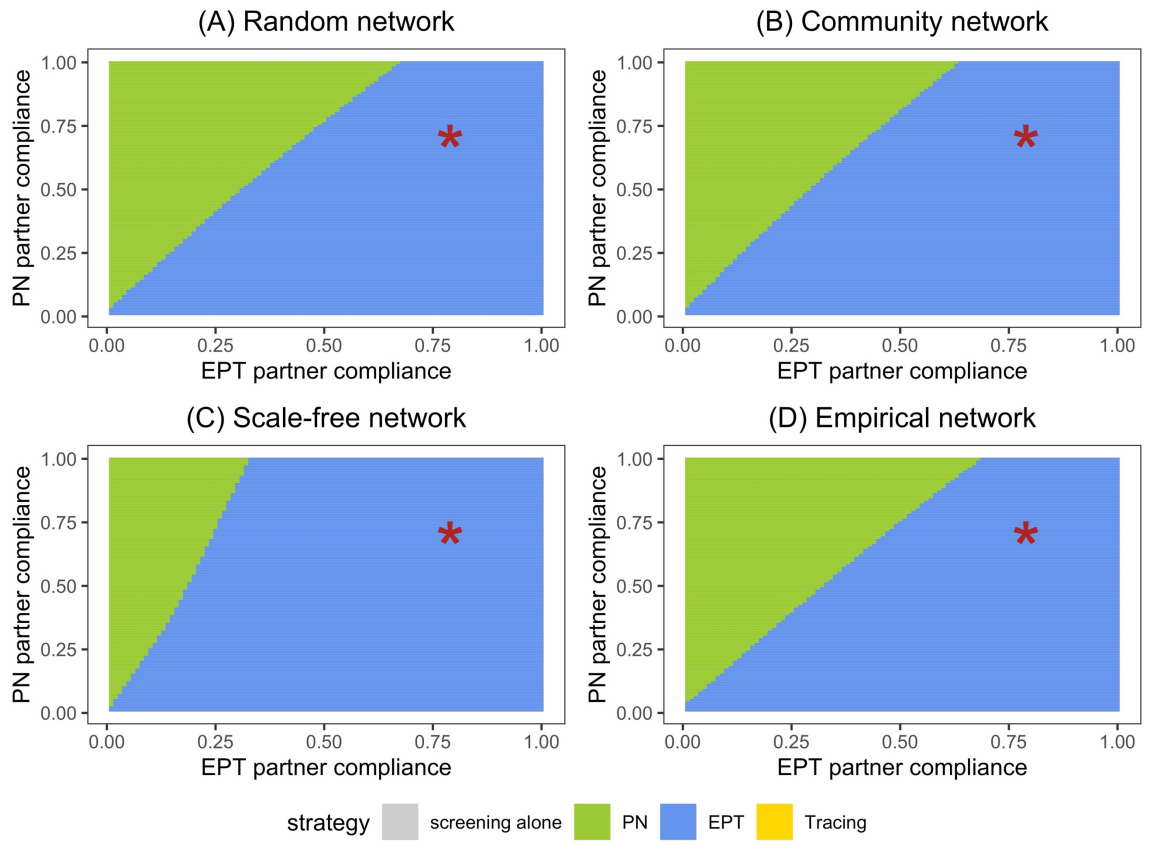

Figure 2.3. The optimal partner management strategy with varying levels of partner compliance using a willingness-to-pay (WTP) threshold = $100 in (A) random, (B) community, (C) scale-free, and (D) empirical networks in the high external force of infection (EFOI) scenario. PN = partner notification; EPT = expedited partner therapy; Tracing = contact tracing. These partner management strategies were implemented in addition to routine screening alone.

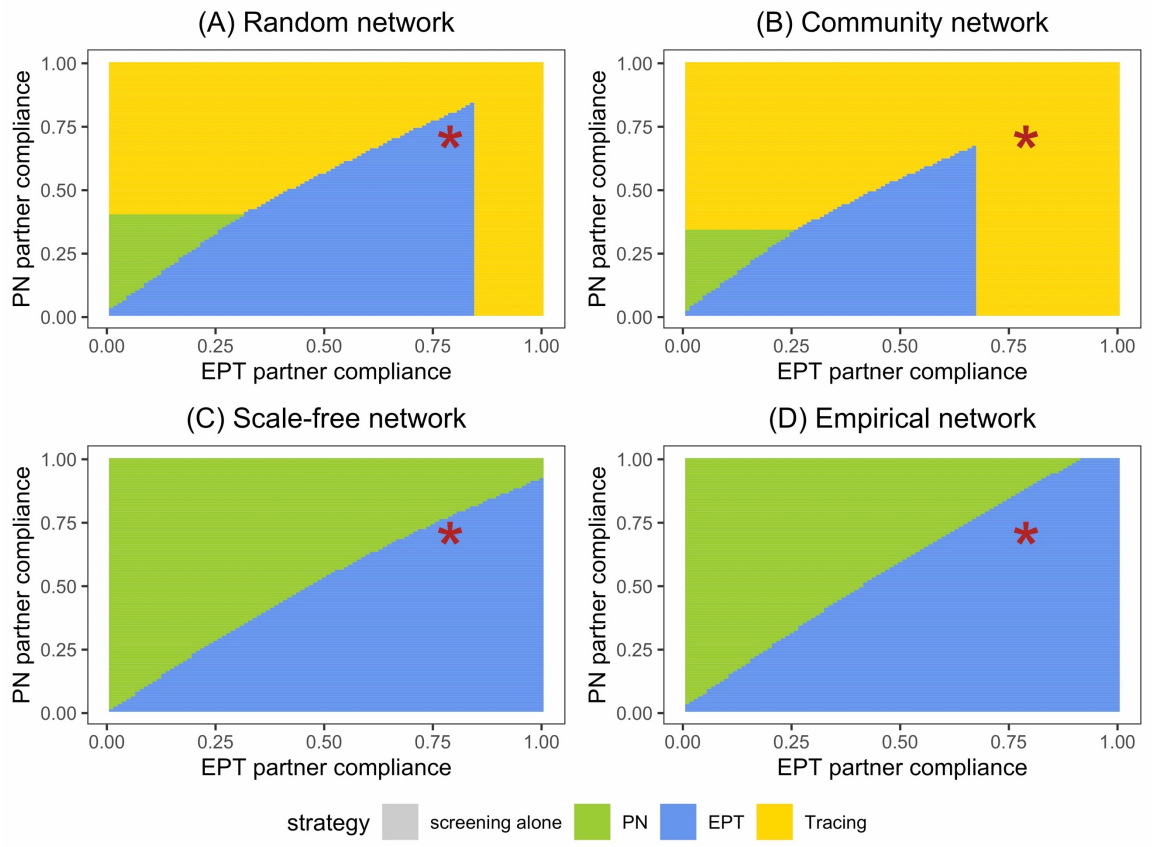

Figure 2.4. The optimal partner management strategy with varying levels of partner compliance using a willingness-to-pay (WTP) threshold = $600 in (A) random, (B) community, (C) scale-free, and (D) empirical networks in the high external force of infection (EFOI) scenario. PN = partner notification; EPT = expedited partner therapy; Tracing = contact tracing. These partner management strategies were implemented in addition to routine screening alone.

2.4 Discussion

Mathematical models evaluating disease control strategies for infectious diseases rarely investigate how the optimal strategy varies with the structure of the underlying contact network. We demonstrated that network structure can result in substantially different

epidemiological and economic outcomes, which in turn affects the efficiency and optimal strategy choice for controlling epidemics. This has implications for model-based approaches that aim to evaluate infectious disease interventions.

The findings based on our model and parameter setting were consistent with the literature.[18–21,65] Without any partner management, we saw that community-structured networks had the least severe epidemiological outcomes. In contrast, scale-free networks tended to accelerate STI spread due to the highly connected individuals, as evidenced by the high correlation between the number of infections and the number of partners. Partner management strategies reduced disease burden across the different types of network structures, but to varying degrees.

The performance of partner management strategies (the number of infected partners tested and/or treated) differed by network structure, impacting the overall efficiency of these strategies. In the base case, PN yielded the least number of sex partner tested and treated in random, community-structured, and empirical networks due to having the lowest patient and partner compliance. However, in scale-free networks, PN yielded the greatest number of treated infected partners due to the much larger number of partners that could be reached compared to contact tracing, which was limited by a maximum operating capacity. In scale-free networks, PN also outperformed EPT, highlighting the importance of tracing through scale-free networks to efficiently identify new infections, something that EPT does not do.

The efficiency of each partner management strategy also differed by network structure under our model and parameter setting. EPT was less efficient (higher ICER) in scale-free networks than in the other network structures. The pattern of the optimal strategy

at different levels of PN and EPT partner compliance also varied with network structure, WTP, and the rate of EFOI. As WTP increased, contact tracing was more likely to be optimal in random and community-structured networks, and in empirical networks at a low EFOI. However, contact tracing was never optimal in scale-free networks regardless of EFOI and in empirical networks under high EFOI.

Our findings showed that the network structure of a population might matter in determining the efficiency and effectiveness of interventions in certain contexts. It is critical to collect pertinent information regarding network structure to inform infectious disease policies that operate over that structure. Although we used stylized network structures, the property of each network structure could inform the process of collecting network information. Key information would include the number of sex partners, the presence of highly connected individuals, and the level of sexual mixing assortativity across different attributes. Properties from other types of network could be considered (e.g., small-world networks).[66,67]

The focus of our study was to investigate if and how the network structure of a population influences the performance and efficiency of infectious disease interventions. The purpose of our analysis was not to directly guide real-world STI policy in MSM. While we included EPT in our study, in practice, EPT is not recommended for MSM due to the high risk of infection with other diseases (e.g., HIV and syphilis) that would go undiagnosed under EPT, but could be detected if partners were tested via PN or contact tracing.[22] Considering these different objectives (reducing the burden of bacterial STIs versus diagnosing more serious co-occurring conditions) would be critical in developing a

model to inform real-world STI policies. Such considerations would increase the value of PN and contact tracing, changing the results of our cost-effectiveness analysis.

Our study is subject to several limitations. We considered PN and EPT as being mutually exclusive strategies. In practice, PN and EPT could be used in combination. The index patient might use PN for partners who are more likely to seek testing, but request EPT for partners who are unwilling to visit clinics.[35] We did not investigate how relationship dynamics might affect the effectiveness and cost-effectiveness of partner management strategies. If a population has a higher partner turnover rate, PN and contact tracing may be preferred over EPT. Moreover, we did not consider the impact of different sexual positioning that is relevant to chlamydial and gonococcal infections and instead assumed a probability of disease transmission that reflects an average of different sexual positioning.[68,69] Furthermore, we did not consider antibiotic resistance that might occur to repeated and frequent treatment or other sources of treatment failure. Treatment failure is most difficult to address under EPT, where the treatment of partners is not overseen by a healthcare provider. While we did not explicitly incorporate treatment failure into our analysis, we do consider lower levels of partner compliance in sensitivity analysis, which approximates the effect of treatment failure under the EPT strategy. Lastly, we only conducted sensitivity analysis on partner compliance parameters; other model parameters, including disease dynamics, sexual behaviors, and diagnostic testing behaviors, were kept fixed. Therefore, the impact of network structures on the effectiveness and efficiency of partner management strategies can only be interpreted for our specific parameter setting.

Our findings suggested that the structure of the underlying contact network might matter in evaluating interventions in infectious diseases in certain contexts. Future CEA

studies that aim to make infectious disease intervention recommendations could be improved by considering the specific network structure, sexual behavior, and screening and compliance behaviors of their relevant population.

Chapter 3
How much should we know about sex? The value of knowing sexual relationships

3.1 Introduction

Cost-effectiveness analysis (CEA) evaluating interventions for a sexually transmitted infection (STI) depends on the underlying sexual contact networks through which the STI propagates. The contact pattern in the networks could affect the disease dynamics and the efficiency of the competing control strategies. For example, a contact network that allows individuals to form concurrent partnerships is more likely to facilitate STI spread compared to a contact network that has more sequential partnerships.[8–10] In addition, under the same disease prevalence, a screening program can be more effective in a population with more sequential partnerships than in a population with more concurrent partnerships.[9,11] The contact pattern among sex partners is shaped by network dynamics, which is the process of relationship formation and dissolution, and is usually informed by estimates from sexual behavioral surveys or reports.[10,28,29,70]

Network dynamics are usually inferred by a combination of measures of sexual behaviors.[10,28,29,70] Key determinants include aggregate network measures such as the number of sex partners in the past 12 months (i.e., annual degree), relationship duration, gap length between the end of a relationship and the onset of the next relationship, and

concurrency (proportion of individuals involved in concurrent partnerships).[10,28,29,70] For instance, while annual degree and concurrency suggest how many sex partners individuals have in a period of time, these measures do not determine how quickly individuals form new partnerships (partnership turnover) and end partnerships.[28,71] By combining the data on relationship duration and gap length, we can determine whether individuals tend to have concurrent partnerships (high concurrency and low partnership turnover) or sequential partnerships in a sexual contact network (low concurrency and high partnership turnover).[28]

It is common to collect or report aggregate measures such the number of partners in a period of time in sexual behavior surveys or reports.[58,72,73] However, detailed sexual behavioral data (e.g., gap lengths, relationship durations, and concurrency) are more difficult to collect or less likely to be reported because these data depend on the respondents' recollection or definition of partnerships (e.g., one-night stands might not be counted as a partnership).[74,75] In addition, to get reliable measures of gap lengths and relationship durations, surveys might ask the respondents to provide the information for a number of partnerships within a period of time (e.g., up to 3 partnerships in the past 12 months).[72,73] This could burden both the interviewers and respondents in the surveying process and potentially increase the cost of conducting a survey.[75,76] Therefore, some small-scale surveys and reports for special populations (e.g., men who have sex with men, sex workers, transgenders, etc.) might focus more on the aggregate measures and ignore collecting or reporting data on detailed sexual behaviors.[58,77,78]

Contact networks parameterized by aggregate measures (e.g., annual degree) are likely to have a spectrum of microstructures or network dynamics in the network.[28,71]

Undetermined network dynamics could result in a wide range of disease transmission dynamics.[9,10,28] Studies have shown how key sexual behavioral data could help determine network dynamics and disease transmission dynamics.[28,29,70] However, no study focuses on how these key sexual behavioral data might help inform better decision and quantifying the value of collecting different key sexual behavioral data in sexual behavioral surveys that aims to inform decision-making.

In this study, we employed partner management strategies for bacterial STIs (e.g., chlamydia and gonorrhea) to evaluate the importance of the key determinants for network dynamics, including relationship durations and concurrency. Partner management strategies such as partner notification (PN) and expedited partner therapy (EPT) aim to alter the probability of disease transmission on the sexual connections between individuals with different intensity and resource requirement.[22] The cost and effectiveness of these types of strategies are dependent on and sensitive to the underlying network dynamics. Therefore, partner management strategies in bacterial STI provide a unique opportunity of investigating to which extent relationship duration and concurrency inform better decision-making. We simulated sexual contact networks with network dynamics parameterized with different levels of sexual behavioral information, including the distribution of annual degree, relationship durations, and concurrency. We conducted a CEA to compare multiple partner management strategies to avert chlamydial infections and chlamydia-induced pelvic inflammatory disease (PID) among women in sexual contact networks with different levels of behavioral information. Finally, we quantified the value of collecting data on relationship durations and concurrency using a value of information (VOI) approach.[79–81]

3.2 Methods

3.2.1 Overview

We developed a dynamic model to simulate the spread of chlamydial infection among a cohort of heterosexual men and women with initial age between 15-24 for 5 years and determine the optimal partner management strategy for this population. We did not allow individuals to age in and out of the population. We implemented a sexual contact network to specify how simulated individuals interact with one another to spread the disease. We compared three calibration scenarios used to fit different sets of observed targets, including the number of sexual partners in the past year (cumulative degree distribution), proportion of population with overlapped relationships in the past year (concurrency), and chlamydia prevalence. Our aim was to determine whether these different calibration scenarios impacted which partner notification strategy was deemed optimal based on a cost-effectiveness analysis (CEA). In addition, we quantified the value of collecting data on relationship durations and concurrency to inform network dynamics by using a value of information (VOI) approach.[79–81] We estimated parameters and observed targets associated with sexual behavior from the National Survey of Family Growth 2015-2017 (NSFG)[72] and published literature. We obtained parameters related to disease dynamics and partner management strategies from published literature. We provide the parameter values, ranges, and source in Table 3.1 and the observed targets in Table 3.2. The simulation model was implemented in Python 3.7.3.[36] The CEA and EVPI were conducted and calculated using R 3.6.2.[82]

3.2.2 Sexual contact networks

We simulated primary and casual relationships in a closed population (without new entry or exit in the population) of 2,000 heterosexual men and women (1,000 men and women, respectively) with the initial age 15-24 in weekly cycles. Each cycle, individuals face a probability of forming one or more new relationship(s), which differs by sex and depends on the individual's current relationship status, following this function:

$$\delta_s \cdot \left(\kappa'^{(primary_i=1)}\right) \cdot \left(\kappa^{(parimary_i=0)\cdot(casaul_i>0)}\right) \quad (3.1)$$

, where δ_s represents the probability of relationship formation by sex ($s = m$ for men and $s = f$ for women), κ' denotes the relative risk of forming new relationships if the individual i has a primary partner, and κ denotes the relative risk of forming new relationships if the individual i only has casual partner(s). Both relative risk factors (κ' and κ) range from 0 to 1, reducing the probability of forming a new relationship. If an individual does not have a partner at the beginning of the cycle, the probability of forming a new relationship is δ_s, which is determined by the inverse of the average gap length between relationships for men ($1/\Delta_m$) and women ($1/\Delta_f$). In this process, the average gap lengths are defined as the time between the end of a relationship and the onset of the subsequent relationship assuming all relationships are formed sequentially without overlaps in the population. We estimated the gap lengths and the relative risk factors (Δ_m, Δ_f, κ', and κ) via calibration. After determining which individuals will form relationships, we matched the selected men and women by the decreasing order of their number of sex partners in the cycle. Individuals could form multiple relationships in each cycle but could only form a relationship with the same person once. We determined whether a newly formed relationship was primary or

casual at the onset of the relationship following the probability of primary partner (ρ), which was estimated via calibration. Only one primary partnership was permitted for each individual at any cycle.

For relationship dissolution, we randomly broke up relationships based on the duration of the relationship, which varied by type of relationship (primary or casual) and number of sex partners in the past year (1 or >1). The average relationship duration was estimated using a Weibull survival model accounting for the type of relationship and the number of sex partners retrospectively in the past 12 months.[72] In the NSFG, the survey collected information for up to three partnerships that existed in the past 12 months, including the type of partnership and the year and month associated with the first and last sex acts with a partner. The survey also asked the respondents about how many sex partners they had in the past 12 months (i.e., annual degree). We focused on the population aged 15-24 who were sexually active in the NSFG. We predicted the monthly hazard rate using the Weibull survival model and converted the monthly hazard to weekly hazard. We then estimated the survival curve over 20 years by exponentiating the negative cumulative weekly hazard. The average relationship duration of a type of relationship was estimated as the area under the survival curve. On average, a casual partnership lasted 100 weeks and 71 weeks for an individual who had a single partner and more than one partner in the past year, respectively. In comparison, a primary partnership had an average of 162 weeks and 102 weeks among individuals who had a single partner and more than one partner in the past year, respectively. The probability of a relationship dissolution for a type of relationship was the inverse of the estimated duration dependent on the number of sex partners in the past year (52 cycles).

Table 3.1. Parameter values, ranges, and sources.

Parameters	Value/Unit	Range	Source
Relationship formation and dissolution			
Average duration of a relationship			
Primary relationship (degree = 1 in the past year) (τ_1^p)	162 weeks	(1, 300)	[72], Calibrated
Primary relationship (degree > 1 in the past year) (τ_2^p)	102 weeks	(1, 300)	[72], Calibrated
Casual relationship (degree = 1 in the past year) (τ_1^c)	100 weeks	(1, 300)	[72], Calibrated
Casual relationship (degree > 1 in the past year) (τ_2^c)	71 weeks	(1, 300)	[72], Calibrated
Average gap length between relationships			
Women (Δ_f)		(0, 100)	Calibrated
Men (Δ_m)		(0, 100)	Calibrated
Probability that a new partner is primary (ρ)		(0, 1)	Calibrated
Relative risk of a relationship formation with an existing primary partnership (κ')		(0, 1)	Calibrated
Relative risk of a relationship formation with ≥ 1 existing casual partnership (κ)		(0, 1)	Calibrated
Sexual behaviors			
Number of sex acts per week (λ)	1.22		[72]
Probability of condom use (η)	43.50%		[72]
Chlamydial infection			
Probability of chlamydial infection from men to women per sex act (β)		(0, 0.45)	[70,83,84], Calibrated
Relative risk of chlamydial infeciton from women to men (γ^{inf})	0.8		[84]
Relative risk reduction of condom use (γ^{condom})	0.6		[52]
Probability of asymptomatic infection			
Women (α_f^{CT})	25%		[85]
Men (α_m^{CT})	5%		[85]
Probability of developing PID given chlamydial infection (P)	10%/year		[86]
Probability of asymptomatic PID (α^{PID})	0.6		[87]

Probability of developing chronic pelvic pain due to PID infection (P^c)	0.180		[88]
Duration of untreated chlamydial infection			
Women ($\sigma_f^{untreat}$)	52 weeks		[61]
Men ($\sigma_m^{untreat}$)	32 weeks		[51]
Annual screening rate			
Women (ψ_f)	50%		[89]
Men (ψ_m)	7%		[90]
Duration of symptomatic chlamydial infection (σ^{symp})	4 weeks		[87]
Treatment duration (σ^{treat})	1 week		[91]
Diagnostic performance			
Sensitivity (***sens***)	90%		[92]
Specificity (***spec***)	100%		[92]
Partner management strategies			
Patient compliance			
Probability of contacting partners (PN) (ϕ^{PN})	0.71		[24,34,93]
Probability of contacting partners (EPT) (ϕ^{EPT})	0.74		[24,34,93]
Partner compliance			
Probability of partners getting tested (PN) (φ^{PN})	0.67		[24,34,93]
Probability of partners getting treated (EPT) (φ^{EPT})	0.79		[24,34,93]
Cost			
Clinic visit for chlamydia ($\mathbf{C}^{clinic}$)	$105.66		[61]
Treatment cost for chlamydia ($\mathbf{C}^{treat}$)	$50.38		[61]
PID lifetime cost ($\mathbf{C}^{PID}$)	$2,922		[94]
Acute PID lifetime cost	$3,136		[94]
Chronic pelvic pain	$9,264		[94]
Reduction in utility		duration	
Symptomatic chlamydial infection (u^{CT})	0.13	1 week	[87]
Symptomatic PID (u^{PID})	0.32	1 week	[87]
Chronic pelvic pain (u^{pain})	0.33	260 weeks	[95]
Annual discount rate (r)	3%		[62]

3.2.3 Disease dynamics

We simulated the spread of chlamydial infection through the sexual contact network following a Susceptible(*S*)-Infected(*I*)-Treated(*T*)-Susceptible(*S*) framework. A susceptible individual (*S*) could be infected by an infected sex partner. The probability of disease transmission per sex act ranged between 0 and 0.45 and was estimated through calibration.[70,83,84] Transmission from an infected individual to a susceptible partner depended on condom use and the number of sex acts. Condom use could reduce transmission by 60%.[52] Based on the NSFG, we estimated that 43.5% of women used condom as the birth control method in the last sex act and an average of 1.22 sex acts per week.[72] An infected individual (*I*) could spontaneously recover back to the susceptible state at a rate of inverse average duration 32 weeks for men and 52 weeks for women.[96,97]

An infected individual could be identified and treated by routine annual screening or partner management for asymptomatic infection, or by seeking out testing for symptomatic infection. The probability of symptomatic infection was 25% among infected women and 5% among infected men.[85] The annual screening rate was 50% among women and 7% among men.[89,90] For symptomatic infection, the average duration for an infected individual to develop symptoms was 4 weeks.[87] We assumed that the symptomatic infected individual would seek out care as soon as the symptoms presented. The sensitivity and specificity of chlamydia testing were 90% and 100%, respectively.[92] We considered the severe consequence of untreated chlamydial infection among women (PID).[94,98] Once diagnosed, the individual was treated (*T*) and stayed abstinent for one week.[99] We assumed no treatment failure in the model. An untreated chlamydial infected woman could develop

PID with a probability of 10% in a year.[86] To simplify the model, we did not model the disease progression of PID and did not allow recovery from PID. The disease dynamics of chlamydial infection was independent of the disease progression of PID in this model.

3.2.4 Partner management strategies

We considered five partner management strategies: partner notification alone (PN), expedited partner therapy alone (EPT), EPT for current partners and PN for past partners (EPTPN1), EPT for monogamous index patients in the past 6 months, otherwise PN (EPTPN2), and routine screening alone (SC: no partner management). PN, the common partner management strategy, relies on patients to notify their sex partners and encourage them to seek out testing. However, the partner testing/treatment rate could be low.[22,24,34,93] The purpose of EPT is developed to increase partner treatment rate by allowing patients to deliver antibiotic regimen to their partners without requiring the partners to be tested.[22,24,34,93] Because EPT is not allowed across all states in the US, we regarded PN as the standard strategy in our model.[100] Both PN and EPT have two compliance parameters: partner compliance and patient compliance. Under PN, patients were likely to notify 71% of the sex partners and 67% of the notified partners would seek out testing.[34,87,93] Under EPT, patients would deliver medication to 74% of the partners and 79% of the partners who received medication would take the medicine.[34,87,93] We assumed the compliance only applied to the current partners. For the past partners, the probability that a past partner being notified decreased over time, following an exponential function $e^{-\frac{[t-T_{ij}^{end}]}{2}}$, where t denotes the current cycle and T_{ij}^{end} reflects the end cycle of a relationship between

individual *i* and *j*. We only allowed individuals to notify or deliver medication to the partners within the past 6 months. In addition to PN alone and EPT alone, we considered two mixed partner management strategies: EPTPN1 and EPTPN2. The compliance behaviors under these mixed partner management strategies followed the same compliance behaviors and the exponential function mentioned above. Finally, we included routine screening alone (SC) to obtain the relative cost and effectiveness of PN.

3.2.5 Calibration scenarios

We considered three calibration scenarios with increasing amounts of information to inform the sexual network model parameters. In scenario 1, we used the chlamydia prevalence (4.2%) and the annual degree distribution for men and women, respectively, as the calibration targets.[72,101] We estimated the annual degree distribution for young men and women, respectively, from the NSFG.[72] In this scenario, we estimated all the parameters associated with relationship formation and dissolution and the probability of transmission per sex act via calibration. In scenario 2, we used the same set of targets as those in scenario 1 and introduced the relationship durations estimated from the NSFG as input parameters.[72] Scenario 3 was enhanced from scenario 2 by adding concurrency, which is defined as the proportion of individuals who had overlapped partnerships in the past year, as one of the calibration targets.[102,103] We estimated concurrency from the NSFG.[72] The estimates of the targets are shown in Table 3.2.

Table 3.2. The estimates, uncertainty, and sources of the calibration targets.

Targets	Mean	SE	Source
Disease			
Chlamydia prevalence	0.042	0.0071	[101]
Sexual behavior			
Distribution of population who had *x* partners last year (Degree distribution)			[72]
Women			
0	6.20%	0.76%	
1	63.40%	2.48%	
2	18.37%	2.26%	
3	5.84%	1.34%	
4	2.04%	0.49%	
5	2.00%	0.66%	
6	1.10%	1.00%	
7+	1.05%	0.40%	
Men			
0	13.57%	1.92%	
1	53.64%	2.29%	
2	17.51%	1.89%	
3	7.38%	1.71%	
4	2.08%	0.51%	
5	2.68%	0.86%	
6	0.49%	0.50%	
7+	2.65%	0.11%	
Proportion of population who had > 1 partner last year (Concurrency)	13%	1.16%	[72]

3.2.5.1 Simulated network measures

We simulated sexual contact networks for each posterior parameter set and computed the simulated network measures that inform network dynamics for each parameter set. The simulated network measures include concurrency (according to the definition used to

estimate concurrency from the NSFG) and casual partnership turnover (average number of new casual partners per year). We focused on casual partnership turnover instead of partnership turnover including both primary and casual partnerships because an individual was allowed to have multiple casual partnerships but only allowed to have a single primary partnership.

3.2.6 Costs and health outcomes

Testing and treatment for chlamydial infection incurred costs to the healthcare sector.[96] In addition, PID could incur cost due to symptomatic PID and chronic pelvic pain.[94] We assumed that a woman who had PID would develop symptom with a probability of 40% and whether a woman developed symptoms did not affect the probability of developing chronic pelvic pain, which is 18%.[88] We calculated the expected costs for a woman who had PID in early ages based on the probability of three events associated with PID: asymptomatic PID and chronic pelvic pain, symptomatic PID, and symptomatic PID and chronic pain.[94] We assumed that asymptomatic PID did not incur any costs. In addition, we ignored other complications caused by PID such as ectopic pregnancy and infertility because we did not include pregnancy in the model.

Primary health outcomes included quality-adjusted life years (QALYs) for women, chlamydia incidence, chlamydia prevalence, average number of chlamydial infections per person, average duration of chlamydial infection, and number of young women who ever had PID. To calculate the QALYs for women, we considered the reduction in health utility due to symptomatic chlamydial infection and PID related consequences.[87,95] For women

who ever developed PID, we calculated their expected utility based on the probability of three events associated with PID and assumed that asymptomatic PID did not reduce utility.

3.2.7 Model simulation

We initialized the sexual contact network with about 3.8% of chlamydial-infected individuals and 880 relationships among 1,000 men and women, respectively. We allowed a 15-year burn-in period for the simulation of sexual contact networks and disease dynamics to stabilize. In the burn-in period, we did not allow individuals to age or accrue health outcomes and costs. After the burn-in period, we calibrated each scenario to the observed sexual behaviors and chlamydia prevalence over 5 years (260 cycles) using ABC-SMC. The calibration process resulted in 1,000 posterior parameter sets for each scenario. For each posterior parameter set in a calibration scenario, we performed 100 simulations to obtain a stable average cost and health outcomes under each of PN, EPT, EPTPN1, EPTPN2, and SC over 5 years (intervention period). After the 5-year intervention period, we projected the lifetime costs with/without early infection of PID and QALYs among women (post-intervention period). We combined the costs and QALYs in the intervention period and post-intervention period under a partner management strategy in a calibration scenario. Both costs and QALYs were discounted annually at 3%.[62]

3.2.8 Cost-effectiveness analysis and value of information analysis

3.2.8.1 Cost-effectiveness analysis

We conducted a CEA comparing between five strategies in each scenario. In each scenario, we first sorted the strategies by an increasing order of their costs. We then eliminated the strongly and weakly dominated strategies (strategies that result in fewer QALYs at a higher cost than the previous strategy or the combination of previous and next strategies) from the list of strategies. Among the undominated strategies, we calculated the incremental cost-effectiveness ratio (ICER), which is the incremental cost per additional QALY gained compared to the previous undominated strategy. The most cost-effective strategy was the strategy with the largest ICER less than the willingness-to-pay (WTP) of $100,000/QALY, which served as the resource constraint in the society.[104] The CEA analysis mentioned above is to determine the most cost-effective strategies by averaging across the parameter sets, but it does not provide information about how likely the decision is to be optimal. To calculate the probability that a strategy is cost-effective, we conducted a CEA at each parameter set in a scenario and selected the most cost-effective strategy at a given WTP threshold. We calculated the proportion that a strategy is cost-effective across all parameter sets at the WTP threshold for each strategy. We repeated this process over a range of WTP thresholds and obtained the cost-effectiveness acceptability curve (CEAC) and the frontier, which consists of the strategies that have the highest probability of being cost-effective across WTP thresholds.[105]

3.2.8.2 Expected value of perfect information

We calculated expected value of perfect information (EVPI) across a range of WTP thresholds for each scenario. We started the calculation with scenario 3 (the scenario with the most complete information in this study) with the following steps.[79] At each WTP threshold, we first calculated the net monetary benefit (NMB = QALYs x WTP – Cost) for each strategy in each parameter set. We identified the overall optimal strategy across all parameter sets by selecting the strategy with the highest expected NMB (average NMB across all parameter sets). In addition, for each parameter set, we identified the optimal strategy by selecting the strategy with the highest NMB. The difference in NMB between the overall optimal strategy and the optimal strategy for a parameter set, which is the opportunity loss of the parameter set, represented the loss of adopting a less optimal strategy given the parameter set. We calculated EVPI at a WTP threshold by averaging all the opportunity loss across all parameter sets. The EVPI calculated was only for the 1000 women in the simulation population; therefore, we calculated the population EVPI by adjusting the EVPI with the female population size (21,345,000) aged 15-24 in the US.[106] The EVPI reflected the maximum that a decision maker should be willing to pay to reduce the uncertainty from all parameters.[79] We followed a similar process to calculate the population EVPI for scenarios 1 and 2. However, at each WTP threshold, the overall optimal strategy in scenarios 1 and 2 was informed by the overall optimal strategy in scenario 3 because scenario 3 used the most complete information (including relationship durations and concurrency) to characterize relationship dynamics. Therefore, the overall optimal strategies informed by scenario 3 should be the most efficient strategy overall among all three scenarios. The EVPI for scenario 2 represented the maximum that a

decision maker should be willing to pay to eliminate the uncertainty from all parameters including the uncertainty due to the lack of data on concurrency. Similarly, the population EVPI for scenario 3 suggested the maximum that a decision maker should be willing to pay to reduce the uncertainty from all parameters including the uncertainty due to the lack of data on both concurrency and relationship durations.

3.2.8.3 Expected value of empirical information

We quantified the expected value of empirical information (EVEI) for concurrency and relationship durations by calculating the difference in EVPI between scenarios 3 and 2 (EVEI of concurrency), and between scenarios 2 and 1 (EVEI of relationship durations). Because the EVPI of scenarios 3 and 2 were calculated with and without the data on concurrency, respectively, the difference in EVPI between the two scenarios represented the value of knowing concurrency in the population. Similarly, the difference in EVPI between scenarios 2 (with the information of relationship durations) and 1 (without the information of relationship durations) represented the value of collecting data on relationship duration.

3.3 Results

3.3.1 Calibration results

We were able to calibrate the annual degree distributions and the chlamydia prevalence in all three calibration scenarios (Figure B.1). The three scenarios resulted in different posterior distributions among parameters calibrated (Table 3.3, Figure B.2, Figure B.3).

On average, the probability that a new partnership is primary was the highest in scenario 1 and the lowest in scenario 3. Scenario 1 yielded longer average relationship durations than the estimates from the NSFG. The gap lengths between relationships decreased as more behavioral information was added in the calibration scenarios. On average, the probability of transmission per sex act increased as the calibration scenario included more behavioral information.

Concurrency and casual partner turnover were negatively correlated in scenario 1 ($r = -0.28$) and scenario 2 ($r = -0.51$), and became slightly positively correlated in scenario 1 ($r = 0.06$) (Figure 3.1). Adding sexual behavioral information reduced the variation in concurrency and casual partnership turnover. Scenario 1 had the highest average concurrency (0.247) and the lowest average casual partnership turnover (0.266), and scenario 3 had the lowest average concurrency (0.130) and the highest average casual partnership turnover (0.461) (Table 3.4). The average simulated network measures of scenario 2 fell in between scenarios 1 and 3. Consistent with concurrency, the average number of sex partners at each time step decreased as we gradually added more sexual behavioral data to calibration scenarios.

Table 3.3. Posterior mean and standard deviation (sd) of parameters.

	Scenario 1		Scenario 2		Scenario 3	
Parameters	mean	sd	mean	sd	mean	sd
Probability of primary partnership ($\boldsymbol{\rho}$)	0.509	0.252	0.446	0.225	0.176	0.110
Duration of casual relationship (annual deg = 1) ($\boldsymbol{\tau}_1^c$)	197	61	–	–	–	–
Duration of casual relationship (annual deg > 1) ($\boldsymbol{\tau}_2^c$)	182	66	–	–	–	–
Duration of primary relationship (annual deg = 1) ($\boldsymbol{\tau}_1^p$)	168	76	–	–	–	–
Duration of primary relationship (annual deg > 1) ($\boldsymbol{\tau}_2^p$)	147	77	–	–	–	–
Gap length (men) ($\boldsymbol{\Delta}_m$)	67	12	52	6	50	8
Gap length (women) ($\boldsymbol{\Delta}_f$)	46	7	38	4	34	4
Relative risk of relationship formation (primary) ($\boldsymbol{\kappa}'$)	0.410	0.276	0.389	0.319	0.462	0.267
Relative risk of relationship formation (casual) ($\boldsymbol{\kappa}$)	0.170	0.207	0.284	0.321	0.044	0.029
Probability of transmission ($\boldsymbol{\beta}$)	0.088	0.027	0.101	0.024	0.187	0.101

Table 3.4. Simulated network measures for each scenario.

	Scenario 1		Scenario 2		Scenario 3	
Network measures	mean	sd	mean	sd	mean	sd
Concurrency	0.247	0.030	0.205	0.026	0.130	0.007
Casual partner turnover	0.266	0.084	0.388	0.130	0.461	0.056
# of partners at a cycle	1.095	0.100	0.932	0.033	0.842	0.033

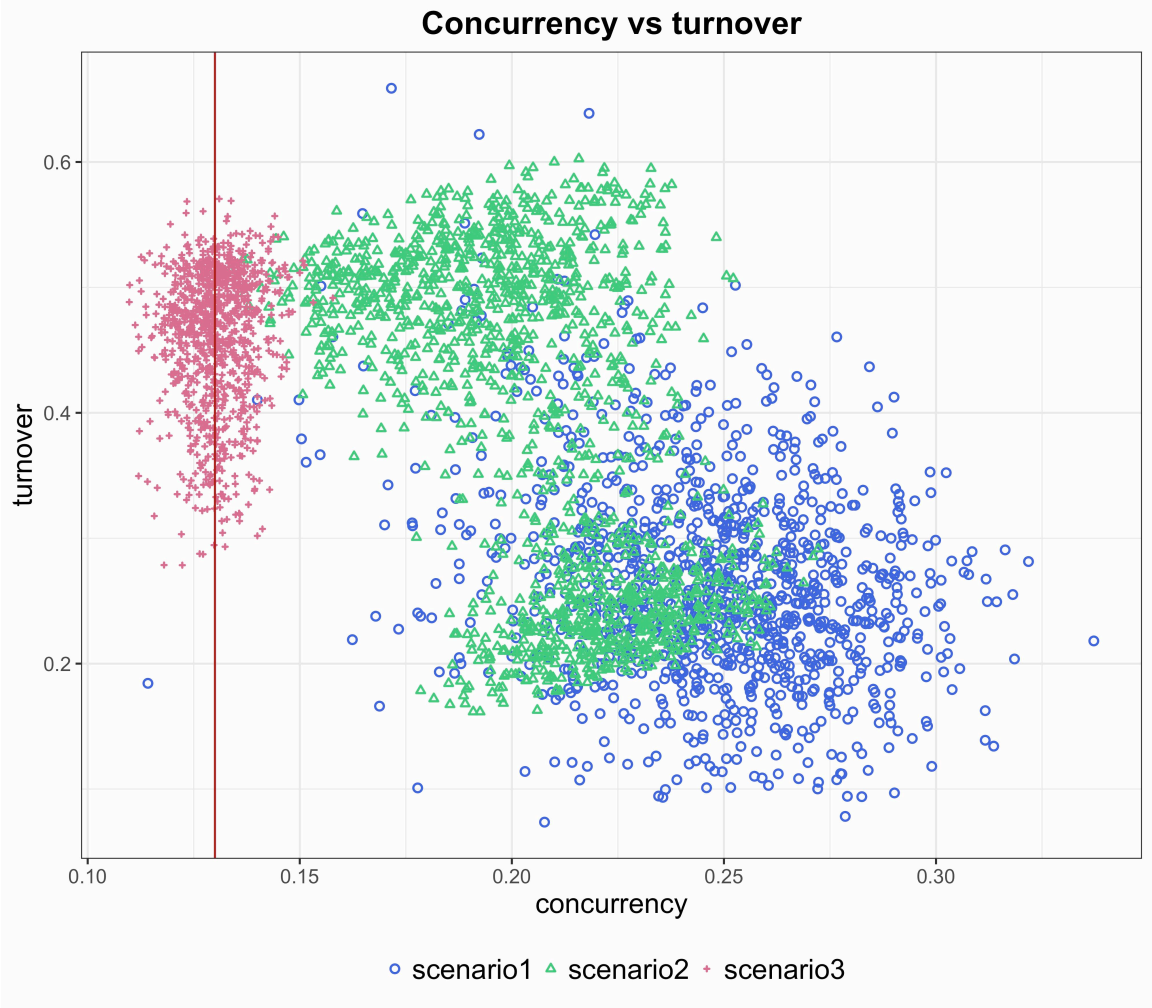

Figure 3.1. The relationship of simulated concurrency and casual partnership turnover for each scenario. The vertical red line is the observed concurrency estimated from the NSFG.

Table 3.5. Average simulated disease outcomes (chlamydia prevalence at the last cycle and cumulative chlamydia and PID incidence over 5 years) and average simulated outcomes for different partner management strategies for each calibration scenario.

Strategy	Chlamydia prevalence	Chlamydia incidence	Pelvic inflammatory disease incidence	No. of screening	No. tested (PN)	No. of true treated (PN)	No. of receiving medication (EPT)	No. of true treated (EPT)	No. of over-treatment (EPT)	No. of index cases via screening	Treated infected partners per index case
Scenario1											
SC†	16.20%	2,461	58	3,781	0	0	0	0	0	766	
PNˆ	4.18%	1,201	22	3,785	828	354	0	0	0	309	1.15
EPT¥	8.33%	1,751	36	3,784	0	0	730	347	226	475	0.73
EPTPN1*	8.26%	1,743	35	3,784	11	5	722	343	222	473	0.74
EPTPN2§	3.38%	1,055	20	3,785	680	277	158	51	53	272	1.21
Scenario2											
SC†	15.05%	2,353	57	3,782	0	0	0	0	0	742	
PNˆ	4.19%	1,180	23	3,785	748	327	0	0	0	312	1.05
EPT¥	7.86%	1,671	35	3,784	0	0	643	315	189	464	0.68
EPTPN1*	7.73%	1,656	35	3,784	17	8	630	309	185	459	0.69
EPTPN2§	3.66%	1,081	21	3,786	595	248	174	61	56	287	1.08
Scenario3											

SC†	13.81%	2,168	54	3,782	0	0	0	0	0	705	
PNˆ	4.13%	1,250	23	3,784	796	391	0	0	0	326	1.20
EPT¥	7.95%	1,712	37	3,784	0	0	587	327	131	487	0.67
EPTPN1*	7.82%	1,700	37	3,784	16	9	579	323	129	482	0.69
EPTPN2§	4.86%	1,321	26	3,784	562	274	260	97	71	356	1.04

† SC: screening alone

ˆ PN: Partner notification

¥ EPT: Expedited partner therapy

* EPTPN1: EPT for current partners and PN for past partners

§ EPTPN2: EPT for partners of index patients who were monogamous for the past 6 months, otherwise PN

3.3.2 Simulation outcomes

The simulation outcomes (chlamydia prevalence at the last time step, cumulative chlamydia and PID incidence over 5 years) are presented in Table 3.5. Without any partner management (screening alone), scenario 1 had the most severe disease burden (chlamydia prevalence, and chlamydia and PID incidence) but scenario 3 had the least. Partner management strategies were able to reduce the disease burden in all scenarios by treating partners of index patients via PN or EPT. In scenarios 1 and 2, EPTPN2 was the most effective strategy to reduce the chlamydia prevalence and avert the most chlamydia and PID incidence. On average, EPTPN2 treated the most infected partners per index case in scenario 1 (1.21 partners) and scenario 2 (1.08 partners) (Table 3.5). In contrast, the most effective strategy in scenario 3 switched to PN, which treated the most infected partners per index case (1.2 partners) (Table 3.5).

3.3.3 Cost-effectiveness analysis

The results of CEA at a WTP of $100,000/QALY are presented in Table 3.6. Screening alone was strongly dominated across all scenarios because it generated the fewest QALYs with the highest cost. EPT was the least costly strategy in all scenarios, following by EPTPN1, EPTPN2, and PN. With a WTP of $100,000/QALY, EPTPN2 was the most cost-effective strategy in scenario 1 (ICER = $1,435/QALY) and scenario 2 (ICER = $1,651/QALY). However, in scenario 3, the most cost-effective strategy switched to PN (ICER = $16,673/QALY) while PN was strongly dominated in scenarios 1 and 2. The change of the most cost-effective strategy reflected the strategy that treated the most

infected partners per index case. The patterns of CEAC were similar in scenarios 1 and 2, where EPTPN2 was most likely to be the cost-effective strategy at WTP thresholds above $5,000/QALY (Figure 3.2). In scenario 3, the cost-effective strategy switched from EPT (WTP < $5,000/QALY), to EPTPN2 (WTP between $5,000/QALY and $15,000/QALY), and to PN (WTP ≥ $20,000/QALY) (Figure 3.2).

3.3.4 Expected value of empirical information

EVPI increased as the WTP threshold increased except for low WTP thresholds between $6,000/QALY and $16,000/QALY (Figure 3.3). In all scenarios, EVPI peaked at WTP = $7,000/QALY, where the cost-effective strategy changed from EPT to EPTPN2 in scenario 3, and at WTP of $16,000/QALY, where the cost-effective strategy switched from EPTPN2 to PN in scenario 3. Between the two peaks, EVPI dropped to much lower values in scenarios 1 and 2 than in scenario 3 because the cost-effective strategy was EPTPN2 in all the scenarios. EPTPN2 in scenarios 1 and 2 were relatively less costly than that in scenario 3 (compared between ICERs). At WTP thresholds greater than $16,000/QALY, while EPTPN2 was the most cost-effective strategy informed in scenario 1 and 2, PN should have been the most cost-effective strategy, informed by scenario 3 with both relationship durations and concurrency. EVPI in scenarios 1 and 2 were substantially higher than the EVPI in scenario 3 because the information in scenario 3 not only reduced the uncertainty but also changed the cost-effective strategy from EPTPN2 to PN. At a WTP of $100,000/QALY, the population EVEI about relationship durations was about $1,163 million and the population EVEI of collecting concurrency measure was about $563 million.

Table 3.6. Cost-effectiveness analysis for each calibration scenario at a willingness-to-pay (WTP) of $100,000 per QALY. The cost-effective strategy is EPTPN2 in both scenarios 1 and 2 but switches to PN in scenario 3.

Strategy	Cost ($)	QALYs	Incremental cost-effectiveness ratio (ICER)
Scenario 1			
EPT¥	516,660	27,374.29	
EPTPN1*	516,729	27,374.36	1,034
EPTPN2§	522,696	27,378.52	1,435
PNˆ	543,632	27,377.83	strongly dominated
SC†	561,963	27,368.31	strongly dominated
Scenario 2			
EPT¥	512,387	27,374.40	
EPTPN1*	512,446	27,374.51	524
EPTPN2§	518,417	27,378.13	1,651
PNˆ	536,636	27,377.68	strongly dominated
SC†	558,639	27,368.61	strongly dominated
Scenario 3			
EPT¥	515,760	27,374.00	
EPTPN1*	515,992	27,374.11	2,130
EPTPN2§	534,615	27,376.80	6,904
PNˆ	546,264	27,377.50	16,673
SC†	549,555	27,369.43	strongly dominated

† SC: screening alone

ˆ PN: Partner notification

¥ EPT: Expedited partner therapy

* EPTPN1: EPT for current partners and PN for past partners

§ EPTPN2: EPT for partners of index patients who were monogamous for the past 6 months, otherwise PN

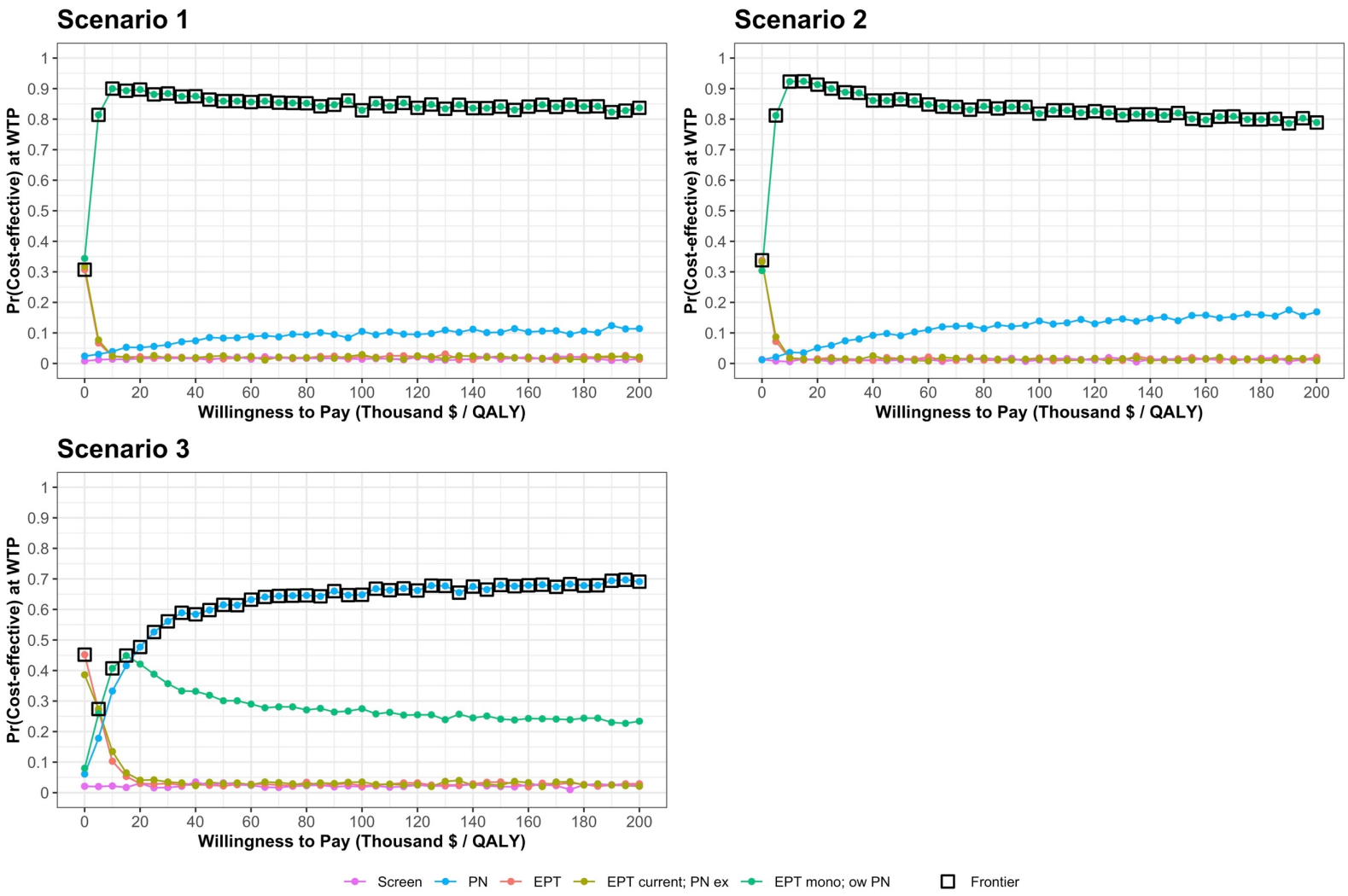

Figure 3.2. Cost-effectiveness acceptability curve for each calibration scenario.

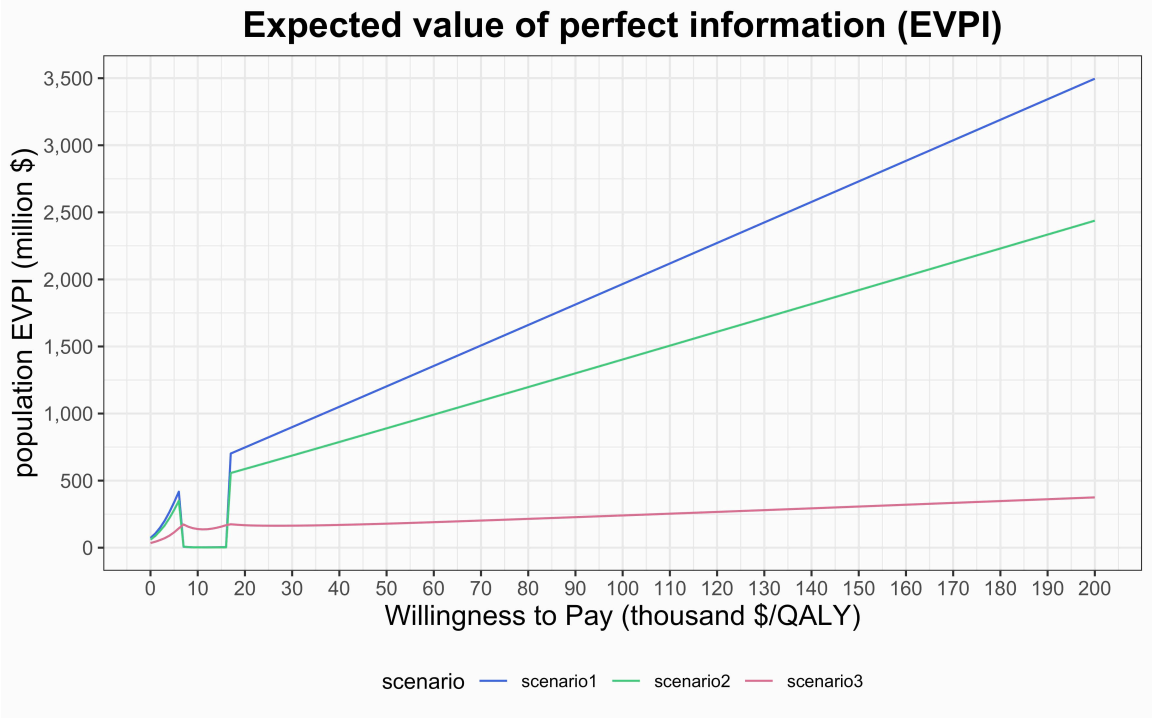

Figure 3.3. Population expected value of empirical information over a range of WTP ($0/QALY – $200,000/QALY).

3.4 Discussion

Mathematical models evaluating disease control strategies for bacterial STIs are often parameterized by sexual behavioral data specific to a population. We demonstrated that including data on relationship durations and concurrency in simulating sexual contact networks can increase the precision in network dynamics, reduce the bias in disease outcomes, and better inform the optimal disease control strategy. We also quantified the value of collecting relationship durations and concurrency, respectively. This has implication in conducting sexual behavioral surveys that are intended to guide disease control strategies for STIs.

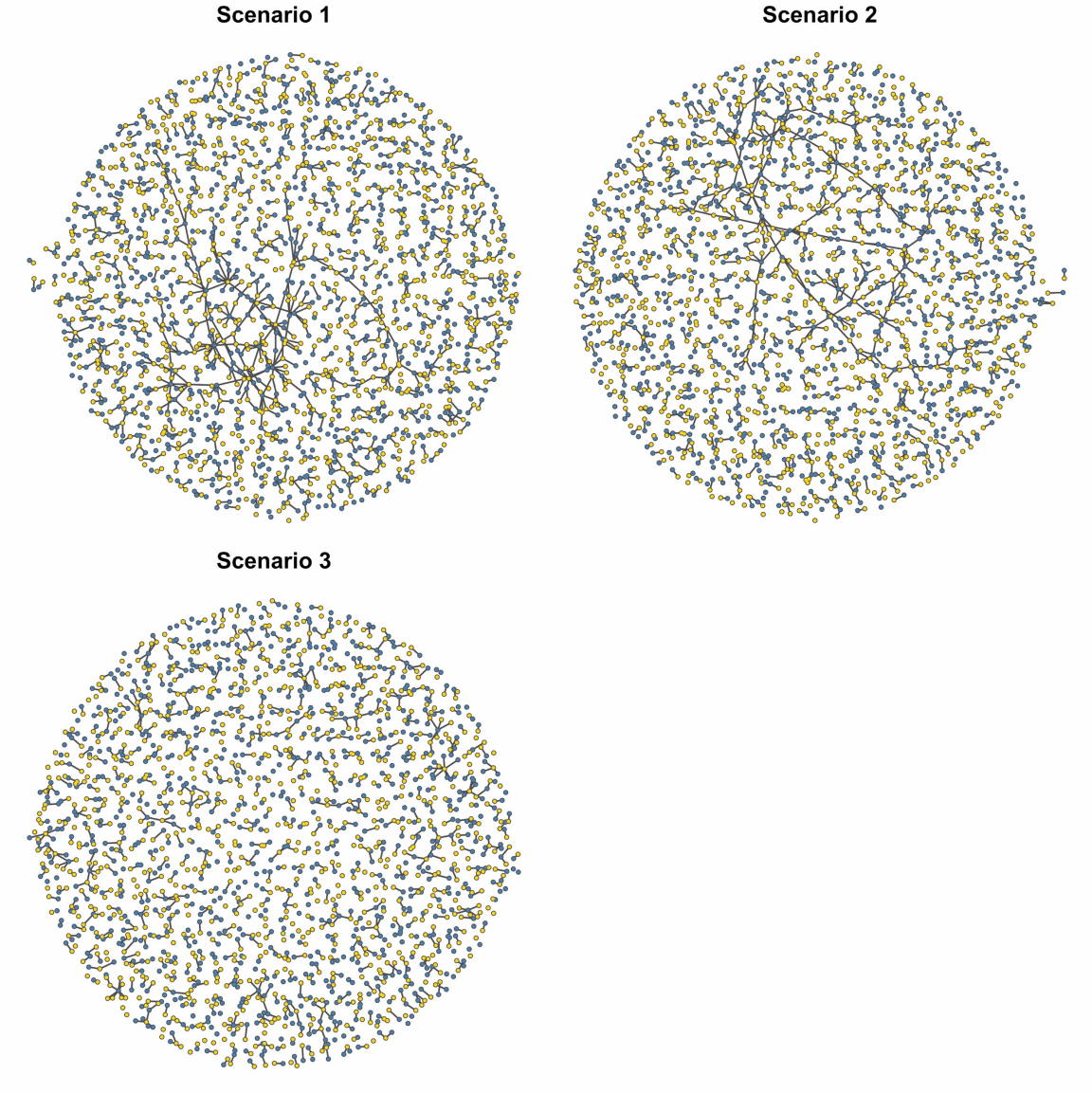

Figure 3.4. A sample of sexual contact network from the posterior parameter sets for each scenario.

Our findings showed that different amounts of sexual behavioral information resulted in very different average network dynamics and structures (Figure 3.4). Consistent with literature, different network dynamics resulted in different disease outcomes under no partner management.[9–11] With only annual degree distributions and chlamydia prevalence

(scenario 1), on average, individuals tended to have long-term concurrent partnerships, facilitating the spread of chlamydial infection. While information about relationship durations could reduce the number of individuals involved in concurrent partnerships and shorten the average relationship durations, the simulated concurrency was still higher than the concurrency estimated from the NSFG. By constraining the concurrency in the calibration process (scenario 3), on average, individuals tended to have more sequential relationships (due to a lower concurrency and a higher casual partnership turnover) than concurrent partnerships. More sequential partnerships yielded lower chlamydia prevalence and fewer chlamydia and PID incidence.

Different network dynamics also affected the relative effectiveness among partner management strategies, and informed different cost-effective strategy. Without the information about concurrency (scenarios 1 and 2), EPTPN2 was likely to be the cost-effective strategy over WTP thresholds and strongly dominated PN, which cost more but generated fewer QALYs. PN was dominated by EPTPN2 because infected individuals who had sexual connections with the partners of monogamous index patients could be reached/tested/treated via their other infected concurrent partners. Therefore, forgoing some opportunities to test partners' partners might not be harmful. Instead, treating partners of monogamous index patients earlier via EPT could reduce reinfection and avoid PID. With the information of concurrency in scenario 3, PN became undominated and performed better than EPTPN2. Compared to the other scenarios, individuals in scenario 3 had fewer partners at each cycle with shorter relationship durations, meaning that an infected individual was less likely to be reached via notification from multiple concurrent infected partners. Therefore, the opportunity of notifying infected partners' partners from any index

case became more valuable. In addition, while an individual had fewer current partners in scenario 3, an individual might have relatively more past partners due to a higher partner turnover. Therefore, foregoing testing partners might miss the opportunities to reach to partners infected current and past partners.

We found that both relationship durations and concurrency are worth collecting. Concurrency has a higher value than relationship durations. Without concurrency, a decision maker might choose EPTPN2 (a less optimal strategy) over PN, resulting in a greater opportunity loss. Our approach is different than the traditional VOI studies, which generally focus on reducing the uncertainty of parameter estimates via increasing the sample size in a study.[79,80] However, in our study, we reduced the uncertainty of concurrency and partnership turnover by adding additional data on sexual behaviors. In addition, the additional sexual behavioral information reduced the bias in network measures by shifting the means of concurrency and partnership turnover. Therefore, the value of knowing the estimates of these sexual behavioral data includes reducing the uncertainty and bias in network measures.

Our study has several limitations. As a simplification, we did not model the disease progression of PID and ignored other complications such as ectopic pregnancy and infertility.[94] We used PID as a proxy of the severe downstream consequence of untreated chlamydial infection. Adding more detailed PID progression to the disease dynamics is unlikely to change the ranking or the relative costs or effectiveness of the partner management strategies in each scenario. Moreover, we did not consider antibiotic resistance due to repeated treatments or overtreating sex partners via EPT because it is currently not a serious concern among chlamydia patients.[107,108] Furthermore, the strategies

discussed in our study were only a subset of partner management strategies. More variations of strategies could be considered. For example, partner management strategies could be provided dependent on the information of partners (e.g., EPT for partners with a low likelihood of seeking care, otherwise PN; EPT for monogamous partners, otherwise PN). However, these types of strategies require the patients to have the information of their partners, which is subject to patients' memory and trust in the relationships.

Our findings suggested that there is value in collecting sexual behavioral information such as relationship durations and concurrency that informs the dynamics of sexual contact networks. Future sexual behavioral survey that aims to inform policy making should collect data to measure network dynamics, especially relationship durations and concurrency. In addition, CEA studies evaluating STI control strategies should include parameters that determine network dynamics to inform better decision.

Chapter 4

Playing sex games: an evolutionary model of partner selection and sexual behavior among men who have sex with men

4.1 Introduction

Among populations at an increased risk of HIV infection, when making decisions regarding sexual encounters, balancing the risk of HIV infection against a desire for sexual activity shapes their sexual behavior, including partner selection, sexual acts (e.g., condom use), and HIV status disclosure. Serosorting, which is to reduce the risk of HIV transmission and acquisition, is a common practice observed in these populations. Serosorting is the sexual practice of unprotected sex with a partner who have the same HIV status (i.e., pure serosorting) and protected sex with a partner who have different or unknown HIV status (i.e., condom serosorting).[30,109] In many countries, both HIV-positive men (14%-44%) and HIV-negative men (25%-38%) might adopt serosorting when they engage in sexual activities.[30] Reducing risk of HIV infection by pure or condom serosorting depends on the quality of the information regarding the HIV status of individuals (informed by testing) and their partners (HIV status disclosure). Therefore, in healthcare settings that encourage frequent HIV testing to reduce HIV undiagnosed rate, serosorting could be an effective harm reducing strategy to avert HIV infections.[110,111]

Serosorting behaviors depend on perceived risk of HIV transmission or acquisition, shaped by HIV prevalence, sexual behavior, treatment, and preventive strategies at individual and population levels. For instance, a lower risk of HIV infection might lead to more unprotected sex with partners who have unknown HIV status. Studies have shown a substantial reduction in condom use among HIV-negative individuals who are on preexposure-prophylaxis (PrEP), which is a daily medication to reduce the risk of acquiring HIV among HIV-negative individuals.[112,113] HIV-positive individuals who are on antiretroviral treatment (ART), which can substantially reduce the risk of HIV transmission to others through viral suppression, may also be less likely to use a condom.[114] However, HIV-positive individuals might still practice protective sex due to concerns of infection with an HIV drug-resistant strain or infection with other sexually transmitted infections.[115,116]

Sexual behaviors (e.g., condom use and partner selection) affect the risk of HIV transmission/acquisition at individual and population levels and have important implications in control strategies for HIV and sexually transmitted infections (STIs). For example, in a population where the majority select sexual partners who have the same HIV status (i.e., seroconcordant partners), contact tracing could be more effective to identify undiagnosed HIV infections among HIV-negative individuals than among HIV-positive individuals. The difference in the effectiveness of contact tracing in different population is because HIV-negative individuals are more likely to encounter an undiagnosed HIV-infected partner than HIV-positive individuals. In addition, the reduction in condom use due to the increased adoption of PrEP among HIV-negative individuals might require redirecting resource to control a rising STI prevalence.[117,118] Most mathematical models

used for cost-effectiveness analyses of HIV/STI control strategies do not incorporate behavioral changes in response to the changes in the risk of HIV/STI transmission. Instead, these models take the behaviors as given (e.g., input parameters of the models) or describe partner selection and sexual behaviors as a linear or polynomial function of HIV prevalence.[110,111,119–121] However, collecting data that can characterize behaviors at various levels of HIV prevalence is difficult, even in the same city or region. In addition, it might require more details (e.g., status disclosure and undiagnosed HIV prevalence) in formularizing the functional form of the interaction between behaviors and levels of HIV prevalence.

Game theory provides a modeling framework to account for the interaction between the perceived HIV infection and sexual behaviors regarding partner selection and the type of sex adopted between partners.[12–14,122] Negotiation between individuals about whether to have sex and the type of sex is governed by an individual's preference (described by a utility function) for different outcomes constraint by the behaviors of the potential sex partners. Many prior studies have explored decision-making about sexual activities using classical game theory, which assumes rationality among individuals.[123,124] Under the rationality assumption, individuals know what the strategies of the potential sex partners adopt and individuals always optimize their utilities and minimize their loss given that their potential sex partners also do the same.[123,124] However, individuals might not fully evaluate the consequences of their actions given the actions of the others, but only follow social norm. Evolutionary game theory, a variation of game theory, relaxes the rationality assumption. In addition, evolutionary game theory can explain the evolution of behaviors (i.e., the process that certain behaviors, strategies, or actions emerge and spread in the

population) by following a specific behavior changing (or updating) rule when an individual is selected to act.[125–128]

While prior studies have employed game theory related methods to characterize partner selection and sexual behaviors, these studies were conducted as a hypothetical scenario with arbitrary utility values and were not validated with data.[12–14,122] These studies did not evaluate how HIV status disclosure might emerge in the population and affect the interactions between two potential sex partners.[12–14,122] In addition, these studies assumed that HIV-positive individuals have little incentive to use condom with any type of sex partners because HIV-positive individuals are already infected. However, HIV-positive individuals might consider condom use to prevent HIV transmission to HIV-negative individuals or prevent co-infection with HIV drug-resistant strains, which could lead to treatment failure of their current treatment.[115]

In this study, we determined the behaviors adopted by men who have sex with men (MSM), which is a population highly affected by HIV infection[129,130], in sexual encounters using an evolutionary game theoretical framework (a variation of game theory).[12,125,126,131] In the evolutionary game theoretical framework, behaviors are described as strategies that guide how an individual will behave in response to the behavior (strategy) of a potential sex partner and their partner's characteristics. In this study, a strategy is characterized by an individual's behavior regarding HIV status disclosure, partner selection, and protective sex (condom use) with each sexual encounter. We implemented a stage game that integrated the disclosure behavior and sexual behavior dependent on the disease status of the individuals and their sexual interactions. We considered two different HIV strains (a drug-resistant strain and a common strain) to capture condom use behavior among HIV-

positive individuals with concordant partners. We calibrated the utilities that best reflected the observed partner selection and sexual behaviors in a web-based survey, ARTnet, among MSM.[132] From these utility values, we then simulate partner selection and sexual behavior among MSM at various levels of HIV prevalence to understand how MSM sexual behaviors might change as a function of HIV prevalence.

4.2 Methods

4.2.1 Overview

We developed a sexual behavior simulation model of 2,000 MSM. We adopted the evolutionary game theory to simulate partner selection and protective sex (i.e., condom use) for non-primary relationships (casual and one-time partners) among these men. We parameterized the sexual behavior model based on published literature and a web-based survey, ARTnet, among 4,904 MSM in cities across the U.S.[132] The ARTnet study elicited the information from the respondents about their characteristics and the characteristics of their partnerships, allowing us to estimate the distribution of the type of sex partners and condom use behavior with different type of sex partners. We determined the set of utility values of different sexual outcomes (unprotected sex, protected sex, and no sex) that fit the observed data via random grid search. Using the best-fit utility values, we simulated partner selection and sexual behavior among MSM at various levels of HIV prevalence. The simulation model was created in Python 3.7.3.[36]

4.2.2 Model

4.2.3 Disease status

The simulation model consisted of 2,000 MSM who are HIV-positive, HIV-negative, or have unknown HIV status. As the base case prevalence, we randomly selected 11% of the population to be HIV-positive based on the estimated prevalence in Seattle, WA.[133] The estimated prevalence in Seattle included both the diagnosed and undiagnosed infections. HIV-positive individuals could be infected with either strain 1 (drug-resistant strain) or strain 2 (common HIV strain).[115] The assumption of two different HIV strains may lead to protective sexual behaviors among the HIV-positive individuals when two HIV-positive individuals interact. We assumed that the prevalence of strain 1 infection was 10% among the HIV-positive individuals. An individual has one of the three disease types, $\theta = \{\mathrm{HIV}-, \mathrm{HIV}^1+, \mathrm{HIV}^2+\}$. However, not all individuals know their true HIV status because they have not been tested recently (among individuals with unknown status) or because they do not know the HIV strain with which they are infected (among HIV-positive individuals). We assumed that 7% of individuals are not tested recently[58]; therefore, these individuals assume that they are HIV-negative while they could be HIV-positive. In addition, we assumed that all HIV-positive individuals do not know their strain, so this is not information that can be disclosed prior to a sexual encounter. An individual's perceived HIV status is $\theta' = \{\mathrm{HIV}-, \mathrm{HIV}+, \mathrm{HIV?}\}$, where HIV? denotes individuals with unknown status.

4.2.4 Partner selection

At each iteration, individuals play a partner selection game with each individual in their interaction networks, which reflects his pool of potential sex partners. We approximated the interaction networks using the annual degree distribution for HIV-positive and -negative men estimated from the ARTnet study (Figure C.1). We followed the configuration model to assign the potential sex partners to each individual.[38] When creating the interaction networks, we assumed assortativity by disease status to allow enough HIV-positive interactions that could potentially form sexual partnerships to reflect observed distribution of the type of sex partners from the ARTnet study. There are only two players in the game. A pair of individuals, *i* and *j*, start the game with either disclosing (D) or hiding (H) the HIV status, $s_i^d(\theta_i') \in \{D, H\}$, where s_i^d indicates the disclosing strategy and θ_i' denotes the HIV status that individual *i* perceives. After HIV status disclosure, each individual makes an offer of unprotected sex (US), protected sex (PS), or no sex (NS) to each other, depending on whether the other individual reveals the same HIV status ($s_i^{\psi}(\theta_i' = \theta_j' | s_j^d(\theta_j') = D)$), different HIV status ($s_i^{\psi}(\theta_i' \neq \theta_j' | s_j^d(\theta_j') = D)$), or hides HIV status ($s_i^{\psi}(\theta_i' | s_j^d(\theta_j') = H)$). The action space of $s_i^{\psi}\left(\theta_i' | s_j^d(\theta_j')\right)$ includes US, PS, and NS. If two individuals offer different type of sex, they agree on the less risky offer. For example, for two different sex offers, US versus PS, the two individuals agree on PS. The complete strategy profile for an individual *i* with a certain disease type θ_i is specified as:

$$s_i(\theta_i') = s_i^d(\theta_i') \cdot s_i^{\psi}\left(\theta_i' = \theta_j' \middle| s_j^d(\theta_j') = D\right) \cdot s_i^{\psi}\left(\theta_i' \neq \theta_j' \middle| s_j^d(\theta_j') = D\right) \cdot s_i^{\psi}\left(\theta_i' \middle| s_j^d(\theta_j') = H\right) \cdot s_i^{\psi}\left(\theta_i' | s_j^d(\theta_j')\right) \quad (4.1)$$

A possible strategy is D/US/NS/US, which reflects that an individual discloses his HIV status (D), offers US to a potential partner with the same HIV status, offers NS to a potential partner with a different HIV status, and offers US to a potential partner who hides his status. To reduce the computational burden, we precluded some actions from the strategy space. First, individuals who know their HIV status are disallowed to offer NS to potential partners who reveal the same status. Second, individuals who know they are HIV-negative are not allowed to offer US to potential partners who disclose an HIV-positive status. Third, individuals who do not know their HIV status cannot disclose their status (i.e., they must always hide their status). The complete strategy space is shown in

Table 4.1.

Table 4.1. The complete strategy profile used in the model.

Individual's perception of his own HIV status	Disclosure behavior	**Sex offer by the HIV status of the encounters**			# of strategies
		Same status	Different status	Unknown status	
HIV–	D/H	US/PS	PS/NS	US/PS/NS	24 strategies
HIV+	D/H	US/PS	US/PS/NS	US/PS/NS	36 strategies
HIV?	H	US/PS	US/PS/NS	US/PS/NS	18 strategies

The preference of the type of sex between a pair of individuals who have the same disease type, θ, follows $\mathrm{US} > \mathrm{PS} > \mathrm{NS}$.[13,14,58] We assumed the individuals in the population are risk averse and altruistic. When two individuals with different disease types interact, both of them are worried about transmitting or acquiring the infection and prefer PS over NS over US. While the preference of the type of sex follows the aforementioned

rankings, the utilities of the sex outcomes are different between HIV-positive and HIV-negative individuals. The payoff matrices for each combination of sex offers between two individuals are displayed in

Table 4.2.[12–14] The utilities in

Table 4.2 assume that the two individuals know the disease status of each other with certainty. However, individuals might not know their own true disease status or the status of the encounters because of undiagnosed HIV infection and lack of information of the strain of HIV infection. To account for the uncertainty, the expected utility to individual *i* interacting with individual *j* is calculated as follows:

$$E_i\left[u_i\left(s_i(\theta_i'), s_j(\theta_j')\right)\right] = \sum_{\theta_i' \in \Theta'} \sum_{\theta_j' \in \Theta'} P(\theta_i|\theta_i') P\left(\theta_j \middle| s_j^d(\theta_j')\right) u_i\left(s_i^{\psi}(\theta_i), s_j^{\psi}(\theta_j)\right) \quad (4.2)$$

where $P(\theta_i|\theta_i')$ is individual *i*'s belief of his true disease type given his perceived HIV status, $P\left(\theta_j \middle| s_j^d(\theta_j')\right)$ is individual *i*'s belief of encounter *j*'s disease type given the disclosing behavior of the encounter, and $u_i\left(s_i^{\psi}(\theta_i), s_j^{\psi}(\theta_j)\right)$ represents the utility of individual *i* depending on the sex offers from himself and the potential sex partner *j* given their true disease types. Individuals estimate $P(\theta_i|\theta_i')$ depending on whether they know their true HIV status through HIV testing. Individuals who are tested know that they are either infected or uninfected with HIV. We did not consider misdiagnosis in the model. HIV-positive individuals estimate a 10% probability of infection with strain 1 for themselves. For individuals who do not know their HIV status, they believe they are HIV-negative. Regarding the estimation of the disease type of the encounter, $P\left(\theta_j \middle| s_j^d(\theta_j')\right)$ depends on the disclosure behavior of the potential sex partner *j*. If a potential sex partner

discloses HIV-negative status, individual *i* estimates that the probability of the potential sex partner being infected with HIV follows $1-\frac{p^{ud}}{p^{ud}+p_i^{HIV-}}$, where p^{ud} denotes the prevalence of undiagnosed HIV infection in the population; p_i^{HIV-} represents the local prevalence of HIV-negative in the interaction network of individual *i*. We assumed that individuals are able to make accurate assessment of the local HIV prevalence in their own interaction networks. If an encounter discloses HIV-positive status, individual *i* believes the information completely but estimates the infection with strain 1 with a probability of 10%. If an encounter hides his status, individual *i* estimates the disease type of the encounter based on the local prevalence of HIV infection adjusted by the probability of infection with either strain. We calibrated utilities, $u_i\left(s_i^{\psi}(\theta_i), s_j^{\psi}\left(\theta_j\right)\right)$, in Table 4.2. The expected utility is calculated based on the perceived HIV status of individuals. For example, the expected utility of individuals who are not tested is calculated following the utility of HIV-negative individuals.

Table 4.2. Utility matrices of different combination of sex offers between individual 1 and individual 2.

Sex offer from individual 1	Sex offer from individual 2		
	US	PS	NS
Both individuals have the same disease type			
US	*a*	*b*	--
PS	*b*	*b*	--
Individuals have different disease types			
US	(*d*, *d*′)	(*e*, *e*′)	(*f*, *f*′)
PS	(*e*, *e*′)	(*e*, *e*′)	(*f*, *f*′)
NS	(*f*, *f*′)	(*f*, *f*′)	(*f*, *f*′)

a ≥ b.

e ≥ f ≥ d or e' ≥ f' ≥ d'.

4.2.5 Updating strategies

Every individual interacts with all potential sex partners in the interaction network using one fixed strategy.[125,126,131,134] An individual could be selected to update his strategy by switching to a better strategy in the population (replacement) or to a new strategy in the strategy space (mutation).[125,126,131] Strategy replacement depends on fitness, the measure of the success of a strategy adopted by individual *i*. The fitness of the strategy *s* adopted by individual i is the average utility across all of his interactions, $\phi_i\left(s_i(\theta_i')\right) = \frac{\sum_j E_i\left[u_i\left(s_i(\theta_i'), s_j\left(\theta_j'\right)\right)\right]}{k_i}$, where k_i denotes the number of interactions that individual i has. Under the process of replacement, individuals can update their strategies based on the fitness of the strategies adopted among the individuals who have the same test status. Therefore, individuals who have unknown disease status can only switch their strategies to the strategies adopted among the individuals with unknown status. At each iteration, we randomly selected 1% of the population for strategy replacement. These selected individuals switch their strategies according to the distribution of the fitness of strategies adopted among the individuals with the same tested disease status, $\frac{\exp\left(c \cdot \phi(s_j(\theta'))\right)}{\sum_k \exp\left(c \cdot \phi(s_k(\theta'))\right)}$, where c is a constant scaling term and $\phi\left(s_j(\theta')\right)$ is the fitness of strategy s_j among the individuals who have a certain perceived disease type.[131] In addition, we randomly selected a fraction of individuals for strategy mutation with a probability of 5×10^{-6} at each iteration.[131,135] The mutation rate was very small such that the mutations did not have a huge influence on

the replacement process. When a mutation occurred, the selected individual might randomly adopt a new strategy from the strategy space with an equal probability.

4.2.6 Analysis of steady-state strategies

We used differential equations to investigate the strategies that can prevail in the population.[12,125,126,131,136] In a well-mixed population, the expected fitness of a strategy s_j adopted by individuals who have a certain perceived disease type follows:

$$\phi\left(s_j(\theta')\right) = \sum_k \sum_l E\left[u\left(s_j(\theta'), s_k(\theta_l')\right)\right] \cdot \rho\left(s_k(\theta_l')\right) \tag{4.3}$$

where $\rho\left(s_k(\theta_k')\right)$ is the fraction of population who adopts strategy s_k given their perceived disease types. The average fitness across all strategies among individuals who have a certain perceived disease type is $\bar{\phi}(\theta') = \sum_j \phi\left(s_j(\theta')\right)$. Therefore, the change in the population who have a certain perceived disease type and adopt strategy s_j follows this replicator dynamics:

$$\dot{\rho}\left(s_j(\theta')\right) = \rho\left(s_j(\theta')\right)\left(\phi\left(s_j(\theta')\right) - \bar{\phi}(\theta')\right) \tag{4.4}$$

The small mutation rate is ignored in the equation. This equation suggests that, among individuals who have a certain perceived disease type, if a strategy is adopted by some individuals, $\rho\left(s_j(\theta')\right) > 0$, and has a fitness greater than the average fitness, the strategy will spread through the population.[125,131,136] Strategies that cannot be replaced by other strategies are the evolutionary stable strategies (ESS).[125,131,137] The ESS in this model depends on the HIV prevalence in the population and the perceived disease type among individuals.

Among HIV-negative individuals, when they interact with concordant potential sex partners, they would prefer US to PS as long as the utility of US is greater than the utility of PS ($a > b$). The higher utility of US than PS with concordant sexual partners provides HIV-negative individuals with the incentive to disclose their status with each other. In particular, when the HIV prevalence is low, HIV-negative individuals are more likely to interact with individuals who have the same disease status. As the utility ratio between US and PS decreases (i.e., utility of US approaches to the utility of PS), the incentive for HIV-negative individuals to disclose diminishes. When HIV-negative individuals interact with HIV-positive individuals who disclose his disease status, HIV-negative individuals would favor PS over NS as long as the utility of PS is greater than the utility of NS ($e > f$). If the potential sex partner has an unknown disease status, the sex offer from HIV-negative individuals would depend on the probability that the potential sex partner is HIV-positive (disease prevalence) and the probability of undiagnosed HIV prevalence. In general, HIV-negative individuals are less likely to offer PS to potential sex partners who have unknown status at a low HIV prevalence than at a high HIV prevalence.

Among HIV-positive individuals, their strategies could be a combination of the best responses to the prevalent strategies adopted among HIV-negative and HIV-positive individuals. At a low HIV prevalence, HIV-positive individuals are less likely to interact with potential sex partners who disclose the same disease status, resulting in little incentive to disclose their disease status to use US with concordant sex partners. At a high HIV prevalence, because HIV-positive individuals are more likely to interact with individuals with the same disease status, they have incentive to disclose status to get a higher utility by offering US to concordant sex partners. Therefore, for the sex offer to potential sex partners

who disclose HIV-positive status, HIV-positive individuals could be indifferent between US and PS at a low HIV prevalence but strongly prefer US at a high HIV prevalence. In addition, due to the concern of co-infection with multiple HIV strains, HIV-positive individuals would maintain a certain level of condom use with concordant sex partners. When HIV-positive individuals interact with HIV-negative individuals who disclose status, HIV-positive individuals could offer either US or PS because HIV-positive individuals can flexibly agree with PS offered by an HIV-negative individual. When HIV-positive individuals interact with potential sex partners who have an unknown status, they prefer PS to US with this type of potential sex partners at a low HIV prevalence but prefer US to PS at a high HIV prevalence.

4.2.7 Simulation and outcomes

Given the combinations of strategies and disease status of a pair of interactions, finding the ESS, or steady-state strategies, is difficult in our study. We used agent-based simulation to find the ESS under the game structure. We assigned disease status to each individual in the population and initialized the behavioral simulation by randomly assigning a strategy to each individual based on his HIV status. We performed 1,000 simulations with 60,000 iterations for each simulation. Strategy replacement and mutation occurred in the course of the simulation by random chance. The model outcomes include: (1) the average distribution of sex partners by partners' HIV status (% of HIV+, HIV–, and HIV? partners) for HIV-positive and HIV-negative individuals, respectively; (2) the average condom use behavior by the partners' HIV status for HIV-positive and HIV-negative individuals, respectively; (3) the average disclosing behaviors (% disclosure) for HIV-positive and HIV-negative

individuals, respectively. The model outcomes are the average of the last 10,000 iterations. We calculated outcomes conditioned on the true HIV status of the individuals.

4.2.8 Calibration

4.2.8.1 Estimating calibration targets

We obtained information about partner selection and sexual behaviors among MSM from the ARTnet study.[132] In our study, we estimated parameters and targets related to partner selection and sexual behaviors from the following measures in the ARTnet study, including the respondents' residence (ZIP codes), PrEP use, HIV status of both the respondents and partners (HIV-positive, HIV-negative, unknown status), non-primary partnerships, and the frequency of protective sex (i.e., condom use) and sex acts in a period of time.

The HIV status was determined by whether a respondent replied a confirmed positive testing in the past. A respondent was HIV-positive if he had a confirmed positive test in the past, and was HIV-negative if he did not have any confirmed positive test. Because the respondents in the ARTnet study were from cities all over the U.S. with varying HIV prevalence, we only focused on the cities with the diagnosed HIV prevalence < 0.1 according to Rosenberg et al. (2016).[138] We matched metropolitan statistical areas to the ZIP code provided by each respondent via the Federal Information Processing Standard codes by county (county FIPS codes) that connects to both the core-based statistical area (CBSA) and ZIP code systems. After identifying the corresponding CBSA for each ZIP code, we were able to match the information of the undiagnosed HIV prevalence to each ZIP code. After the matching process (matching the diagnosed HIV prevalence to each ZIP code), the representative cities with the diagnosed HIV prevalence < 0.1 included Seattle,

Minneapolis, Detroit, and Boston, and had a total of 1,430 respondents (129 HIV-positive respondents).

The ARTnet study collected information of up to five partnerships in the past year from the respondents. We only focused on partner selection and protective sex among the non-primary (casual or one-time) partnerships in MSM. Regarding partner selection, the ARTnet study asked the respondents about the HIV status of each sex partner. We categorized the answers to HIV-positive, HIV-negative, or unknown status (partner has never been tested, has not been tested recently/uncertain, or I do not know). We estimated the distribution of the type of sex partners (HIV-positive, HIV-negative, or unknown) by the HIV status of the respondents. With respect to protected sex, we excluded the respondents who used PrEP as an HIV prevention method from estimation, and estimated the probability of protected sex by calculating the proportion of sex acts with condom use for each type of partnership. Both the distribution of the type of sex partners and the probability of protected sex by the type of sex partners were the calibration targets.

4.2.8.2 Calibration process

We calibrated the utilities in

Table 4.2 based on the HIV prevalence, 11%, reported from Seattle, WA to fit the calibration targets using the random grid search method. The targets included the distribution of sex partners by the HIV status of the partners, and the proportion of protected sex by the HIV status of the partners (Table 4.4). We randomly sampled 500 sets of utility values from the utility space following the relationship shown in
Table 4.2. In addition, we assumed that all utilities were all between 0 and 1, and unprotected sex among HIV-positive concordant partners had the highest utility value 1.

We then calculated the log likelihood for each set of utilities. We selected the set of utilities with the largest log likelihood for further analysis. Using the utilities calibrated, we simulated sexual behaviors at different HIV prevalence: 5%, 10%, 15%, 18%, 20%, 25%, 30%, and 40%.

4.3 Results

4.3.1 Calibration results

The set of utility values that best reflected the observed data is shown in Table 4.3. Overall, the range of the utility values was smaller among HIV-negative individuals (0.71-0.75) than among HIV-positive individuals (0.61-1). Most interestingly, HIV-negative individuals were indifferent between US and PS with concordant sexual partners, whereas HIV-positive individuals strongly favored US (1) over PS (0.76) with concordant sexual partners.

Table 4.3. Utility values by different types of partnerships.

	HIV status of individual	
	HIV-	HIV+
Concordant sexual partners		
US	0.75	1
PS	0.75	0.76
NS	0.72	0.7
Discordant sexual partners		
US	0.71	0.61
PS	0.75	0.76
NS	0.72	0.7

Table 4.4 presents the simulation outcomes generated from the set of utilities at 11% HIV prevalence. On average, the local prevalence was 9.9% in the interaction networks of HIV-negative individuals and 32.6% for HIV-positive individuals, respectively. Due to a low rejection rate (0.8% of interactions resulted in rejections), the HIV prevalence among the sex partners was similar to the local prevalence among the potential sex partners in the interaction networks. HIV-negative individuals were more likely to disclose their status (67.1%) than HIV-positive individuals (60.3%). For status disclosure among sex partners, the distribution of the type of sex partners generally followed the pattern in the ARTnet study. For HIV-negative individuals, 5.8% of sex partners were HIV-positive, 33.4% were partners with unknown status, and the majority of the partners was HIV-negative. For HIV-positive individuals, the majority of the sex partners was HIV-negative (45.1%). While the data showed that the proportions of HIV-positive partners and partners with unknown status were similar for HIV-positive individuals, the simulation outcomes showed a lower proportion of HIV-positive partners (20.2%) than partners with unknown status (34.8%). Regarding protected sex, the simulation resulted in much higher condom use among MSM than the data. For discordant partnerships, the simulation results showed more than 95% of condom use while the data showed much lower condom use, 51% reported from HIV-negative individuals and 37% reported from HIV-positive individuals. On average, both HIV-negative and -positive individuals were more likely to use condom with partners who hide status than concordant partners, following the pattern in the data.

Table 4.4. Distribution of sex partners and condom use. The targets were estimated from the ARTnet study. The simulation outcomes were the average behavioral outcomes across 1,000 simulations.

	HIV status of individuals			
	HIV-negative		HIV-positive	
Proportion	Targets (S.E.)	Simulation outcomes (S.D.)	Targets (S.E.)	Simulation outcomes (S.D.)
Local HIV prevalence among sexual encounters				
		9.9%		32.6%
		(1.44%)		(2.88%)
True HIV status of partners				
HIV-positive		9.6%		33.2%
		(1.5%)		(3.43%)
HIV-negative		90.4%		66.8%
		(1.5%)		(3.43%)
Disclosure of status				
		67.1%		60.3%
		(30.87%)		(40%)
HIV status based on partner disclosure				
HIV-positive	3.1%	5.8%	27.9%	20.2%
	(1.07%)	(4.11%)	(3.0%)	(13.71%)
HIV-negative	67.6%	60.8%	46.0%	45.1%
	(0.725%)	(27.99%)	(2.64%)	(21.34%)
Unknown	29.3%	33.4%	26.1%	34.8%
	(1.03%)	(28.62%)	(2.63%)	(26.57%)
Protected sex by partners' HIV status				
HIV-positive	51%	95.6%	8%	33.8%
	(9.03%)	(12.2%)	(3.55%)	(35.16%)
HIV-negative	58%	71.1%	37%	96.7%
	(1.71%)	(30.99%)	(5.20%)	(7.64%)
Unknown	66%	86.9%	42%	82%
	(2.76%)	(16.85%)	(7.35%)	(26.48%)

4.3.2 Prevalent strategies

We calculated the prevalence of each strategy by averaging the proportion of the population adopting the strategy across all 1,000 simulations. Among HIV-negative individuals, the two most prevalent strategies were D/PS/PS/PS (20.97%) and D/US/PS/PS (17.5%). The difference between these two strategies was the type of sex offered when an HIV-negative individual interacted with a concordant sexual encounter who disclosed status (PS versus US). However, these two strategies were likely to result in the same utility because HIV-negative individuals were indifferent between US and PS when they interacted with concordant sexual encounters. Therefore, one strategy could be slowly replaced by the other as the other strategy appeared in the population (Figure 4.1), resulting in a negative correlation between the two strategies, -0.27 (Figure 4.2).

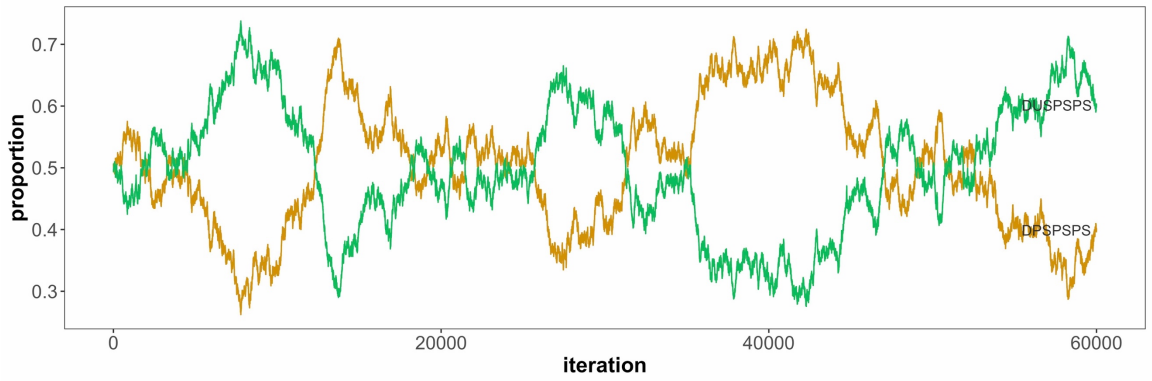

Figure 4.1. Evolution of the top two strategies, D/US/PS/PS versus D/PS/PS/PS, among HIV-negative individuals over 60,000 iterations. The y-axis represents the proportion of population adopting each strategy.

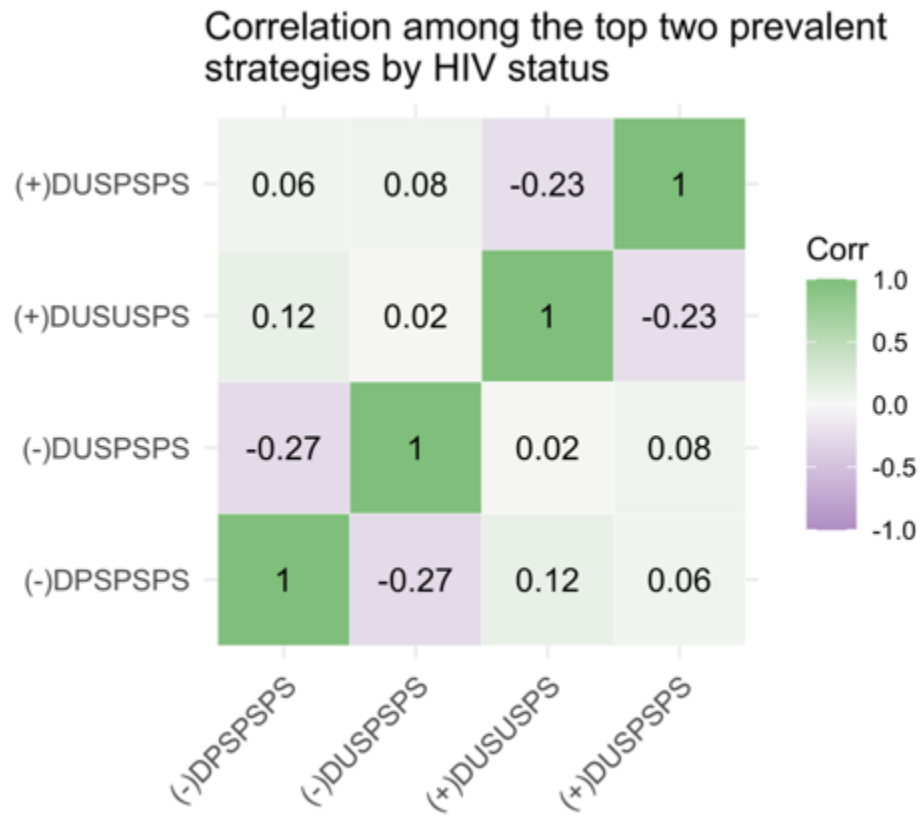

Figure 4.2. Correlation coefficients among strategies with a prevalence greater than 10%. These strategies are HIV-status specific. For example, the strategy "(-)DPSPSPS" represents the strategy D/PS/PS/PS adopted among HIV-negative individuals. Similarly, the strategy "(+)DUSUSPS" represents the strategy D/US/US/PS adopted among HIV-positive individuals.

Among HIV-positive individuals, the top two most prevalent strategies were D/US/US/PS (17.07%) and D/US/PS/PS (15.44%). Although these two strategies differed in the type of sex offered to a discordant partner (US versus PS) who disclose, the two strategies could result in a similar utility. The similar utility between US and PS with discordant partners among HIV-positive individuals was because HIV-negative individuals commonly offered PS to HIV-positive individuals who disclose. Because individuals were

flexible in accepting a less risky option (PS in this case) if offered by a potential sex partner, US with discordant partners in the strategy D/US/US/PS did not result in a worse utility than the strategy D/US/PS/PS among HIV-positive individuals.

4.3.3 Levels of HIV prevalence

Using the utilities calibrated to the sexual behavior outcomes in ARTnet, we conducted simulations extrapolating the behavioral outcomes of these utility values to different levels of HIV prevalence, ranging from 5% to 40%. We presented the simulation trends in Figure 4.3. For the composition of sex partners, the proportion of partners with unknown status was stable across HIV prevalence for both HIV-positive and -negative individuals. For HIV-negative individuals, the proportion of HIV-negative partners gradually decreased but the trend of HIV-positive partners gradually increased as HIV-prevalence increased. For HIV-positive individuals, the changes in the proportions of HIV-positive and HIV-negative sex partners were non-linear in terms of the levels of prevalence, following an S shape for the proportion of HIV-positive sex partners and an inverse S shape for the proportion of HIV-negative sex partners. Protected sex with discordant sex partners remained at a high level across HIV prevalence. HIV-negative individuals gradually increased condom use with concordant partners and partners with unknown status. In contrast, HIV-positive individuals reduced condom use with partners with the same status and unknown status. Regarding disclosure behavior, the average proportion of HIV-negative individuals who disclosed slightly decreased as prevalence increased. Because the utility ratio between US and PS with concordant partners was 1 among HIV-negative individuals, HIV-negative individuals had less incentive to disclose, especially at higher levels of HIV prevalence. In

comparison, the proportion of HIV-positive individuals who disclosed substantially increased from 58%, lower than the proportion in HIV-negative individuals, to 75%, higher than the proportion in HIV-negative individuals.

4.4 Discussion

Mathematical models for STI often simplify the decision-making process between two individuals who are potentially engaged in sexual partnerships. However, this decision-making process – whether to disclose disease status, to have sex with an encounter, or to offer protected or unprotected sex – could provide insights in developing STI control strategies. In this study, we employed an evolutionary game theoretic framework to explore the interactions between the decisions related to sexual activities, disease prevalence, and strategies offered by two potential sex partners by parameterizing the model using the ARTnet study.[132]

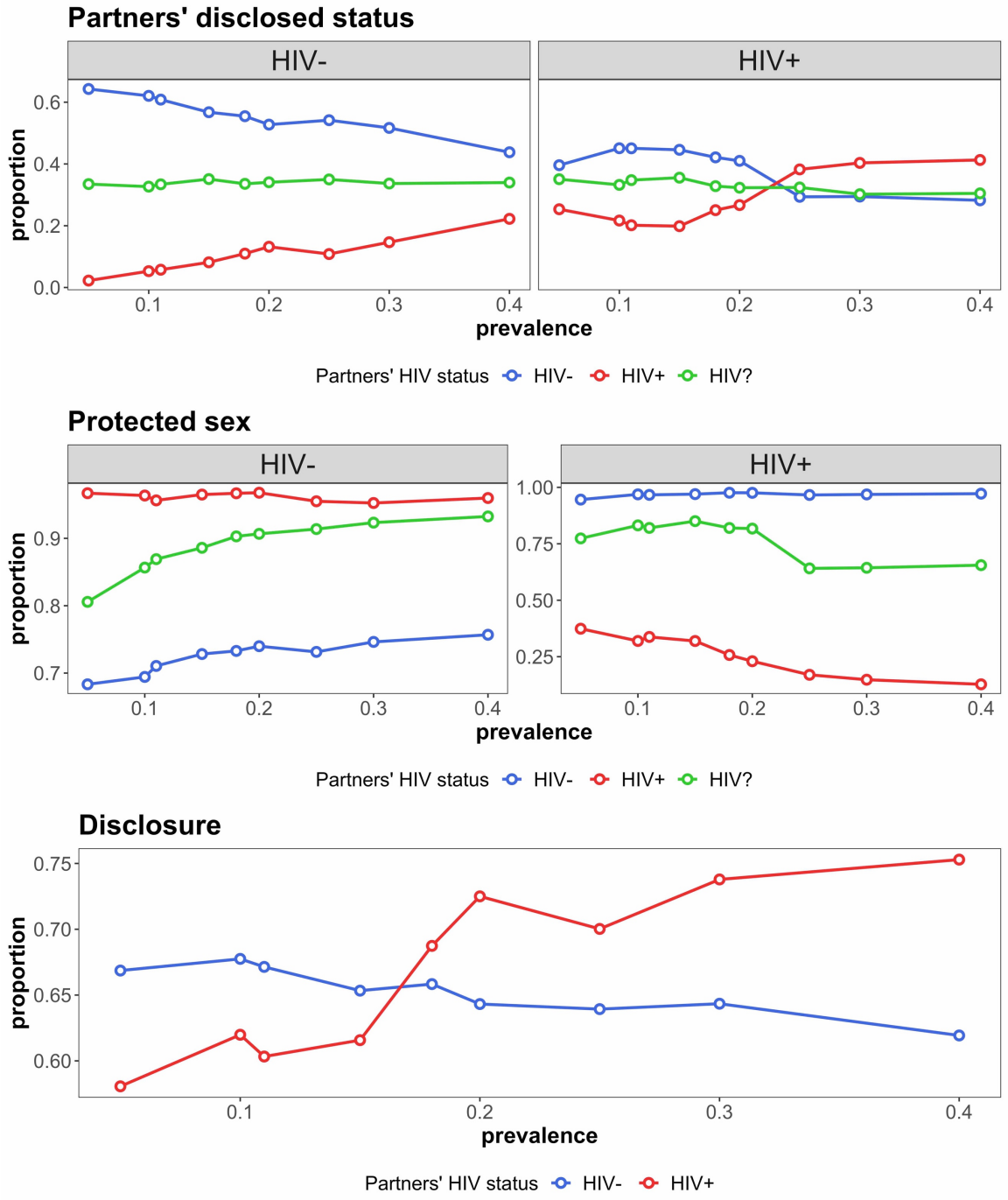

Figure 4.3. The average simulated trends of partner selection, protected sex, and disclosure behavior across different HIV prevalence in the population.

Unlike prior studies that employ game theoretical frameworks to model sexual behaviors, we calibrated the utilities of the sex outcomes to match observed sexual behaviors in MSM. We also allowed the utilities to be different between HIV-positive and -negative individuals.[12–14] Studies employing the game theoretic framework for sexual behaviors usually assumed the same utilities of sex outcomes with concordant partners and different utilities of unprotected sex with discordant partners between HIV-positive and -negative individuals.[12–14] However, our calibration results showed that HIV-negative individuals might value the sex outcomes differently than HIV-positive individuals. In order to match observed sexual behavior, HIV-negative individuals were estimated to value unprotected sex with concordant partners at a lower level than HIV-positive individuals do, and might be indifferent between unprotected sex and protected sex with concordant partners. The reason behind the different utilities might be that HIV-negative individuals are more risk averse than HIV-positive individuals. HIV-negative individuals might still be concerned of acquiring other STIs when they interact with concordant partners, reflecting on the high condom use with concordant partners in the ARTnet study. Among HIV-positive individuals, they reported a higher condom use with HIV-negative partners and partners with unknown status than for HIV-positive partners in the ARTnet study, reflecting on a lower utility of unprotected sex than no sex with discordant partners. This behavior observed in data implied that the assumption that HIV-positive individuals always favored unprotected sex with any type of partners might not be realistic. HIV-positive individuals might be concerned with infecting uninfected individuals or acquiring difference STI or drug-resistant HIV strain.

The simulated outcomes suggested more condom serosorting than pure serosorting in the population. Individuals could not adopt pure serosorting effectively because of imperfect testing and imperfect HIV status disclosure among the partners. In our model, 7% of the population did not know their true HIV status. Therefore, these people were unable to do pure serosorting. Second, the calibration results showed a higher utility of protected sex than no sex. Therefore, protected sex was favored over no sex when individuals interact with a discordant encounter or an encounter with unknown status. Furthermore, if the common strategy was to reject sex with any encounter who disclosed a different HIV status, individuals had incentive to hide their status, which potentially provided them a different type of sex offer. For the offer to partners with unknown status, both protected and unprotected sex were more preferable than no sex at a low HIV prevalence because individuals, especially HIV-negative individuals, could take the risk with an increase in utility. Therefore, rejections did not happen frequently in our model across HIV prevalence.

This model allowed us to predict how behavior might change for different levels of HIV prevalence. We found that the composition of partners and behaviors changed with HIV prevalence. We found that HIV-negative individuals were more likely to have HIV-positive partners as the prevalence increased. Partners with discordant status maintained a high level of condom use. Although the proportion of partners with unknown status remained stable, HIV-negative individuals increased condom use with this type of partners due to the expectation of an increased risk of interacting with individuals with unknown status. Even though HIV-negative individuals might not practice pure serosorting at a high HIV prevalence, HIV-negative individuals were more likely to adopt risk-reduction

methods to prevent infection. Condom use also increased among interactions between concordant HIV-positive partners due to the increased undiagnosed prevalence. However, HIV-positive individuals were less likely to use condom with partners who had unknown status and concordant HIV-positive partners. As the prevalence increased, status disclosure increased among HIV-positive individuals and surpassed the proportion of HIV-negative individuals.

These behavioral changes have an important implication in interventions in STIs and HIV. Compared to HIV-positive individuals, HIV-negative individuals might be less likely to disclose their status at a high prevalence in general. In addition to maintaining and increasing status disclosure among HIV-positive individuals, intervention programs could also focus on increasing status disclosure among HIV-negative individuals and allow disclosure to be easier.[139] Moreover, condom use promotion could be important among HIV-positive individuals, especially at a high HIV prevalence. While HIV-positive individuals are more likely to have concordant partners at a high HIV prevalence, they might decrease condom use, resulting in increased risk of STI infections or coinfection with other HIV strains. Coinfection with STI or with other HIV strains might undermine the effect of treatment, requiring a change to other treatment that might be more expensive. The increase in condom use among HIV-negative individuals is a positive behavioral change that could prevent both STI and HIV infection.

Our study is subject to some limitations that open avenue for future work. First, we used the observed degree distribution of actual sex partners in the ARTnet study to approximate the interaction network of potential sex partners. Individuals are likely to interact with potential sex partners before they meet another individual who agrees to have

sex. Therefore, the observed number of sex partners is the product of the decision-making process among all the potential interactions that one reaches. However, it is difficult to collect information about the number of rejections before a partnership is formed. With more. Precise data available using electronic surveys and samplings, this limitation can be addressed in a future study. Second, in this model, we assumed that the decision behind making a sexual contact depends only on the HIV status of the individuals, their potential sex partners, and a desire to have sex. However, in reality, the decision also depends on other characteristics of the encounters, including the PrEP or ART use, attractiveness, socio-economic status, and personality, etc. As a simplification, our model did not consider these factors. Future work can include a more detailed model to capture these factors. Third, we calibrated utilities of different sex outcomes using survey data, which might be subject to reporting errors. For example, HIV-negative individuals reported higher condom use with discordant partners than HIV-positive individuals. However, the report of condom use behavior with discordant partners should be similar between the two groups. In addition, HIV-negative individuals reported lower condom use with discordant partners than with concordant partners. This counterintuitive pattern might suggest that HIV-negative individuals who decide to have sex with HIV-positive individuals have a different set of utilities, which was not captured in the utility ranking or in the model. Finally, our model did not fit the condom use behavior that well. In general, condom use across all types of partners was overestimated for both HIV-positive and -negative individuals. Condom use was very high for sexual contacts with discordant partners at all levels of HIV prevalence. Among HIV-negative individuals, unprotected sex was not considered for sex with discordant partners in the strategy space. Among HIV-positive individuals, they had little

incentive to offer unprotected sex because they were assumed to be altruistic. For condom use with concordant partners, the reason why the utility calibrated resulted in more protected sex than the observed data might be that we limited random search among the utility values with two decimal places. If we allowed random search among utilities in a finer scale, we might be able to find a set of utilities that fit the observed data better. The combination of protected sex with concordant and discordant partners yielded a higher protected sex with partners who have unknown status.

Our study demonstrated a framework of modeling partner selection and sexual behavior in the context of STI and HIV infection. This model could be useful for providing insights on sexual behavior and disclosure behavior and guide policies that aim to change behaviors in this context. Future study is warranted to estimate the utilities and parameters required to inform sexual contact networks.

Chapter 5
Conclusion

This dissertation investigated the influence of macrostructure and the microstructure of sexual contact networks on the effectiveness and cost-effectiveness of STI control strategies. In addition, this dissertation explored the interaction between disclosure behaviors, partner selection, sexual behaviors, and the risk of HIV infection using an game theoretical framework.

In Chapter 2, we investigated how the cost-effective partner management strategy varied with four stylized sexual contact networks: random, community-structured, scale-free, and empirical networks. We found that the optimal STI control strategy varied with the structure of sexual contact networks, the partner compliance rate, the external force of infection, and the resource constraint. In general, contact tracing was too resource-intensive to implement in scale-free networks because contact tracing was unable to follow up enough sex contacts to treat a large number of STI infections and reinfections due to the hubs. Therefore, in scale-free networks, only PN and EPT were competing for the optimal strategy depending on the combination of patient and partner compliance rate. In random and community-structured, the optimal strategy was either PN or EPT in a resource limited setting. Contact tracing was only optimal when the partner compliance rate was very high under a low external force of infection. As the resource available increased in the society,

contact tracing became more likely to be optimal in random and community-structured networks. For empirical networks, the pattern of optimal strategies was different between a low external force of infection and a high external force of infection. In empirical networks, the pattern of optimal strategies followed the pattern in community-structured networks under a low external force of infection, whereas followed the pattern in scale-free networks under a high external force of infection.

In Chapter 3, we evaluated the importance of different information of sexual behaviors that help characterize relationship dynamics, including relationship durations and concurrency, following the decision theoretical framework. Our study suggested that lack of data on sexual behaviors could affect the relationship dynamics in the population, ranging from high concurrency and low partnership turnover to low concurrency and high partnership turnover. The variation of the microstructure in the contact network might lead to less efficient STI control strategy. Therefore, collecting data on relationship durations and concurrency is important in cost-effectiveness analysis studies to better inform STI control strategies. Furthermore, we quantified the value of empirical information of relationship durations and concurrency. We found that missing information of concurrency impacted more on the accuracy of policy recommendation than missing information of relationship durations because adding concurrency in the modeling process may change the cost-effective strategy.

In Chapter 4, we modeled the decision-making process – disclose HIV status and negotiating whether to have protected or unprotected sex – between sexual encounters in response to the risk of HIV infection in MSM using the evolutionary game theory. We calibrated the utilities for different sexual outcomes: unprotected sex, protected sex, and

no sex to the observed behaviors. We found that HIV-negative individuals have different utilities than HIV-positive individuals, different than the utilities commonly used in other game theory studies. The model suggested more condom serosorting than pure serosorting in the populations at increased risk of HIV infection. Individuals would adopt risk reduction methods when they had sex with potential sex partners who had different or unknown status. At different levels of HIV prevalence, our simulation model projected that HIV-positive individuals were less likely to use condom with partners with the same or unknown status at a high prevalence than at a low prevalence. However, protected sex increased among HIV-negative individuals as the prevalence increased. Moreover, HIV-positive individuals were more likely to disclose status at a high prevalence than at a low prevalence.

5.1 Implications and future directions

The implication of this dissertation work is three-fold. First, collecting information regarding the macrostructure of the contact pattern in the population is important to compare disease control strategies in infectious diseases, especially for strategies that are highly dependent on connections. While we focused on stylized network structures in this dissertation, the findings suggested the importance to collect information regarding the highly connected individuals and the characteristics that form assortativity in contact networks. Inclusion of these structures could make a difference in the recommendation of the disease control strategies. In addition to these macrostructures, future studies could evaluate how important other macrostructures such as the clustering coefficients or small world properties might influence the recommendation of the optimal strategy that control

infectious diseases. Second, collecting information that can accurately characterize relationship dynamics might recommend more efficient infectious disease control strategies and reduce the opportunity loss of misallocating resources. In this dissertation, we focused on two measures, concurrency and relationship durations, that can improve the accuracy of simulating the relationship dynamics in a population. However, future studies can evaluate and quantify the values of other measures that determine the relationship dynamics, including the gap length between relationships and the number of life-time partners. In addition, studies can investigate what the least amount of information is required to determine the relationship dynamics in a population. Third, inclusion of disclosure behavior and risk reduction behaviors in infectious disease modeling could influence the relative effectiveness of disease control strategies. These behaviors could also vary with disease prevalence. These findings have important policy implications about how disease control strategy could be designed in response to the changes in behaviors. Future studies can integrate a more realistic model for behaviors under infectious diseases in cost-effectiveness analysis.

Bibliography

1. Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2018*.; 2019. Accessed April 25, 2020. https://www.cdc.gov/std/stats18/default.htm
2. Newman MEJ. Spread of epidemic disease on networks. *Physical Review E*. 2002;66(1). doi:10.1103/PhysRevE.66.016128
3. Newman MEJ. Random graphs as models of networks. *arXiv:cond-mat/0202208*. Published online February 12, 2002. Accessed February 3, 2019. http://arxiv.org/abs/cond-mat/0202208
4. Pastor-Satorras R, Vespignani A. Epidemic Spreading in Scale-Free Networks. *Physical Review Letters*. 2001;86(14):3200-3203. doi:10.1103/PhysRevLett.86.3200
5. Salathé M, Jones JH. Dynamics and Control of Diseases in Networks with Community Structure. Fraser C, ed. *PLoS Computational Biology*. 2010;6(4):e1000736. doi:10.1371/journal.pcbi.1000736
6. Keeling M. The implications of network structure for epidemic dynamics. *Theoretical Population Biology*. 2005;67(1):1-8. doi:10.1016/j.tpb.2004.08.002
7. Eames KTD, Keeling MJ. Modeling dynamic and network heterogeneities in the spread of sexually transmitted diseases. *Proceedings of the National Academy of Sciences*. 2002;99(20):13330-13335. doi:10.1073/pnas.202244299

8. Althaus CL, Turner KM, Mercer CH, et al. Effectiveness and cost-effectiveness of traditional and new partner notification technologies for curable sexually transmitted infections: observational study, systematic reviews and mathematical modelling. *Health Technology Assessment*. 2014;18(2). doi:10.3310/hta18020

9. Althaus CL, Heijne JCM, Herzog SA, Roellin A, Low N. Individual and Population Level Effects of Partner Notification for Chlamydia trachomatis. Goldstein E, ed. *PLoS ONE*. 2012;7(12):e51438. doi:10.1371/journal.pone.0051438

10. Kretzschmar M, Morris M. Measures of concurrency in networks and the spread of infectious disease. *Mathematical Biosciences*. 1996;133(2):165-195. doi:10.1016/0025-5564(95)00093-3

11. Robinson K, Cohen T, Colijn C. The dynamics of sexual contact networks: Effects on disease spread and control. *Theoretical Population Biology*. 2012;81(2):89-96. doi:10.1016/j.tpb.2011.12.009

12. Hayashi MAL, Eisenberg MC. Effects of adaptive protective behavior on the dynamics of sexually transmitted infections. *Journal of Theoretical Biology*. 2016;388:119-130. doi:10.1016/j.jtbi.2015.08.022

13. Schroeder KD, Rojas FG. A Game Theoretical Analysis of Sexually Transmitted Disease Epidemics. *Rationality and Society*. 2002;14(3):353-383. doi:10.1177/1043463102014003004

14. Tully S, Cojocaru M, Bauch CT. Coevolution of risk perception, sexual behaviour, and HIV transmission in an agent-based model. *Journal of Theoretical Biology*. 2013;337:125-132. doi:10.1016/j.jtbi.2013.08.014

15. Keeling MJ, Eames KTD. Networks and epidemic models. *Journal of The Royal Society Interface*. 2005;2(4):295-307. doi:10.1098/rsif.2005.0051

16. May RM, Lloyd AL. Infection dynamics on scale-free networks. *Physical Review E*. 2001;64(6). doi:10.1103/PhysRevE.64.066112

17. Griffin RH, Nunn CL. Community structure and the spread of infectious disease in primate social networks. *Evolutionary Ecology*. 2012;26(4):779-800. doi:10.1007/s10682-011-9526-2

18. Kiss IZ, Green DM, Kao RR. Infectious disease control using contact tracing in random and scale-free networks. *Journal of The Royal Society Interface*. 2006;3(6):55-62. doi:10.1098/rsif.2005.0079

19. Kiss IZ, Green DM, Kao RR. Disease Contact Tracing in Random and Clustered Networks. *Proceedings: Biological Sciences*. 2005;272(1570):1407-1414.

20. House T, Keeling MJ. The Impact of Contact Tracing in Clustered Populations. Meyers LA, ed. *PLoS Computational Biology*. 2010;6(3):e1000721. doi:10.1371/journal.pcbi.1000721

21. Armbruster B, Brandeau ML. Contact tracing to control infectious disease: when enough is enough. *Health Care Management Science*. 2007;10(4):341-355. doi:10.1007/s10729-007-9027-6

22. Centers for Disease Control and Prevention. Recommendations for Partner Services Programs for HIV Infection, Syphilis, Gonorrhea, and Chlamydial Infection. *MMWR*. 2008;57.

23. Kissinger P, Mohammed H, Richardson-Alston G, et al. Patient-Delivered Partner Treatment for Male Urethritis: A Randomized, Controlled Trial. *Clinical Infectious Diseases*. 2005;41(5):623-629. doi:10.1086/432476

24. Golden MR, Handsfield HH, Hogben M, Helmers JRL, Holmes KK. Effect of Expedited Treatment of Sex Partners on Recurrent or Persistent Gonorrhea or Chlamydial Infection. *The New England Journal of Medicine*. Published online 2005:10.

25. Hogben M, Collins D, Hoots B, O'Connor K. Partner Services in Sexually Transmitted Disease Prevention Programs: A Review. *Sexually Transmitted Diseases*. 2016;43:S53-S62. doi:10.1097/OLQ.0000000000000328

26. Gift TL, Kissinger P, Mohammed H, Leichliter JS, Hogben M, Golden MR. The Cost and Cost-Effectiveness of Expedited Partner Therapy Compared With Standard Partner Referral for the Treatment of Chlamydia or Gonorrhea: *Sexually Transmitted Diseases*. 2011;38(11):1067-1073. doi:10.1097/OLQ.0b013e31822e9192

27. Tuite A, Fisman D, National Collaborating Centre for Infectious Diseases (Canada). *Agent-Based Modeling of Chlamydia Trachomatis Transmission in a Canadian Subpopulation: Report for the National Collaborating Centre for Infectious Diseases*.; 2014. Accessed February 8, 2019. http://www.deslibris.ca/ID/244348

28. Schmid BV, Kretzschmar M. Determinants of Sexual Network Structure and Their Impact on Cumulative Network Measures. Salathé M, ed. *PLoS Comput Biol*. 2012;8(4):e1002470. doi:10.1371/journal.pcbi.1002470

29. Turner K, Adams E, Gay N, Ghani A, Mercer C, Edmunds WJ. Developing a realistic sexual network model of chlamydia transmission in Britain. *Theor Biol Med Model*. 2006;3(1):3. doi:10.1186/1742-4682-3-3

30. Cassels S, Katz DA. Seroadaptation among Men Who Have Sex with Men: Emerging Research Themes. *Curr HIV/AIDS Rep*. 2013;10(4):305-313. doi:10.1007/s11904-013-0188-2

31. Neumann PJ, Cohen JT, Weinstein MC. Updating Cost-Effectiveness — The Curious Resilience of the $50,000-per-QALY Threshold. *New England Journal of Medicine*. 2014;371(9):796-797. doi:10.1056/NEJMp1405158

32. Jackson MO, Lopez-Pintado D. Diffusion and Contagion in Networks with Heterogeneous Agents and Homophily. *arXiv:11110073 [physics]*. Published online October 31, 2011. Accessed February 3, 2019. http://arxiv.org/abs/1111.0073

33. Ward H, Bell G. Partner notification. *Medicine*. 2014;42(6):314-317. doi:10.1016/j.mpmed.2014.03.013

34. Ferreira A, Young T, Mathews C, Zunza M, Low N. Strategies for partner notification for sexually transmitted infections, including HIV. Cochrane STI Group, ed. *Cochrane Database of Systematic Reviews*. Published online October 3, 2013. doi:10.1002/14651858.CD002843.pub2

35. Temkin E, Klassen AC, Mmari K, Gillespie DG. A Qualitative Study of Patients' Use of Expedited Partner Therapy. *Sexually Transmitted Diseases*. 2011;38(7):651-656. doi:10.1097/OLQ.0b013e31820cb206

36. Python Software Foundation. *Python Language Reference, Version 3.7.* https://www.python.org

37. HIV/AIDS Epidemiology Unit, Public Health – Seattle & King County and the Infectious Disease Assessment Unit, Washington State Department of Health. *HIV/AIDS Epidemiology Report, First Half 2013*.

38. Newman MEJ, Strogatz SH, Watts DJ. Random graphs with arbitrary degree distributions and their applications. *Physical Review E*. 2001;64(2). doi:10.1103/PhysRevE.64.026118

39. Raymond HF, McFarland W. Racial Mixing and HIV Risk Among Men Who Have Sex with Men. *AIDS and Behavior*. 2009;13(4):630-637. doi:10.1007/s10461-009-9574-6

40. Mustanski B, Birkett M, Kuhns LM, Latkin CA, Muth SQ. The Role of Geographic and Network Factors in Racial Disparities in HIV Among Young Men Who have Sex with Men: An Egocentric Network Study. *AIDS and Behavior*. 2015;19(6):1037-1047. doi:10.1007/s10461-014-0955-0

41. Mustanski B, Morgan E, Janulis P, Newcomb ME. Individual and Network Factors Associated With Racial Disparities in HIV Among Young Men Who Have Sex With Men: Results From the RADAR Cohort Study. *J Acquir Immune Defic Syndr*. 2019;80(1):7.

42. Tieu H-V, Liu T-Y, Hussen S, et al. Sexual Networks and HIV Risk among Black Men Who Have Sex with Men in 6 U.S. Cities. Switzer WM, ed. *PLOS ONE*. 2015;10(8):e0134085. doi:10.1371/journal.pone.0134085

43. Newman MEJ. Fast algorithm for detecting community structure in networks. *Physical Review E*. 2004;69(6). doi:10.1103/PhysRevE.69.066133

44. Liu Z, Hu B. Epidemic spreading in community networks. *Europhysics Letters (EPL)*. 2005;72(2):315-321. doi:10.1209/epl/i2004-10550-5

45. Liljeros F, Edling CR, Amaral LAN, Stanley HE, Åberg Y. The web of human sexual contacts. *Nature*. 2001;411(6840):907.

46. Schneeberger A, Mercer CH, Gregson SAJ, et al. Scale-Free Networks and Sexually Transmitted Diseases: A Description of Observed Patterns of Sexual Contacts in Britain and Zimbabwe. *Sexually Transmitted Diseases*. 2004;31(6):380-387. doi:10.1097/00007435-200406000-00012

47. Wall KM, Stephenson R, Sullivan PS. Frequency of Sexual Activity With Most Recent Male Partner Among Young, Internet-Using Men Who Have Sex With Men in the United States. *Journal of Homosexuality*. 2013;60(10):1520-1538. doi:10.1080/00918369.2013.819256

48. Eaton LA, West TV, Kenny DA, Kalichman SC. HIV Transmission Risk among HIV Seroconcordant and Serodiscordant Couples: Dyadic Processes of Partner Selection. *AIDS and Behavior*. 2009;13(2):185-195. doi:10.1007/s10461-008-9480-3

49. Trivedi PK, Zimmer DM. Copula Modeling: An Introduction for Practitioners. *Foundations and Trends® in Econometrics*. 2006;1(1):1-111. doi:10.1561/0800000005

50. Regan DG, Wilson DP, Hocking JS. Coverage Is the Key for Effective Screening of *Chlamydia trachomatis* in Australia. *The Journal of Infectious Diseases*. 2008;198(3):349-358. doi:10.1086/589883

51. Xiridou M, Vriend HJ, Lugner AK, et al. Modelling the impact of chlamydia screening on the transmission of HIV among men who have sex with men. *BMC Infectious Diseases*. 2013;13(1). doi:10.1186/1471-2334-13-436

52. Warner L, Stone KM, Macaluso M, Buehler JW, Austin HD. Condom Use and Risk of Gonorrhea and Chlamydia: A Systematic Review of Design and Measurement Factors Assessed in Epidemiologic Studies: *Sexually Transmitted Diseases*. 2006;33(1):36-51. doi:10.1097/01.olq.0000187908.42622.fd

53. HIV/AIDS Epidemiology Unit, Public Health – Seattle & King County and the Infectious Disease Assessment Unit, Washington State Department of Health. *HIV/AIDS Epidemiology Report, Second Half 2012*.; 2012.

54. Bartelsman M, Vaughan K, van Rooijen MS, de Vries HJC, Xiridou M. Impact of point-of-care management on the transmission of anogenital gonococcal infections among men who have sex with men in Amsterdam: a mathematical modelling and cost-effectiveness study. *Sexually Transmitted Infections*. Published online September 23, 2017:sextrans-2017-053159. doi:10.1136/sextrans-2017-053159

55. Geisler WM. Duration of Untreated, Uncomplicated *Chlamydia trachomatis* Genital Infection and Factors Associated with Chlamydia Resolution: A Review of Human Studies. *The Journal of Infectious Diseases*. 2010;201(S2):104-113. doi:10.1086/652402

56. Farley TA, Cohen DA, Elkins W. Asymptomatic sexually transmitted diseases: the case for screening. *Preventive Medicine*. 2003;36(4):502-509. doi:10.1016/S0091-7435(02)00058-0

57. Korenromp EL, Sudaryo MK, de Vlas SJ, et al. What proportion of episodes of gonorrhoea and chlamydia becomes symptomatic? *International Journal of STD & AIDS*. 2002;13(2):91-101. doi:10.1258/0956462021924712

58. HIV/AIDS Epidemiology Unit, Public Health – Seattle & King County and the Infectious Disease Assessment Unit, Washington State Department of Health. *HIV/AIDS Epidemiology Report*.; 2015.

59. Rao DW, Carr J, Naismith K, Golden M. *Washington HIV Prevention Project – Key Findings, 2017*. Washington State Department of Health, Public Health—Seattle & King County; 2017. Accessed November 4, 2019. https://www.doh.wa.gov/Portals/1/Documents/5620/WashingtonHIVPreventionProjectKeyFindings2017.pdf

60. Centers for Disease Control and Prevention: US Public Health Service. *Preexposure Prophylaxis for the Prevention of HIV Infection in the United States—2017 Update: A Clinical Practice Guideline.* Centers for Disease Control and Prevention; 2018. Accessed November 4, 2019. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf

61. Owusu-Edusei K, Chesson HW, Gift TL, et al. The Estimated Direct Medical Cost of Selected Sexually Transmitted Infections in the United States, 2008: *Sexually Transmitted Diseases*. 2013;40(3):197-201. doi:10.1097/OLQ.0b013e318285c6d2

62. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russel LB. Recommendations of the Panel on Cost-Efectiveness in Health and Medicine. *JAMA*. 1996;276(15):6.

63. National Research Council. *Assessing the Reliability of Complex Models: Mathematical and Statistical Foundations of Verification, Validation, and Uncertainty Quantification.* NRC; 2012.

64. Barton RR. Metamodeling: a state of the art review. In: *Proceedings of Winter Simulation Conference*. IEEE; 1994:237-244. doi:10.1109/WSC.1994.717134

65. Eames KTD, Keeling MJ. Contact Tracing and Disease Control. *Proceedings: Biological Sciences*. 2003;270(1533):2565-2571.

66. Kuperman M, Abramson G. Small world effect in an epidemiological model. *Phys Rev Lett*. 2001;86(13):2909-2912. doi:10.1103/PhysRevLett.86.2909

67. Watts DJ, Strogatz SH. Collective dynamics of 'small-world' networks. 1998;393:3.

68. Baker J, Plankey M, Josayma Y, et al. The Prevalence of Rectal, Urethral, and Pharyngeal *Neisseria gonorrheae* and *Chlamydia trachomatis* among Asymptomatic Men Who Have Sex with Men in a Prospective Cohort in Washington, D.C. *AIDS Patient Care and STDs*. 2009;23(8):585-588. doi:10.1089/apc.2008.0277

69. Kent CK, Chaw JK, Wong W, et al. 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*. 2005;41(1):67-74. doi:10.1086/430704

70. Althaus CL, Turner KME, Schmid BV, Heijne JCM, Kretzschmar M, Low N. Transmission of *Chlamydia trachomatis* through sexual partnerships: a comparison between three individual-based models and empirical data. *J R Soc Interface*. 2012;9(66):136-146. doi:10.1098/rsif.2011.0131

71. Boily MC, Asghar Z, Garske T, Ghani AC, Poulin R. Influence of Selected Formation Rules for Finite Population Networks with Fixed Macrostructures: Implications for Individual-Based Model of Infectious Diseases. *Mathematical Population Studies*. 2007;14(4):237-267. doi:10.1080/08898480701612873

72. National Center for Health Statistics (NCHS). *2015-2017 National Survey of Family Growth Public-Use Data and Documentation*. CDC National Center for Health Statistics; 2018. http://www.cdc.gov/nchs/nsfg/nsfg_2015_2017_puf.htm

73. Erens B, Phelps A, Clifton S, et al. Methodology of the third British National Survey of Sexual Attitudes and Lifestyles (Natsal-3). *Sex Transm Infect*. 2014;90(2):84-89. doi:10.1136/sextrans-2013-051359

74. Catania JA, Gibson DR, Chitwood DD, Coates TJ. Methodological Problems in AIDS Behavioral Research: Influences on Measurement Error and Participation Bias in Studies of Sexual Behavior. :24.

75. Carballo M, Cleland J, Carael M, Albrecht G. A cross national study of patterns of sexual behaviour. *Journal of Sex Research*. 1989;26(3):287-299. doi:10.1080/00224498909551516

76. Porter SR, Whitcomb ME, Weitzer WH. Multiple surveys of students and survey fatigue. *New Directions for Institutional Research*. 2004;2004(121):63-73. doi:10.1002/ir.101

77. Lee S-J, Cho Y-H, Ha U-S, Kim SW, Yoon MS, Bae K. Sexual behavior survey and screening for chlamydia and gonorrhea in university students in South Korea. *Int J Urol*. 2005;12(2):187-193. doi:10.1111/j.1442-2042.2005.01013.x

78. Morris CN, Morris SR, Ferguson AG. Sexual Behavior of Female Sex Workers and Access to Condoms in Kenya and Uganda on the trans-Africa Highway. *AIDS Behav*. 2009;13(5):860-865. doi:10.1007/s10461-008-9431-z

79. Claxton KP, Sculpher MJ. Using Value of Information Analysis to Prioritise Health Research: Some Lessons from Recent UK Experience. *PharmacoEconomics*. 2006;24(11):1055-1068. doi:10.2165/00019053-200624110-00003

80. Jutkowitz E, Alarid-Escudero F, Choi HK, Kuntz KM, Jalal H. Prioritizing Future Research on Allopurinol and Febuxostat for the Management of Gout: Value of Information Analysis. *PharmacoEconomics*. 2017;35(10):1073-1085. doi:10.1007/s40273-017-0526-0

81. Yokota F, Thompson KM. Value of Information Literature Analysis: A Review of Applications in Health Risk Management. *Med Decis Making*. 2004;24(3):287-298. doi:10.1177/0272989X04263157

82. R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing; 2019. https://www.R-project.org/

83. Gray RT, Beagley KW, Timms P, Wilson DP. Modeling the Impact of Potential Vaccines on Epidemics of Sexually Transmitted *Chlamydia trachomatis* Infection. *J INFECT DIS*. 2009;199(11):1680-1688. doi:10.1086/598983

84. Low N, McCarthy A, Macleod J, et al. Epidemiological, social, diagnostic and economic evaluation of population screening for genital chlamydial infection. *Health Technol Assess*. 2007;11(8). doi:10.3310/hta11080

85. Meyers DS, Halvorson H, Luckhaupt S. Screening for Chlamydial Infection: An Evidence Update for the U.S. Preventive Services Task Force. :9.

86. Herzog SA, Althaus CL, Heijne JC, et al. Timing of progression from Chlamydia trachomatisinfection to pelvic inflammatory disease: a mathematical modelling study. *BMC Infect Dis*. 2012;12(1):187. doi:10.1186/1471-2334-12-187

87. Gift TL, Gaydos CA, Kent CK, et al. The Program Cost and Cost-Effectiveness of Screening Men for Chlamydia to Prevent Pelvic Inflammatory Disease in Women: *Sexually Transmitted Diseases*. 2008;35(Supplement):S66-S75. doi:10.1097/OLQ.0b013e31818b64ac

88. Hu D, Iii EWH, Goldie SJ. Screening for Chlamydia trachomatis in Women 15 to 29 Years of Age: A Cost-Effectiveness Analysis. *Annals of internal medicine*. 2004;141(7):501-513.

89. Centers for Disease Control and Prevention. *Chlamydia Screening Percentages Reported by Commercial and Medicaid Plans by State and Year*. Centers for Disease Control and Prevention Accessed April 9, 2020. https://www.cdc.gov/std/chlamydia/chlamydia-screening-2014.htm

90. Satterwhite CL, Torrone E, Meites E, et al. Sexually Transmitted Infections Among US Women and Men: Prevalence and Incidence Estimates, 2008. *Sexually Transmitted Diseases*. 2013;40(3):187-193. doi:10.1097/OLQ.0b013e318286bb53

91. Workowski K. Chlamydia and gonorrhea. *Annals of Internal Medicine*. 2013;158(3).

92. Watson EJ, Templeton A, Russell I, et al. The accuracy and efficacy of screening tests for Chlamydia trachomatis: a systematic review. *Journal of Medical Microbiology*. 2002;51(12):1021-1031. doi:10.1099/0022-1317-51-12-1021

93. Kissinger P, Schmidt N, Mohammed H, et al. Patient-Delivered Partner Treatment for Trichomonas vaginalis Infection: A Randomized Controlled Trial: *Sexually Transmitted Diseases*. 2006;33(7):445-450. doi:10.1097/01.olq.0000204511.84485.4c

94. Yeh JM, Hook EW, Goldie SJ. A Refined Estimate of the Average Lifetime Cost of Pelvic Inflammatory Disease: *Sexually Transmitted Diseases*. 2003;30(5):369-378. doi:10.1097/00007435-200305000-00001

95. Smith KJ, Tsevat J, Ness RB, Wiesenfeld HC, Roberts MS. Quality of Life Utilities for Pelvic Inflammatory Disease Health States: *Sexually Transmitted Diseases*. 2008;35(3):307-311. doi:10.1097/OLQ.0b013e31815b07dd

96. Owusu-Edusei K, Chesson HW, Gift TL, et al. The Estimated Direct Medical Cost of Selected Sexually Transmitted Infections in the United States, 2008: *Sexually Transmitted Diseases*. 2013;40(3):197-201. doi:10.1097/OLQ.0b013e318285c6d2

97. Xiridou M, Vriend HJ, Lugner AK, et al. Modelling the impact of chlamydia screening on the transmission of HIV among men who have sex with men. *BMC Infect Dis*. 2013;13(1):436. doi:10.1186/1471-2334-13-436

98. Hu D, Hook EW, Goldie SJ. The Impact of Natural History Parameters on the Cost-Effectiveness of Chlamydia trachomatis Screening Strategies: *Sexually*

Transmitted Diseases. 2006;33(7):428-436. doi:10.1097/01.olq.0000200577.46261.b0

99. Centers for Disease Control and Prevention. *2015 Sexually Transmitted Diseases Treatment Guidelines - Chlamydial Infections*. Centers for Disease Control and Prevention; 2015. Accessed April 9, 2020. https://www.cdc.gov/std/tg2015/chlamydia.htm

100. Centers for Disease Control and Prevention. *Legal Status of Expedited Partner Therapy (EPT)*. Centers for Disease Control and Prevention Accessed April 9, 2020. https://www.cdc.gov/std/ept/legal/default.htm

101. Miller WC, Ford CA, Morris M, et al. Prevalence of Chlamydial and Gonococcal Infections Among Young Adults in the United States. :8.

102. Sawers L. Measuring and modelling concurrency. *Journal of the International AIDS Society*. 2013;16(1):17431. doi:10.7448/IAS.16.1.17431

103. Nelson SJ, Manhart LE, Gorbach PM, et al. Measuring Sex Partner Concurrency: It's What's Missing That Counts. *Sexually Transmitted Diseases*. 2007;PAP. doi:10.1097/OLQ.0b013e318063c734

104. Neumann PJ, Cohen JT, Weinstein MC. Updating Cost-Effectiveness — The Curious Resilience of the $50,000-per-QALY Threshold. *N Engl J Med*. 2014;371(9):796-797. doi:10.1056/NEJMp1405158

105. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ*. 2001;10(8):779-787. doi:10.1002/hec.635

106. United Nations, Department of Economic and Social Affairs, Population Division. *World Population Prospects 2019, Online Edition. Rev. 1.*; 2019. Accessed May 28, 2020. https://population.un.org/wpp/Download/Standard/Population/

107. Sandoz KM, Rockey DD. Antibiotic resistance in Chlamydiae. *Future Microbiology*. 2010;5(9):1427-1442. doi:10.2217/fmb.10.96

108. Somani J, Bhullar VB, Workowski KA, Farshy CE, Black CM. Multiple Drug–Resistant *Chlamydia trachomatis* Associated with Clinical Treatment Failure. *J INFECT DIS*. 2000;181(4):1421-1427. doi:10.1086/315372

109. Ronn M, White PJ, Hughes G, Ward H. Developing a Conceptual Framework of Seroadaptive Behaviors in HIV-Diagnosed Men Who Have Sex With Men. *Journal of Infectious Diseases*. 2014;210(suppl 2):S586-S593. doi:10.1093/infdis/jiu482

110. Cassels S, Menza TW, Goodreau SM, Golden MR. HIV serosorting as a harm reduction strategy: evidence from Seattle, Washington. *AIDS*. 2009;23(18):2497-2506. doi:10.1097/QAD.0b013e328330ed8a

111. Wilson DP, Regan DG, Heymer K-J, Jin F, Prestage GP, Grulich AE. Serosorting May Increase the Risk of HIV Acquisition Among Men Who Have Sex With Men: *Sexually Transmitted Diseases*. 2010;37(1):13-17. doi:10.1097/OLQ.0b013e3181b35549

112. Chen Y-H, Guigayoma J, McFarland W, Snowden JM, Raymond HF. Increases in Pre-exposure Prophylaxis Use and Decreases in Condom Use: Behavioral Patterns Among HIV-Negative San Francisco Men Who have Sex with Men, 2004–2017. *AIDS Behav*. 2019;23(7):1841-1845. doi:10.1007/s10461-018-2299-7

113. Holt M, Lea T, Mao L, et al. Community-level changes in condom use and uptake of HIV pre-exposure prophylaxis by gay and bisexual men in Melbourne and Sydney, Australia: results of repeated behavioural surveillance in 2013–17. *The Lancet HIV*. 2018;5(8):e448-e456. doi:10.1016/S2352-3018(18)30072-9

114. Kalichman SC, Price D, Eaton LA, et al. Diminishing Perceived Threat of AIDS and Increasing Sexual Risks of HIV Among Men Who Have Sex with Men, 1997–2015. *Arch Sex Behav*. 2017;46(4):895-902. doi:10.1007/s10508-016-0934-9

115. Redd AD, Quinn TC, Tobian AA. Frequency and implications of HIV superinfection. *The Lancet Infectious Diseases*. 2013;13(7):622-628. doi:10.1016/S1473-3099(13)70066-5

116. Crepaz N, Marks G, Liau A, et al. Prevalence of unprotected anal intercourse among HIV-diagnosed MSM in the United States: a meta-analysis: *AIDS*. 2009;23(13):1617-1629. doi:10.1097/QAD.0b013e32832effae

117. Montaño MA, Dombrowski JC, Dasgupta S, et al. Changes in Sexual Behavior and STI Diagnoses Among MSM Initiating PrEP in a Clinic Setting. *AIDS Behav*. 2019;23(2):548-555. doi:10.1007/s10461-018-2252-9

118. Traeger MW, Schroeder SE, Wright EJ, et al. 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*. 2018;67(5):676-686. doi:10.1093/cid/ciy182

119. Kok S. Modelling the impact of serosorting and seroadaptation on the spread of HIV in men who have sex with men. Published online 2010.

120. Volz E, Frost SDW, Rothenberg R, Meyers LA. Epidemiological bridging by injection drug use drives an early HIV epidemic. *Epidemics*. 2010;2(3):155-164. doi:10.1016/j.epidem.2010.06.003

121. Miller JC, Volz EM. Incorporating Disease and Population Structure into Models of SIR Disease in Contact Networks. Barrat A, ed. *PLoS ONE*. 2013;8(8):e69162. doi:10.1371/journal.pone.0069162

122. Tully S, Cojocaru M, Bauch CT. Sexual behavior, risk perception and HIV transmission can respond to HIV antiviral drugs and vaccines through multiple pathways. *Sci Rep*. 2015;5(1):15411. doi:10.1038/srep15411

123. Binmore K. *Playing for Real: A Text on Game Theory*. Oxford Univeristy Press; 2007.

124. Fudenberg D, Tirole J. *Game Theory*. The MIT Press; 1991.

125. Nowak MA. *Evolutionary Dynamics: Exploring the Equations of Life*. Harvard University Press; 2006.

126. Nowak MA, Tarnita CE, Antal T. Evolutionary dynamics in structured populations. *Phil Trans R Soc B*. 2010;365(1537):19-30. doi:10.1098/rstb.2009.0215

127. Perc M, Gómez-Gardeñes J, Szolnoki A, Floría LM, Moreno Y. Evolutionary dynamics of group interactions on structured populations: a review. *J R Soc Interface*. 2013;10(80):20120997. doi:10.1098/rsif.2012.0997

128. Santos FC, Pacheco JM, Lenaerts T. Evolutionary dynamics of social dilemmas in structured heterogeneous populations. *Proceedings of the National Academy of Sciences*. 2006;103(9):3490-3494. doi:10.1073/pnas.0508201103

129. Centers for Disease Control and Prevention. *HIV and Gay and Bisexual Men*. Centers for Disease Control and Prevention; 2019. Accessed April 19, 2020. https://www.cdc.gov/hiv/pdf/group/msm/cdc-hiv-msm.pdf

130. Campsmith ML, Rhodes PH, Hall HI, Green TA. Undiagnosed HIV prevalence among adults and adolescents in the United States at the end of 2006. *Journal of Acquired Immune Deficiency Syndromes*. 2010;53:619-624.

131. Szabó G, Fáth G. Evolutionary games on graphs. *Physics Reports*. 2007;446(4-6):97-216. doi:10.1016/j.physrep.2007.04.004

132. Weiss KM, Goodreau SM, Morris M, et al. Egocentric sexual networks of men who have sex with men in the United States: Results from the ARTnet study. *Epidemics*. 2020;30:100386. doi:10.1016/j.epidem.2020.100386

133. Luo W, Katz DA, Hamilton DT, et al. Development of an Agent-Based Model to Investigate the Impact of HIV Self-Testing Programs on Men Who Have Sex With Men in Atlanta and Seattle. *JMIR Public Health Surveill*. 2018;4(2):e58. doi:10.2196/publichealth.9357

134. Traulsen A, Semmann D, Sommerfeld RD, Krambeck H-J, Milinski M. Human strategy updating in evolutionary games. *Proceedings of the National Academy of Sciences*. 2010;107(7):2962-2966. doi:10.1073/pnas.0912515107

135. Wu B, Gokhale CS, Wang L, Traulsen A. How small are small mutation rates? *J Math Biol*. 2012;64(5):803-827. doi:10.1007/s00285-011-0430-8

136. Hauert C, Szabó G. Game theory and physics. *American Journal of Physics*. 2005;73(5):405-414. doi:10.1119/1.1848514

137. Adami C, Schossau J, Hintze A. Evolutionary game theory using agent-based methods. *Physics of Life Reviews*. 2016;19:1-26. doi:10.1016/j.plrev.2016.08.015

138. Rosenberg ES, Grey JA, Sanchez TH, Sullivan PS. Rates of Prevalent HIV Infection, Prevalent Diagnoses, and New Diagnoses Among Men Who Have Sex With Men in US States, Metropolitan Statistical Areas, and Counties, 2012-2013. *JMIR Public Health Surveill*. 2016;2(1):e22. doi:10.2196/publichealth.5684

139. Centers for Disease Control and Prevention. Disclosure of HIV Status. Accessed April 22, 2020. https://wwwn.cdc.gov/hivrisk/decreased_risk/communication/disclosure.html

Appendix A
Supplementary material for Chapter 2

A.1 Supplementary tables

Table A.1. The mean and standard deviation (sd) of the disease incidence, disease prevalence, total infected person-months, and average duration of infection (month) in the two-year time horizon for the base case analysis at a low external force of infection (EFOI). The values were calculated using 10,000 simulations.

Strategy		**Prevalence**	**Incidence**	**Total infected person-months**	**Average duration of infection (month)**
Random networks					
Screening	mean	0.7%	105	364	3.44
	sd	0.3%	37	141	0.34
PN	mean	0.6%	97	327	3.34
	sd	0.3%	34	125	0.34
EPT	mean	0.6%	95	316	3.31
	sd	0.3%	33	121	0.35
Tracing	mean	0.5%	91	302	3.27
	sd	0.2%	31	113	0.35
Community-structured networks					
Screening	mean	0.6%	99	346	3.47
	sd	0.3%	34	132	0.35
PN	mean	0.6%	91	309	3.36
	sd	0.2%	31	115	0.35

EPT	mean	0.5%	89	298	3.32
	sd	0.2%	29	109	0.35
Tracing	mean	0.5%	86	287	3.29
	sd	0.2%	28	106	0.36
Scale-free networks					
Screening	mean	13.5%	2,762	5,933	2.13
	sd	1.4%	565	1,413	0.11
PN	mean	8.8%	2,311	4,070	1.75
	sd	1.0%	498	965	0.07
EPT	mean	9.7%	2,342	4,097	1.74
	sd	1.1%	504	970	0.06
Tracing	mean	12.7%	2,634	5,481	2.06
	sd	1.5%	599	1,449	0.12
Empirical networks					
Screening	mean	1.0%	151	474	3.12
	sd	0.5%	66	215	0.28
PN	mean	0.8%	127	384	3.00
	sd	0.4%	52	163	0.29
EPT	mean	0.7%	123	365	2.97
	sd	0.3%	49	153	0.29
Tracing	mean	0.6%	115	337	2.92
	sd	0.3%	45	139	0.30

Table A.2. The mean and standard deviation (sd) of outcomes related to partner management strategies in the two-year time horizon for the base case analysis at a low external force of infection (EFOI). The values were calculated using 10,000 simulations.

Strategy		**# of individuals screened or tested**	**# of index cases**	**Total # of partners in the past 6 months among the index case**	**average # of partners in the past 6 months of the index case**	**% partners infected**	**# of partners reached**	**# of partners tested / treated under partner management**	**# of infected partners who were treated**
Random networks									
Screening*	mean	6,340	17	62	3.63	17.2%			
	sd	41	8	28	1.65	5.1%			
PN$	mean	6,352	20	81	4.09	15.8%	22	12	4
	sd	41	9	39	1.96	4.3%	11	7	3
EPT†	mean	6,340	17	62	3.63	17.2%	23	15	5
	sd	41	8	28	1.65	5.1%	11	8	3
Tracing§	mean	6,358	21	85	4.04	14.8%	33	19	7
	sd	42	9	40	1.90	4.0%	16	10	4
Community-structured networks									
Screening*	mean	6,340	17	59	3.56	17.9%			
	sd	40	7	26	1.58	5.5%			
PN$	mean	6,351	19	77	4.06	16.6%	21	12	4
	sd	40	9	36	1.91	4.7%	11	6	3
EPT†	mean	6,340	17	59	3.56	17.9%	22	14	5
	sd	40	7	26	1.58	5.5%	10	7	3

Tracing[§]	mean	6,358	21	82	4.00	15.4%	31	19	6
	sd	41	9	39	1.89	4.3%	16	10	4
Scale-free networks									
Screening[*]	mean	6,340	1,316	6,050	4.60	11.2%			
	sd	40	330	1,216	0.92	1.2%			
PN[$]	mean	7,588	1,377	9,013	6.54	13.0%	3,119	1,247	402
	sd	305	352	1,950	1.42	1.3%	716	304	108
EPT[†]	mean	6,340	1,316	6,050	4.60	11.2%	2,945	1,279	341
	sd	40	330	1,216	0.92	1.2%	632	305	91
Tracing[§]	mean	6,521	1,293	8,484	6.56	16.8%	551	277	114
	sd	46	351	1,808	1.40	1.8%	71	38	24
Empirical networks									
Screening[*]	mean	6,340	32	154	4.80	12.6%			
	sd	40	16	75	2.35	3.1%			
PN[$]	mean	6,367	35	199	5.74	12.0%	50	27	8
	sd	42	17	102	2.94	2.8%	27	15	5
EPT[†]	mean	6,340	32	154	4.80	12.6%	53	33	9
	sd	40	16	75	2.35	3.1%	27	16	5
Tracing[§]	mean	6,380	36	200	5.56	11.2%	72	42	12
	sd	45	17	100	2.80	2.6%	37	23	7

Table A.3. Cost-effectiveness analysis of various partner management strategies in each network structure at a low external force of infection (EFOI) in base case analysis. The mean and standard deviation (sd) of total cost and total infected person-months were calculated using the 10,000 simulations.

Strategy		**Total infected person-months**	**Cost**	**Incremental benefit**	**Incremental cost**	**ICER**
Random networks						
Screening*	mean	364	624,229			
	sd	141	4,014			
EPT†	mean	316	624,969	47	740	16
	sd	121	4,071			
PN$	mean	327	625,570			Strongly dominated
	sd	125	4,163			
Tracing§	mean	302	630,051	15	5,081	344
	sd	113	5,242			
Community-structure networks						
Screening*	mean	346	624,216			
	sd	132	3,965			
EPT†	mean	298	624,910	48	695	14
	sd	109	4,007			
PN$	mean	309	625,494			Strongly dominated
	sd	115	4,068			
Tracing§	mean	287	629,831	11	4,920	442
	sd	106	5,124			
Scale-free networks						
Screening*	mean	5,933	696,735			
	sd	1,413	18,974			
EPT†	mean	4,097	751,400	1,835	54,666	30
	sd	970	32,094			
Tracing§	mean	5,481	776,818			Strongly dominated
	sd	1,449	29,058			
PN$	mean	4,070	821,395	27	69,994	2,557
	sd	965	49,336			
Empirical networks						

Screening*	mean	474	625,089			
	sd	215	4,045			
EPT†	mean	365	626,547	109	1,458	13
	sd	153	4,220			
PN$	mean	384	627,862			Strongly dominated
	sd	163	4,554			
Tracing§	mean	337	637,482	28	10,935	388
	sd	139	8,250			

A.2 Supplemental Figures

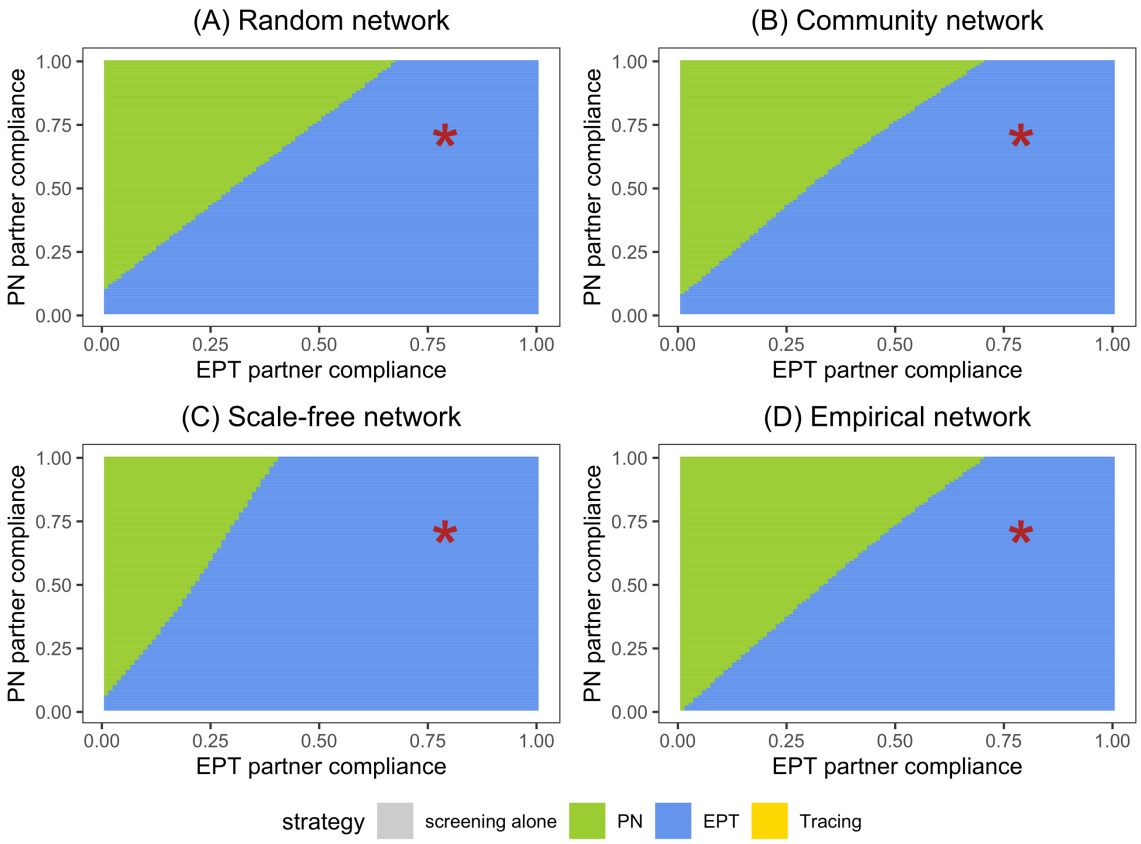

Figure A.1. The optimal partner management strategy with varying levels of partner compliance using a willingness-to-pay (WTP) threshold = $100 in (A) random, (B) community, (C) scale-free, and (D) empirical networks in the low external force of infection (EFOI) scenario. PN = partner notification; EPT = expedited partner therapy; Tracing = contact tracing. These partner management strategies were implemented in addition to routine screening alone.

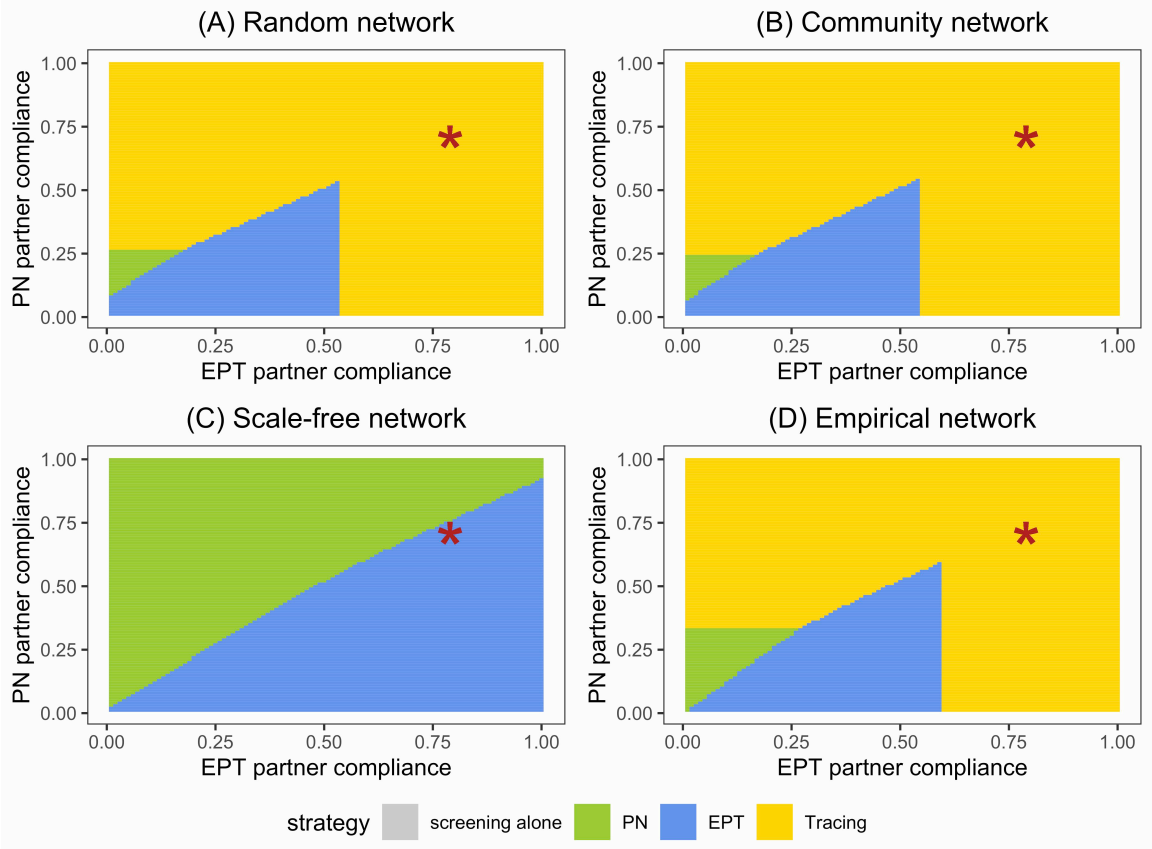

Figure A.2. The optimal partner management strategy with varying levels of partner compliance using a willingness-to-pay (WTP) threshold = $600 in (A) random, (B) community, (C) scale-free, and (D) empirical networks in the low external force of infection (EFOI) scenario. PN = partner notification; EPT = expedited partner therapy; Tracing = contact tracing. These partner management strategies were implemented in addition to routine screening alone.

Appendix B

Supplementary material for Chapter 3

B.1 Supplementary figures

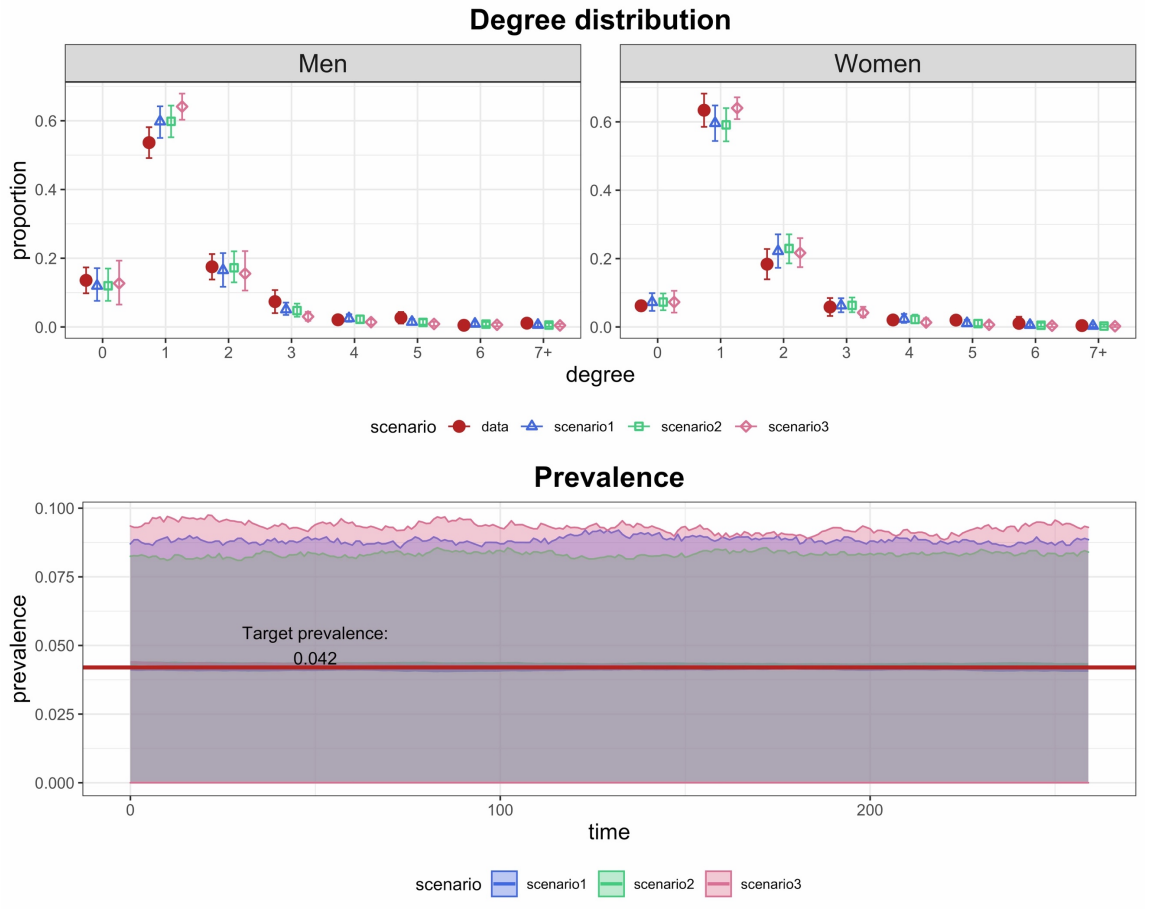

Figure B.1. Targets and simulated results from posterior parameters. The top panel includes the annual degree distribution estimated from the NSFG and simulated annual degree distribution by men and women for each scenario. The bottom panel presents the observed

chlamydia prevalence (4.2%) and the simulated chlamydia prevalence (the lines are the mean prevalence and the shaded areas cover the 95% credible intervals) for each scenario.

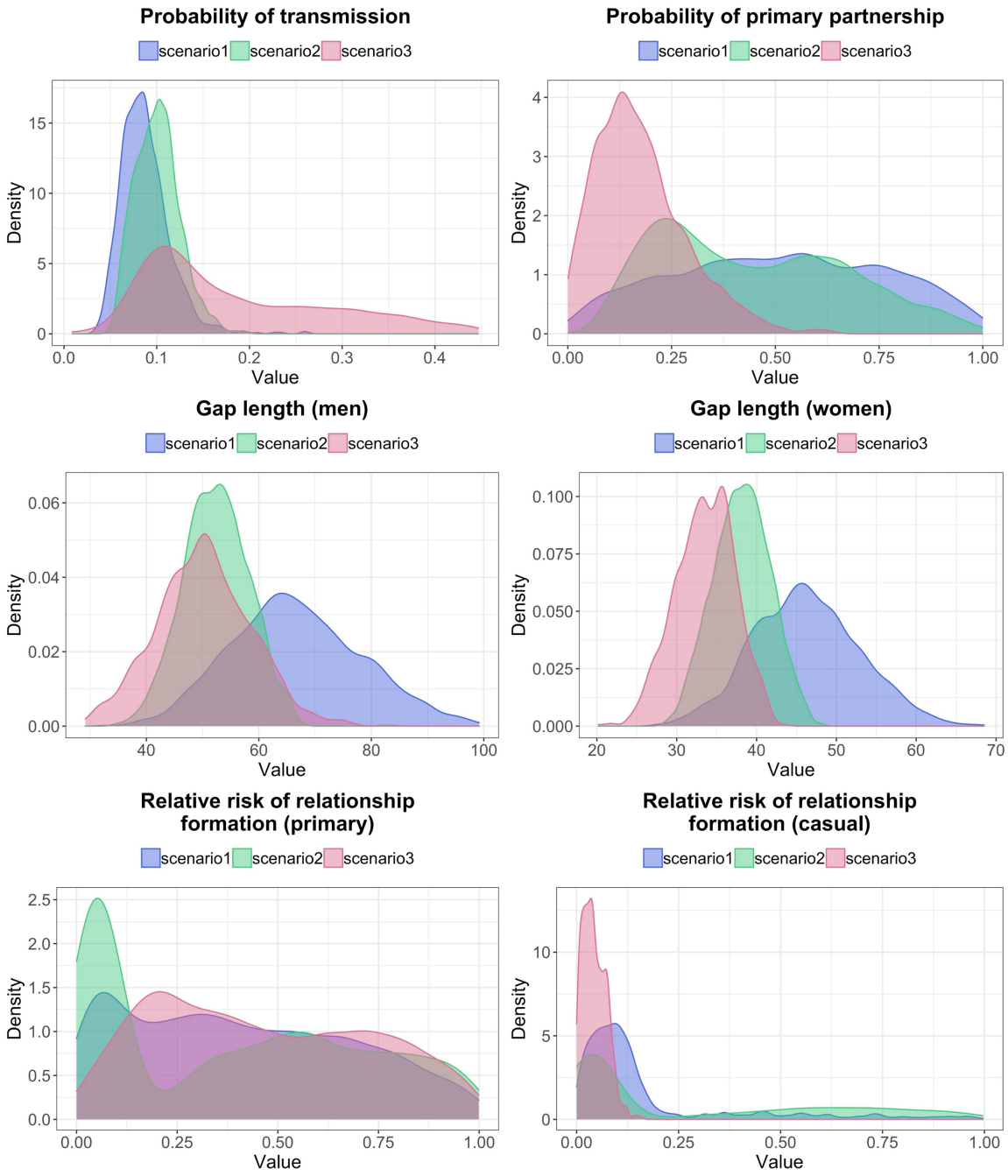

Figure B.2. Posterior distribution from the 1,000 posterior parameter sets for each scenario. The posterior distributions include the probability of transmission per sex act, probability that a relationship is primary, the gap lengths between relationships for men and women,

and relative risk of relationship formation for individuals who have primary partnerships or for individuals who have only casual partnerships.

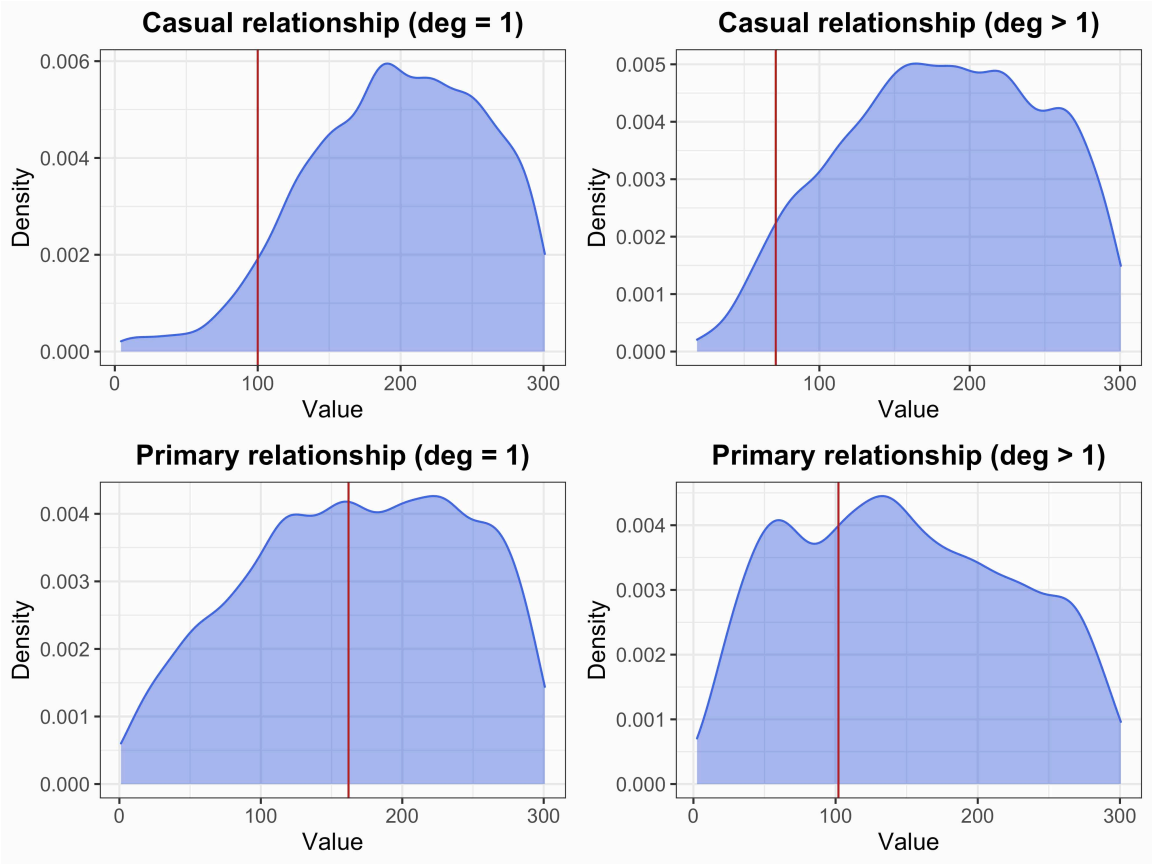

Figure B.3. Posterior distributions for relationship durations in scenario 1 (blue shaded area) and the estimated relationship durations from the NSFG (red vertical lines).

Appendix C

Supplementary material for Chapter 4

C.1 Supplementary figures

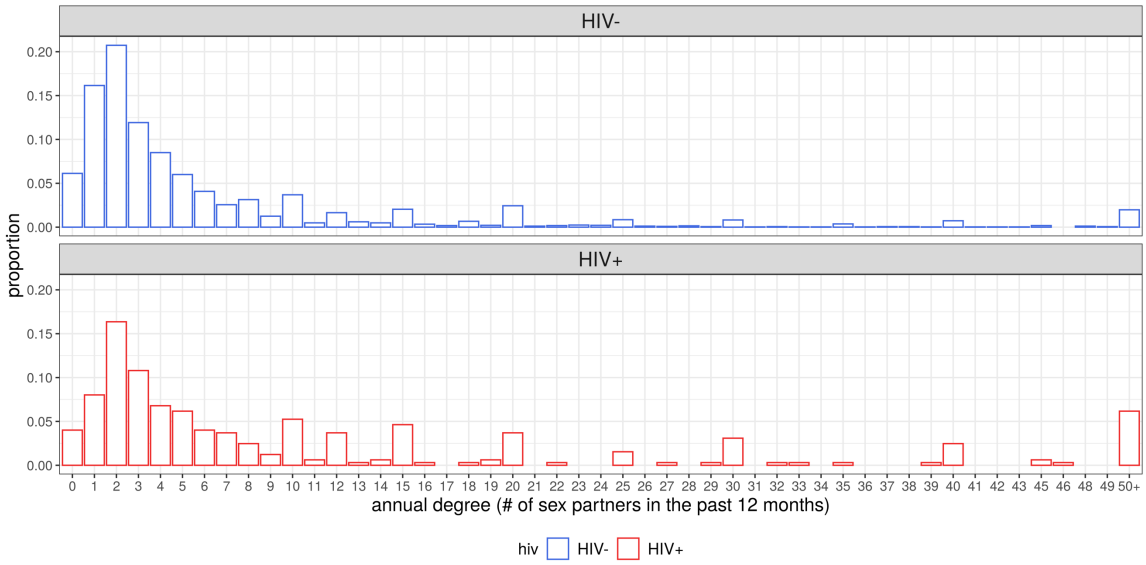

Figure C.1. Degree distribution by HIV status of the respondents in the ARTnet study.