The Minnesota Journal of Undergraduate Mathematics

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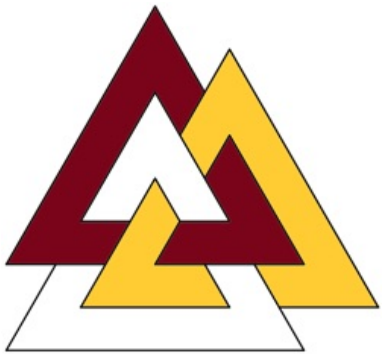

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1. Introduction

Since its first appearance in 1959, HIV has posed a serious threat to public health, both within the United States and internationally. Although treatments for the disease have become increasingly effective, a cure remains elusive. Of growing concern is the uneven incidence of HIV across demographic groups – and in particular, within America's incarcerated population, where the rate of HIV infection remains six times the national average [1]. Compounding the problem, rates of intravenous drug use among incarcerated individuals frequently exceed 30% [4], providing an avenue for not just occasional but widespread transmission of HIV via contaminated needles. The recent U.S. opioid epidemic also raises some concerns about rising HIV infection rates caused by intravenous drug use.

Here we present a stochastic model for the spread of HIV within a community that explicitly accounts for the spread of disease via contaminated needles as well as via sexual transmission. Stochastic models are particularly valuable for understanding epidemic behavior because, even within a single population, different outbreaks of the same disease do not behave identically. Such models allow us to capture naturally occurring random variation among individuals within a population, while also effectively modeling large-scale behavior of the disease. Our model takes its inspiration from existing models for the spread of diseases such as malaria [5], which are not ordinarily transmissible directly between individuals, but instead rely on a vector species (such as the mosquito) to transmit the infection.

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2. Compartmental Stochastic Model for the Spread of HIV

Our work extends the stochastic model for HIV developed by Gani, Blount, & Yakowitz (1997). This compartmental model assumes a fixed population of individuals, with regular inflows and outflows of a fixed number of individuals. It operates in discrete time (this makes it more computationally tractable than an analogous model in continuous time). We choose a prison as the real-world analogue of a community of individuals that satisfies these constraints.

The defining feature of compartmental models is that, to make the behavior of the disease easier to track, the population is divided into multiple mutually exclusive groups whose respective sizes evolve over time. In the Gani, Blount and Yakowitz model, there are two such groups. The first, the *suceptibles*, is comprised of those who are not HIV-positive but could potentially contract the disease. The second group, the *infected class* consists of those who are HIV positive. At each discrete unit of time, the number of individuals within each group, or compartment, is tracked. Thus at any given time we can determine the overall behavior of the disease. However, the infection status of any individual is not of interest.

Because there is no possibility for recovery from or immunity to HIV, individuals move from the class of susceptible individuals into the class of infected individuals and remain there. This model captures the overall dynamics of the spread of HIV within a closed system. We will develop and extend this model in Section 3 to specifically capture the actions of unsafe intravenous drug use on the spread of the disease.

2.1. **Elaboration of Model.**

Here we present the model given by Gani, Blount, & Yakowitz. In a population of N individuals with a regular turnover of $n < N$ individuals an each time step t, there are two possible routes by which the total number of infections within the prison, $I(t)$, can increase and one by which it can decrease.

Individuals may become infected as a result of contact with another infected individual. We assume that individuals make a single sexual contact at each time step and mix homogeneously; that is, each individual is equally likely to have contact with all other individuals. (This is in contrast to concrete scenarios in which individuals often make contact with friends and family more often than strangers.) We further assume that infections are independent of one another. For each of the $N - I(t)$ susceptible individuals in the population at time t, the probability p of being infected in a given time step is proportional to the size of the infected class; that is, $p = \beta I(t)$ for some positive constant β. Let $M(t)$ be the number of infections created by this mixing. Further, we assume that infections are independent from person to person. This gives that $M(t)$ has a binomial distribution with $N - I(t)$ total trials and success (e.g., infection) probability $\beta I(t)$. We denote this as

$$M(t) \sim \text{Bin}(N - I(t), \beta I(t)).$$

Individuals may also enter the system (as a result of the regular turnover) already having contracted an HIV infection, which occurs within the world outside the model at some rate μ. Viewing the event of a single individual entering the model with an existing infection as a single Bernoulli trial with probability of success μ, we have that the total number

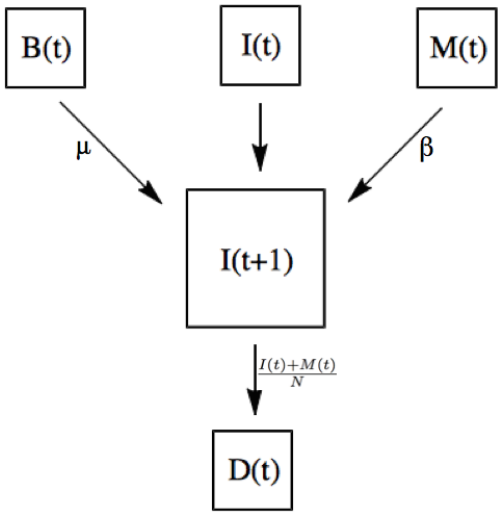

FIGURE 1. Population Flow in a Stochastic Compartmental Model

of infected individuals entering the model, $B(t)$, at any given time step also follows a binomial distribution:

$$B(t+1) \sim \text{Bin}(n, \mu).$$

At each time step the same number n individuals leave the population as enter it. We assume that these individuals are selected uniformly at random from the population. Let the number of individuals leaving the population at time step t who are infected with HIV be denoted $D(t)$. Conditional on $I(t)$, this distribution is hypergeometric. The hypergeometric distribution describes the probability of k successes in n draws from a finite population of size N that contains exactly K successes, as when counting the number k of red candies drawn when n total candies are drawn without replacement from a bowl containing K red candies and N white candies. Such a distribution is denoted Hypergeom(K, N, n)

In this model, we view an infected individual who is selected to leave the prison as being a "success" and a susceptible individual as a "failure"; at each time step, n prisoners total are selected to leave the prison, giving us

$$D(t+1) \sim \text{Hypergeom}(I(t)+M(t), N-I(t)-M(t), n).$$

The number of infected individuals within the population at time $t+1$ is equal to the size of the infected class at time t plus new infections from mixing and new infections from immigration minus the number of infected prisoners who have left the prison:

$$I(t+1) = I(t) + M(t) + B(t) - D(t).$$

The dynamics of this compartmental model are illustrated in Figure 1. The model defies an exact analysis. Results are typically derived through simulation. For a detailed discussion of the analysis and results in this particular model, see Gani, Yakowitz & Blount (1997).

While this model does a good job providing insights into the overall behavior of HIV within a population, it cannot be used to analyze the disparities in the ways in which

HIV affects populations that use intravenous drugs differently from those that do not. To address this, we introduce a model of our own that is designed to to capture this information.

3. Treating HIV as a Vector-Host Disease

To capture the role of shared needles in transmitting HIV within a population, we look to vector-host models for the spread of diseases such as malaria. Vector-host diseases are transmitted not through person-to-person contact, but rather through the action of a vector species. For example, in the case of malaria, mosquitoes are considered the vectors and humans are considered hosts; a mosquito becomes infected after biting an infected human, and an infected mosquito can then spread the disease to a susceptible human by biting them. In this way, the disease spreads only from vector to host and from host to vector.

We treat intravenous needles for HIV as if they were mosquitoes for malaria, that is as vectors for the disease. This allows us to adapt the standard compartmental model for HIV transmission to specifically capture this action. Unlike traditional vector-host models, however, our model also allows the disease to be transmitted without the action a vector (from human to human, via organic contact).

Individuals in the population are separated by drug-use status (i.e., whether or not they use intravenous drugs). Henceforth, we use a superscript d to denote variables and parameters associated with the drug-using group of individuals. We must track the vectors (i.e., the needles) in this model. We will denote variables and parameters associated with the needles in the population with a superscript v. In denoting total population sizes, for example, N is taken to mean the number of individuals who do not use drugs, N^d the size of the drug-using group, and N^v the number of needles available within the population.

At each discrete time step, all individuals mix uniformly and spread infection. Following that is a simultaneous inflow and outflow of individuals from the population. Finally, a drug-use phase of infection occurs: drug-using individuals each choose a needle uniformly at random to use drugs during this phase. We assume that the population of human individuals is of fixed size $N + N^d$. We also assume that there are a constant number N^v of needles within the prison at any time, of which n^v are randomly selected and exchanged for uninfected needles at each time step.

As in the previous model, assume that individuals make a single sexual contact during each time step after mixing homogeneously. Infections that result from mixing between infected and uninfected individuals (conditioned on the number of infected individuals at the previous time step) follow, as before, a binomial distribution:

$$M(t) \sim \text{Bin}(N - I(t), \beta \cdot (I(t) + I^d(t)))$$
$$M^d(t) \sim \text{Bin}(N^d - I^d(t), \beta \cdot (I(t) + I^d(t)))$$

We explicitly assume here that contacts between individuals are exclusively sexual contacts. The means of these variables, conditioned on the number of infectives present in the drug-free and drug-using populations, are given below. These means follow directly from properties of the binomial distribution.

$$E[M(t)] = (N - I(t)) \cdot \beta \cdot (I(t) + I^d(t))$$
$$E[M^d(t)] = (N^d - I^d(t)) \cdot \beta \cdot (I(t) + I^d(t))$$

Following these initial infections, individuals who use drugs interact with the population of needles, and infections are transmitted between those populations. Although it may not be immediately obvious, such infections follow an identical mechanism of action as infections transmitted through sexual contact. The probability of contacting an infection is, as before, proportional to the size of the infected class. We have $B^v(t)$ as the number of needles infected by drug users and $Q^d(t)$ as the number of drug users infected through contact with infected needles. The random variables associated with these movements (conditioned on $I^d(t-1)$ and $I^v(t-1)$) are as follows:

$$B^v(t) \sim \text{Bin}(H - I^v(t), \zeta \cdot I^d(t))$$
$$Q^d(t) \sim \text{Bin}(N^d - (I^d(t) + M^d(t)), \eta \cdot I^v(t))$$

where ζ represents the rate of disease transmission from infectious drug users to susceptible needles and η represents the rate of disease transmission from infectious needles to susceptible drug users. The corresponding expectations are:

$$E[B^v(t)] = (H - I^v(t)) \cdot (\zeta \cdot I^d(t))$$
$$E[Q^d(t)] = (N^d - (I^d(t) + M^d(t))) \cdot (\eta \cdot I^v(t))$$

Following internal transmission of HIV, the model now considers the simultaneous inflow of infected humans and outflow of both infected humans and infected needles. These variables are calculated in much the same way as they were in the previous model:

$$B(t) \sim \text{Bin}(n, \mu)$$
$$B^d(t) \sim \text{Bin}(n^d, \mu)$$
$$D(t) \sim \text{HyperGeom}(N, I(t) + M(t), n)$$
$$D^d(t) \sim \text{HyperGeom}(N^d, I^d(t) + M^d(t) + Q^d(t), n^d)$$
$$D^v(t) \sim \text{HyperGeom}(H, I^v(t) + B^v(t), n^v)$$

The expectations of these variables, which follow as properties of the binomial and hypergeometric distributions, are as follows:

$$E[B(t)] = n \cdot \mu$$
$$E[B^d(t)] = n^d \cdot \mu$$
$$E[D(t)] = \frac{n}{N}(I(t) + M(t))$$
$$E[D^d(t)] = \frac{n^d}{N^d}(I^d(t) + M^d(t) + Q^d(t))$$
$$E[D^v(t)] = \frac{n^v}{H}(I^v(t) + B^v(t))$$

This information allows us to calculate the mean of $I(t+1)$ and $I^d(t+1)$ conditioned on $I(t)$ and $I^d(t)$ respectively; however, the closed form expression for this quanity is extremely cumbersome. The dependence of, for example, $M(t)$ on $I^d(t)$ and, in turn, on $Q^d(t)$, $B^v(t)$, and so on, makes using such a formula without the assistance of computational software undesirable.

We do, however, include a recursive decomposition of the conditional expectations of $I(t)$ and $I^d(t)$, which is the basis for numerical computations:

$$E[I(t+1)|I(t)] = I(t) + E[M(t)] + E[B(t)] - E[D(t)]$$
$$E[I^d(t+1)|I^d(t)] = I^d(t) + E[M^d(t)] + E[B^d(t)] + E[Q^d(t)] - E[D^d(t)]$$

4. Model Insights

In this section we discuss the behavior of the model as revealed by our simulation study. Simulations were conducted using the computer software package R. The code used can be found in the Appendix.

The general behavior of all three populations (drug users, non-drug users, and needles) follows the pattern approximating logistic growth that manifests in the traditional compartmental model for the spread of HIV. The logistic behavior can be seen in Figure 2. At the beginning of the outbreak, disease incidence is low. It then increases sharply, exhibiting near exponential growth. Finally a plateau is reached at a certain level of infectivity.

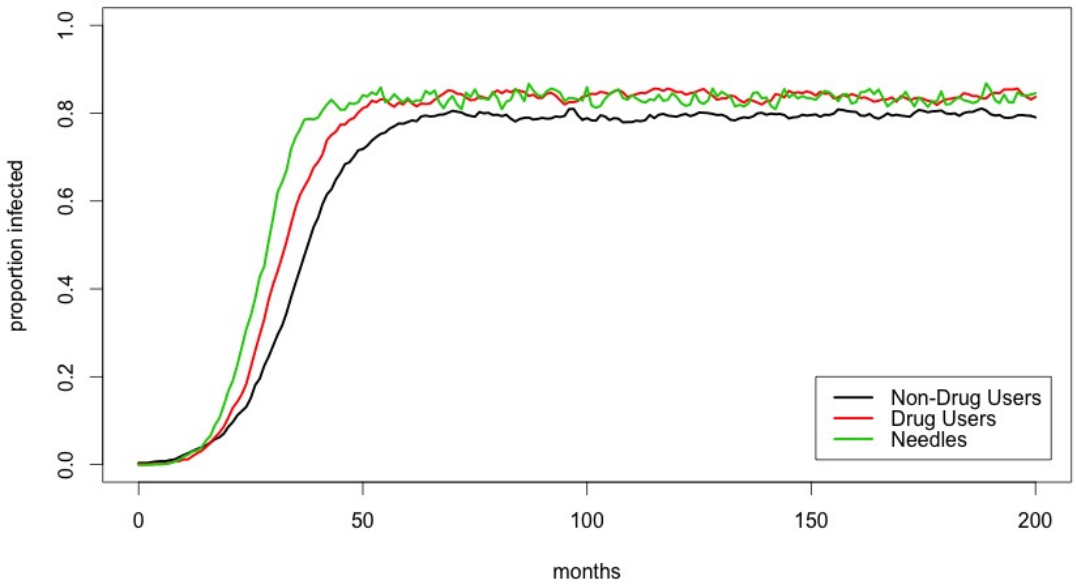

Figure 2. Incidence of HIV among drug users, non-drug users and needles

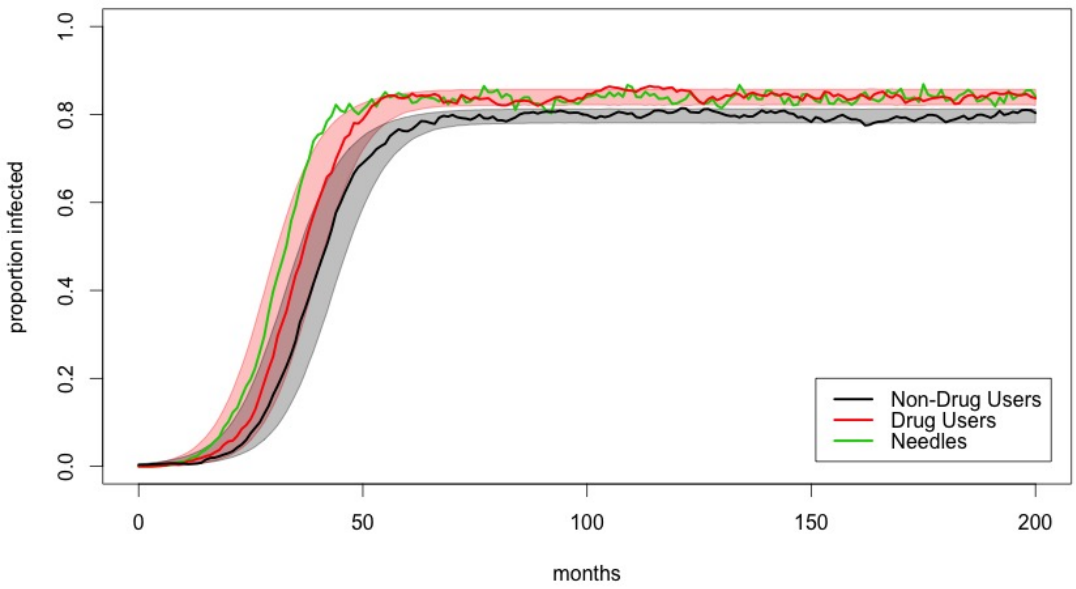

FIGURE 3. 95% confidence intervals for the incidence of HIV among drug users and non-drug users

Of interest is the behavior of the three populations relative to one another. In all simulations, a high rate of infection among the vector population (needles) precipitates high levels of infection in the drug-using population, which in turn precipitates high levels of infectivity among the population that does not use drugs.

Comparison to the conventional model developed earlier also shows that when the disease is allowed to spread through vector channels as well as through sexual contact, even the population of individuals that does not use drugs experiences a comparatively elevated incidence of disease when vector transmission is allowed, even though they are never exposed to the vectors directly. This is a result of continued sexual contact with a population for which the disease has a higher rate of transmissibility.

The stochastic model allows for finding 95% confidence intervals for the proportion of drug users and non-drug users who are infected at each time step. The results (Figure 3) show that in at least 95% of cases, the drug-using population has a higher final incidence of HIV than the non-drug-using population.

4.1. **The impact of a needle exchange program on epidemic dynamics.** One way the increased levels of HIV transmission (in the presence of drug use) have been addressed in applied situations is by implementing a needle exchange program. In theory, this limits the rate of infection in the population of needles and therefore reduces the gap between infection in drug-using and drug-avoiding groups within a population. Because this model has a built-in rate at which needles leave the population (and are replaced by new and therefore uninfected needles when they do so), we can examine the effect of a

hypothetical needle exchange program on the incidence of HIV within the population. In the most extreme (and effective) case, when every needle is exchanged before it can be shared with another individual, the two human populations will have probabilistically identical behavior. However, achieving such a high level of regular turnover may be difficult or impossible in reality, either because doing so is prohibitively expensive, or because drug users are reluctant to exchange their needles. .

Figures 4 and 5 illustrate the effect of increasing the rate of needle exchange within the population to 25% and 50% respectively. When a quarter of all needles are exchanged each month, the gap between the drug-using and non-drug-using populations persists. When half of all needles are exchanged, the percentage of infected needles drops precipitously and the two human populations have similar levels of infectivity throughout the epidemic. Analyzing the mean behavior of these processes reveals that increasing the availability of uninfected needles within the population is associated with a corresponding increase in the average length of time the disease takes to reach half its carrying capacity within the population (illustrating an exponential growth period that both begins later and occurs more slowly than in the case in which there is no attempt to reduce the availability of infected needles).

4.2. **Reduced Sexual Transmissibility.** Thus far, we have assumed that the disease is not treated in any way (and, critically, that individuals do not change their behavior when infected with HIV). In reality, however, a number of treatments for HIV exist and infected individuals rarely continue the same behavior when they learn that they have tested positive for the disease. Anti-retroviral drugs reduce the quantity of the virus present within an individual (and, therefore, the likelihood of transmission during sexual contact); quarantine reduces contact between infected and susceptible individuals; and convincing individuals to practice safe sex reduces the incidence of unprotected sexual contact. All of these treatment methods have the net effect of reducing the transmissibility of HIV within the population.

To illustrate the effect exchanging needles has on a population with a greatly reduced rate of sexual transmission of the disease, we simulate outbreaks where 25% and 50% of needles are exchanged at each time step for uninfected ones.

The impact of reducing the transmissibility of HIV via intravenous drug use is greatly magnified when sexual transmissibility is reduced (thus allowing transmission of the disease via intravenous drug use to play an outsize role in the spread of the disease). Examining Figures 6 and 7, it is quite clear that increasing the availability of uninfected needles within the population is associated with a corresponding increase in the average length of time the disease takes to reach half its carrying capacity within the population. And while the impact of a needle exchange program was modest in the absence of any other measures to mitigate the outbreak, the impact of such an exchange is several times larger when intravenous drug use is the primary avenue of transmission for the disease. It is also quite clear (and true for the mean of the process) that exchanging a larger proportion of needles had the effect of reducing the prevalence of HIV among individuals who do not use drugs.

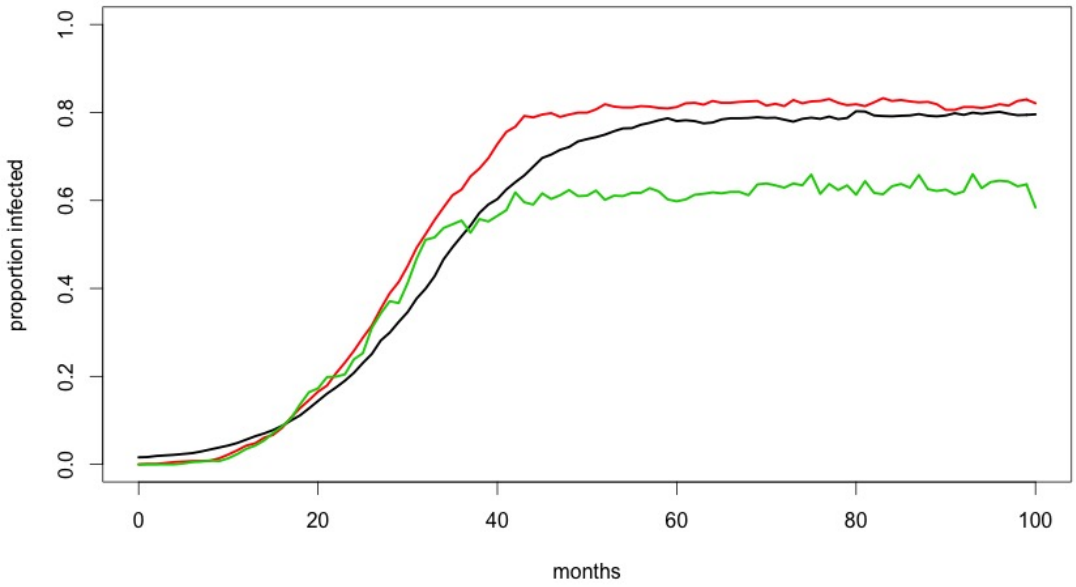

FIGURE 4. Incidence levels for drug users, non-drug users and needles, 25% of needles exchanged each month.

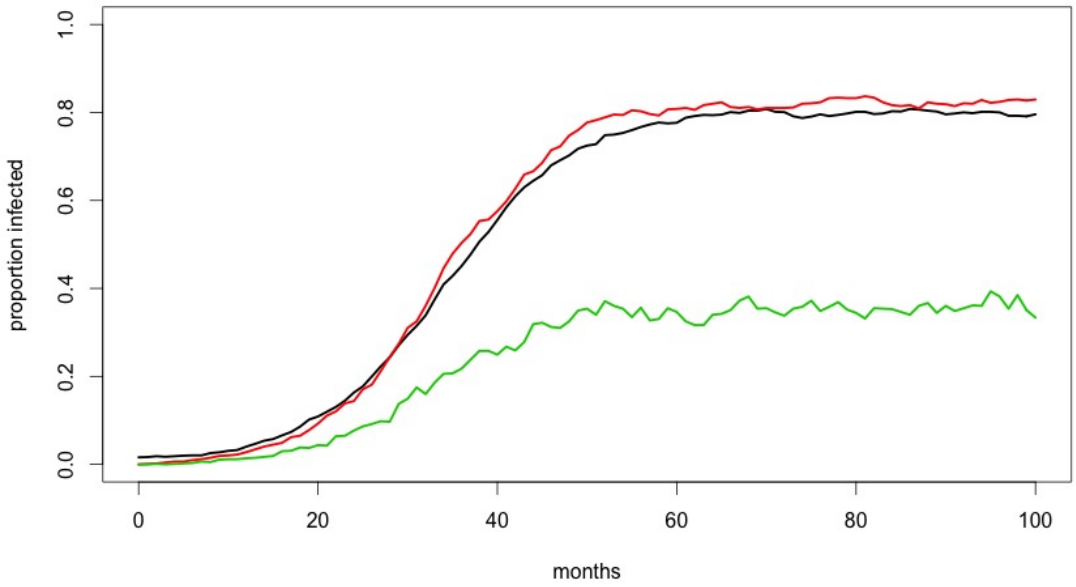

FIGURE 5. Incidence levels for drug users, non-drug users and needles, 50% of needles exchanged each month.

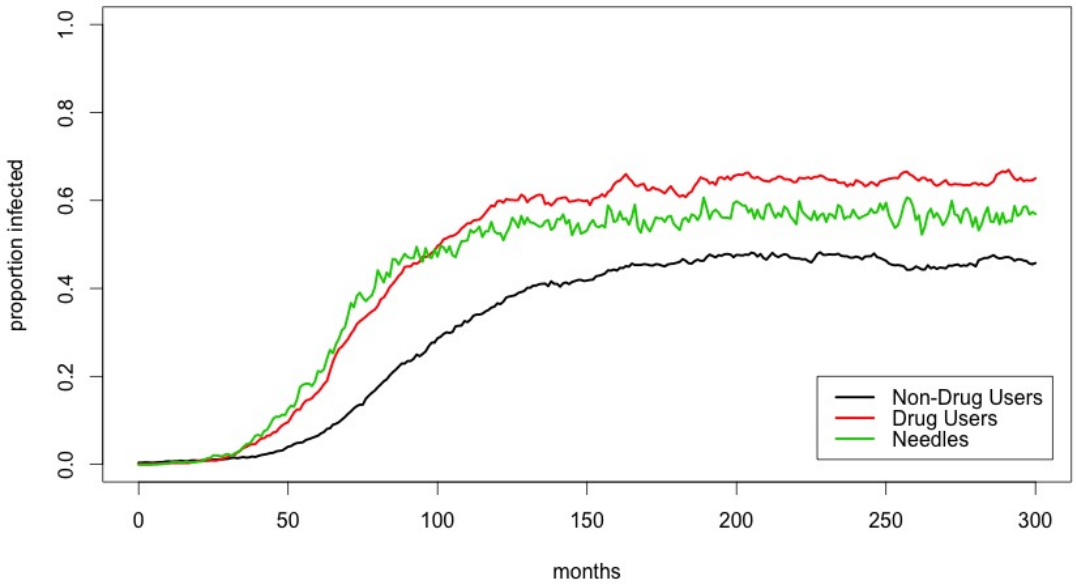

FIGURE 6. Infection rates with reduced sexual transmissibility paired with 25% of needles cleaned per month

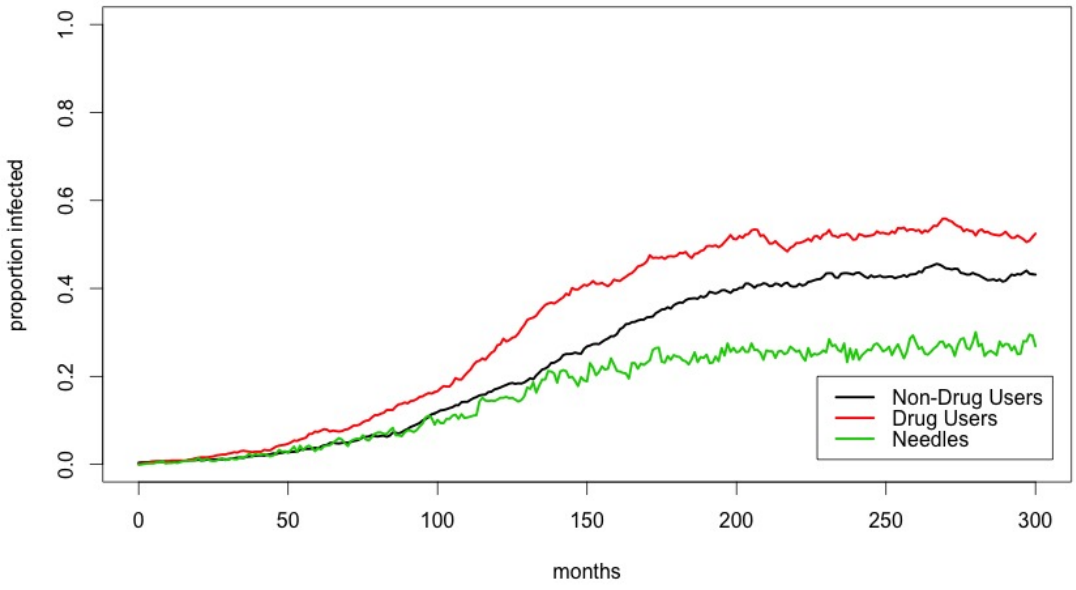

FIGURE 7. Infection rates with reduced sexual transmissibility paired with 50% of needles cleaned per month

4.3. **Model Sensitivity.** The parameters of greatest concern to anyone interested in the model's application are 1) the probability that an infected drug user passes the disease to a needle during the course of drug use (denoted by ζ), 2) the rate of transmissibility of the disease through sexual contact (denoted by β), 3) the probability that a drug user contacts HIV after using a contaminated needle (denoted by η). While the values of the parameters used in the previous sections are derived from previous research, we use one-at-a-time (OAT) testing to check the model's sensitivity to perturbations in parameter values. In OAT testing, we change the value of a single parameter and hold all others constant. We then observe simulation results for a wide range of possible parameter values and assess the impact of changing any given parameter.

We test ζ for values between 0.55 and 0.95 and η for values between 0 and 1. We find that the model is robust to changes in the values of these parameters, with the final proportion of infected prisoners remaining nearly constant for all values. Of particular interest is the size of the gap between the proportion of infected drug users and non-drug users; for modest perturbations, this gap does not change significantly.

We test β for values between 2 and 5, values suggested by the body of research on HIV. The model is quite sensitive to changes in the sexual transmissibility of the disease. However, this is not immediately concerning. β does not directly impact the transmissibility of HIV via vectors. Furthermore, epidemiologists expect some variation in the transmissibility of a disease within different communities (as a result of different behavior or immunological makeup). This variation is reflected in varying values of β and results in different epidemics. Refer back to section 4.2 for a discussion on the pairing of a low sexual transmissibility with high vector transmissibility.

5. Summary

The contribution of this study is to extend and adapt the basic compartment model of Gani, et al. to allow for both person-to-person and vector-to-person transmission of HIV within a closed community. Doing so allows us to better understand the behavior of individuals who are at high and low risk of becoming infected.

Our model shows that allowing individuals to exchange previously-used needles for clean ones reduces both the outsize level of infection within the drug-using population and the equilibrium level of infection present in the population that does not use drugs. This is consistent with the actual implementation of such programs, but it provides quantitative insight into the reach of the effect of such endeavors.

The model leaves room for future development and analysis. Much remains to be done in the analysis of the AIDS epidemic, especially as rates of intravenous drug use climb in proportion to the ongoing opioid epidemic. However, this model is novel in its capacity to bridge the gap between a conventional understanding of the spread of HIV and a more nuanced approach that can be used to help target prevention therapies at the individuals at highest risk of contacting the disease.

6. Acknowledgments

This paper developed from our Senior Comprehensive Exercise (Comps) at Carleton College in the Fall and Winter of 2015-2016. We would like to sincerely thank our Comps advisor, Professor Bob Dobrow, PhD, as well as the Carleton College Mathematics and Statistics Department, and our friends and family for their guidance and support throughout this learning experience.

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7. Appendix

7.1. **Index of Parameters.**

Parameter	Description	Value	Citation
N	Population (no drugs)	1562	
n	Monthly Turnover (no drugs)	53	[3]
N^d	Population (uses drugs)	938	[4]
n^d	Monthly Turnover (uses drugs)	32	[3]
μ	USA HIV Rate	0.004	[8]
R_0	Reproduction Number	3	[13]
β	Transmission Rate (human-to-human)	0.00001	[13]
N^v	Needle Population	938	
n^v	Monthly Turnover	94	
ζ	Transmission Rate (human-to-needle)	0.85	[11, 10]
η	Transmission Rate (needle-to-human)	0.065	[10]

7.2. **Code For Vector-Host Model.**

```
# General parameters:

r <- 200                                  # number of steps in the simulation
N <- 1562                                 # population of non drug-users
Nd <- 938                                 # population of drug users
n <- 53                                   # population turnover per step
                                          (no drug use)
nd <- 32                                  # population turnover per step
                                          (drug use)
mu <- 0.004                               # incidence of the disease in the
                                          population outside ours
r0 <- 3                                   # R_0
beta <- r0 * (n / N) * (1 / (N - n))      # transmissibility parameter
zeta <- 0.85                              # P(infectious drug user passes
                                          disease to needle | contact)
eta <- 0.065                              # P(susceptible drug user gets
                                          disease from needle | contact)
theta <- 0.1                              # P(disease does not survive on the
                                          needle)

##############################################################################

## Storage for simulation data:

# Needle Population:
```

```
H <- 938                        # population of needles
IV <- c(0, rep(NA, r))          # infected needles
Biv <- rep(NA, r)               # new needles infected with HIV
Div <- rep(NA, r)               # HIV+ needles which are replaced or on which
                                the infection dies
newYd <- rep(NA, r)             # new infections created by needle use
susIV <- rep(NA, r)             # susceptible needles used by HIV+ drug users
infIV <- rep(NA, r)             # infective needles used by HIV- drug users

# Drug-free Host Population:
M <- rep(NA, r)                 # new infections created by mixing (no IV
                                contact)
B <- rep(NA, r)                 # storage for HIV-positive births and
                                immigrants
D <- rep(NA, r)                 # storage for HIV-positive deaths and
                                emigrants
Y <- c(6, rep(NA, r))           # storage for HIV+ individuals in the
                                population with 25 initially infected

# Drug-using Host Population:
drugshiv <- rep(NA, r)          # number of HIV+ drug users
Md <- rep(NA, r)                # storage for new infections created by
                                mixing (non-intravenous contact)
Mdi <- rep(NA, r)               # storage for new infections created by
                                mixing with needles
Bd <- rep(NA, r)                # storage for HIV-positive births and
                                immigrants
Dd <- rep(NA, r)                # storage for HIV-positive deaths and
                                emigrants
Yd <- c(0, rep(NA, r))          # storage for HIV+ individuals in the
                                population with 25 initially infected

##############################################################################

## Run the simulation:

for(i in 1:r){

## Mixing phase:
  M[i] <- rbinom(1, N - Y[i] + Nd - Yd[i], beta * (Y[i] + Yd[i]))
       # infections transmitted NOT through drug use (organically)
  Md[i] <- rhyper(1, M[i], N + Nd - Y[i] - Yd[i] - M[i], Nd - Yd[i])
       # of those, which infections took place in drug users
  M[i] <- M[i] - Md[i]
       # the remainder of infections took place in non-drug users
```

```
## Drug-use phase:
  Mdi[i] <- rbinom(1, Nd - (Yd[i] + Md[i]), eta*(IV[i])/H)
  Biv[i] <- rbinom(1, H - IV[i], zeta*(Yd[i] + Md[i])/Nd)

## Natural population turnover phase:
  B[i] <- rbinom(1, n, mu)
       # infectious "births" among non drug users
  Bd[i] <- rbinom(1, nd, mu)
       # infectious "births" among drug users
  D[i] <- rhyper(1, Y[i] + M[i], N - (Y[i] + M[i]), n)
       # infectious "deaths" among non drug users
  Dd[i] <- rhyper(1, Yd[i] + Md[i] + Mdi[i], Nd - (Yd[i] + Md[i] +
  Mdi[i]), nd)
       # infectious "deaths" among drug users
  Div[i] <- rbinom(1, IV[i] + Biv[i], theta)
       # needles on which the disease dies


## Count total infected before continuing to next step in simulation
  Yd[i+1] <- Yd[i] + Md[i] + Bd[i] - Dd[i] + Mdi[i]
       # total infected drug users
  IV[i+1] <- IV[i] - Div[i] + Biv[i]
       # total infectious needles
  Y[i+1] <- Y[i] + M[i] + B[i] - D[i]
       # total infectious non-drug users
}
```

Student biographies

Michelle Marinello: Michelle Marinello is a mathematics major at Carleton College. She will be graduating with the class of 2017.

Rachel Martin: Rachel Martin graduated from Carleton College in 2016 with a degree in Mathematics. She is currently working as a medical scribe in an ER in Minneapolis, and will be entering the class of 2021 at the University of Colorado School of Medicine.

Evan Olawsky: (*Corresponding author:* olaws004@umn.edu) Evan Olawsky graduated from Carleton College in 2016 with a degree in statistics. He is currently working towards his PhD in biostatistics at the University of Minnesota-Twin Cities.

Margaret Sauer: Margaret Sauer graduated in 2016 from Carleton College with a degree in mathematics. Margaret is currently employed at the Federal Reserve Bank of Minneapolis, where she works as a research analyst.