The impact of the effectiveness of needle exchange programs on addiction-treatment dynamics

Mayra Coronado [1], Natalia de la Torre [2], Omari Gill Jr [3], Aidan Grennell[4], Romarie Morales[5], Aprillya Lanz[6], Muntaser Safan[5]

[1] Department of Mathematics, Regis University, Denver, Colorado

[2] Department of Mathematics, Mary Baldwin College, Staunton, Virginia

[3] Department of Engineering, Clark Atlanta University, Atlanta, Georgia

[4] Department of Mathematics, Western Carolina University, Cullowhee, North Carolina

[5] Applied Mathematics for the Life and Social Sciences, Arizona State University, Tempe, Arizona

[6] Department of Mathematics, Norfolk State University, Norfolk, Virginia

Abstract

The aim of this research is to determine the impact of needle exchange programs as motivation for intravenous drug users to seek treatment for addiction. A mathematical model of the dynamics of a population of drug users that incorporates a needle exchange program is formulated. We define the basic addiction reproduction number for the proposed model and explore its role in the prevalence and control of needle-sharing drug addiction. Specifically, the local stability of the injection-addiction free and endemic equilibria are determined. Sensitivity analysis is conducted to determine the impact of perturbations of key parameters on the basic reproduction number and endemic level of the subpopulations. Results include a notable impact of the ineffectiveness of the needle exchange program on the proportion of the subpopulation in treatment. Furthermore, conditions necessary for an injection-addiction free population are determined.

1 Introduction

Intravenous (IV) drug use is a chronic problem in many communities within the United States. Although recreational IV drug use has decreased in the past twenty years, heavy injection drug use remains a serious issue across many different demographics [7]. Among the many issues associated with injection drug use, disease spread is a significant problem in IV drug user (IDU) communities due to lack of access to sterile injection equipment [11]. Thus, many IDUs share needles and injection equipment, allowing diseases such as hepatitis B virus (HBV) and human immunodeficiency virus (HIV) to be transmitted quickly throughout an IDU population [5].

There are two distinct approaches when considering IV drug addiction. The most common method, which is referred to as the abstentionist model, encourages IDUs to seek treatment through rehabilitation centers [9]. This approach focuses on changing behavior to abstain from drug use and tends to be most effective if an IDU is self-motivated to seek treatment [3]. The other approach is a harm-reduction model, which recognizes that not all IDUs have the desire or ability to change their behavior. Harm reduction, also called harm minimization, risk reduction, or risk minimization, approaches addiction with a series of goals, seeking to minimize risk associated with using injection drugs [9]. Although there are many different manifestations of harm reduction practices, the most common approach to minimizing risk with respect to IV drug use is providing access to a needle exchange program.

Needle exchange programs (NEPs), also called syringe exchange programs, provide a location for IDUs to dispose of used syringes in exchange for obtaining clean injection equipment. Emerging in the late 1980's as a response to the growing epidemic of HIV among IDUs, NEPs were illegal in many locations in North America [9]. By the late 1980's, NEPs had been developed through the Department of Health in several major cities, including New York City and Seattle [9]. As of 2008, there were almost 200 active NEPs across the United States [3, 5].

The purpose of an NEP is two-fold: first, it seeks to eliminate needle-sharing behaviors, therefore minimizing the risk of disease spread in a community. Second, NEPs help remove used needles from a community by providing a safe, appropriate place for needle disposal [9]. Harm reduction

approaches, by definition, do not explicitly aim to change addicts' behavior; however, over 90% of NEPs in the United States offer resources, counseling, and information on treatment and rehabilitation programs for addiction, and awareness of treatment options is one of the main reasons IDUs choose to seek treatment [3, 5]. Since NEPs are an easy way to distribute information about treatment resources, it is important to understand what, if any, role NEPs have on IV drug users ultimately seeking treatment.

In 1989, Edward Kaplan produced the most widely-used mathematical model to study the effectiveness of an NEP in decreasing disease spread among IDUs in New Haven, Connecticut [11, 14, 12]. Building on his earlier work, Kaplan constructed a theory of needle circulation as a method of quantifying how long a needle remained active in an IDU population [13]. Kaplan's approach treated the needles as a population and created a method of tracking the needles, which helped rectify inaccurate data that was self-reported by IDUs on needle-sharing habits and injection patterns. David Greenhalgh and Fraser Lewis expanded Kaplan's work in 2001 by examining the interactions between three different classes of infected needles and three classes of infected addicts, concluding that there is a strong relationship between the spread of disease and the ways in which addicts and needles interact [8]. In general, most of the mathematical models that consider NEPs are focused on the spread of diseases, such as HIV and HBV, in IDU populations. Regarding addiction models, White and Comiskey created a model to describe the dynamics of a heroin-addicted population [19]. They considered those who are susceptible to begin using heroin, those in active addiction, and those in treatment, allowing for relapse from treatment to heroin use. The White-Comiskey model described the dynamics within a population of IDUs from an abstentionist framework, and does not consider the role of NEPs in an addict population.

Our research synthesized these approaches, considering the impact of an NEP on the addiction process. The model we present does not consider the impact of NEPs on the spread of diseases among IDUs as the Kaplan and Greenhalgh models do, but amends the White-Comiskey model to consider the impact of an NEP on IDUs seeking treatment. By defining the parameters that lead to and from the NEP in relation to one another, we establish a relationship between these parameters that defines the overall effectiveness of the program. Furthermore, we consider the

injection-addiction free equilibrium, the point at which no one in the population is engaging in IV drug use. We determine what conditions are necessary with the presence of an NEP to maintain a basic reproduction number less than one; that is, what conditions lead to the cession of IV drug use within a population.

There are several relevant questions to address from this model construction. First, at what minimum rate must people begin utilizing an NEP to create a population free from needle-sharing behavior? In correlation, at what maximum rate may people leave the NEP to maintain population dynamics free from needle-sharing behavior? Third, what impact does the effectiveness of the NEP have on the endemic level of treatment? Finally, which parameters are most important to the overall system? To address these questions, we consider two models. First, we consider a model that includes a relapse rate from treatment. Second, we consider an amended model where relapse is not taken into account. Although the rate of relapse is high among injection drug users, the purpose of this research is to study the impact of NEPs on those entering treatment and is not concerned with the impact of relapse on the injection-addiction system [2].

2 Formulation of the Model

We adapt the model proposed by White and Comiskey [19] and consider a non-constant population of people engaging in IV drug use. As a result of interactions with IDUs, people will either begin using injection drugs and transition to a population that shares needles with one another or remain free from injection-addiction until death. People in the needle-sharing population will either seek treatment, begin using an NEP, or continue sharing needles until death. People using the NEP will either abandon the program and resume sharing needles, seek treatment, or remain in the NEP until death. Figure (2) shows a diagram for the transition between population states and Table (1) defines the model parameters and states. Those in treatment will either relapse to addiction and sharing needles or remain isolated from injection drug use until death. In constructing this model, we make the following assumptions:

- The total population is a population of addicts that mix homogeneously and varies in size.

- IV drug use is initiated through contact with someone already engaged in IV drug use; thus, only the needle-sharing population has contact with the non-IDU population.
- Not all IDUs will utilize an NEP; thus, we define an ineffectiveness rate in Equation (6).
- Some portion of the IDU population using an NEP will abandon the program.
- Those in treatment are not engaging in IV drug use and are therefore isolated from needle-using communities.
- When relapse is considered, addicts relapse into risky behavior; thus, relapse only returns to a needle-sharing population.

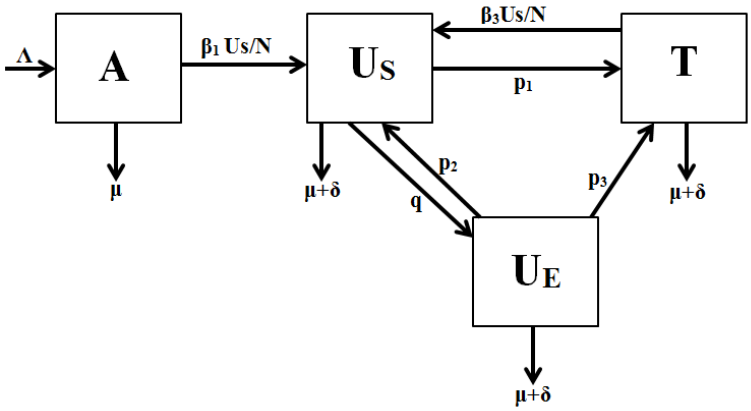

Figure 1: This figure shows the representation of a population of drug users as they transition through injection drug abuse, possible interaction with an NEP, and treatment for addiction.

The dyamics of the population are governed by the following system of ordinary differential equations:

$$\dot{A} = \Lambda - \beta_1 A\frac{U_S}{N} - \mu A \tag{1}$$

$$\dot{U_S} = \beta_1 A\frac{U_S}{N} - (q + p_1 + \mu + \delta)U_S + p_2 U_E + \beta_3 T\frac{U_S}{N} \tag{2}$$

$$\dot{U_E} = qU_S - (\delta + \mu + p_2 + p_3)U_E \tag{3}$$

$$\dot{T} = p_1 U_S + p_3 U_E - (\delta + \mu)T - \beta_3 T\frac{U_S}{N} \tag{4}$$

$$\dot{N} = \Lambda - \mu N - \delta(U_S + U_E + T) \tag{5}$$

where

$$N = A(t) + U_S(t) + U_E(t) + T(t).$$

Table 1: Parameter Definitions

Parameter	Definition	Unit	Reference
A	population susceptible to IV drug use	People	[6, 10, 15]
U_S	population engaged in IV drug use and share needles	People	[6, 10, 15, 18]
U_E	population engaged in IV drug use using an NEP	People	[15]
T	population in treatment for IV drug addiction	People	[4]
N	total population	People	[1, 10]
Λ	recruitment rate	people	[1, 6, 10, 17]
β_1	rate at which someone transitions to IV drug use	time^{-1}	[16]
β_3	rate of relapse	time^{-1}	[2]
μ	natural death rate	time^{-1}	[10]
δ	drug-related death rate	time^{-1}	[6, 10, 17]
p_1	rate at which people sharing needles seek treatment	time^{-1}	[4, 6, 10, 18]
p_2	rate at which people stop using an NEP	time^{-1}	[6, 10, 18]
p_3	rate at which people who use an NEP seek treatment	time^{-1}	[4, 18]
q	rate at which people begin using an NEP	time^{-1}	[6, 10, 18]

Equation (1) describes the average rate of change in the number of addicts (A) susceptible to transitioning to IV drug addiction by considering a recruitment rate (Λ) and subtracting number of individuals that exits via positive contact between an IDU and the susceptible population (β_1), or via natural death (μ). Equation (2) represents the average rate of change in the population of IDUs who exchange needles (U_S) with assumed homogenous mixing. Susceptible individuals

enter the needle-sharing compartment through positive contact with an IDU. Intravenous drug users may enter this compartment if they abandon an NEP and begin sharing needles with other IDUs. The population exits this compartment by entering the treatment class (p_1), through natural death or drug-related death (μ and δ, respectively), or by engaging with an NEP (q). Equation (3) represents the average rate of change in population of IDUs actively using an NEP, entering the U_E population directly from the U_S population. Those in an NEP may seek treatment for addiction (p_3), abandon the NEP (p_2), or die through natural causes (μ) or as a result of drug abuse (δ). We consider the rate at which people leave the U_E compartment, disregarding death, as $p_2 + p_3$. Thus, the ineffectiveness of the NEP is defined as the ratio of rates of people leaving the NEP to return to needle-sharing behavior, and is represented by the parameter α, where

$$\begin{aligned} \alpha &= \frac{p_2}{p_2 + p_3}, \\ p_2 &= \frac{\alpha}{1-\alpha} p_3. \end{aligned}$$

Equation (4) describes the average rate of change in the population seeking treatment (T) for intravenous drug addiction. Entry to the T compartment is through both the population of IDUs who are in an NEP and the population of IDUs who are sharing needles.

Analysis of Injection-Addiction Model with Relapse

We consider the case where $\beta_3 > 0$ and thus, there is some relapse from treatment to the population engaged in sharing needles.

Basic Reproductive Number

The basic reproductive number, R_0, is defined as the average number of secondary cases produced by one case of sharing needles during the time when an IDU is introduced into a population of addicts that is completely free from needle-sharing. Thus, R_0 is given by

$$
\begin{aligned}
R_0 &= \frac{\beta_1(p_2+p_3+\mu+\delta)}{(p_1+q+\mu+\delta)(p_2+p_3+\mu+\delta)-p_2q}, \\
&= \frac{\beta_1}{q+p_1+\mu+\delta}\left[\frac{1}{1-\Delta}\right] \\
&= \tilde{R_0}+\frac{\Delta}{1-\Delta}
\end{aligned}
$$

where

$$
\begin{aligned}
\tilde{R_0} &= \frac{\beta_1}{q+p_1+\mu+\delta}, \\
\Delta &= \frac{qp_2}{(p_2+p_3+\mu+\delta)(q+p_1+\mu+\delta)}.
\end{aligned}
$$

Here, $\tilde{R_0}$ is the basic reproduction number if the NEP is fully effective; that is, if $p_2 = 0$, then R_0 is represented by $\tilde{R_0}$. Thus, R_0 is the sum of two terms: one term represents the basic reproductive number for a fully effective NEP, and the other term is an excess reproductive number due to the waning of the NEP.

R_0 can also be written as

$$
R_0 = \frac{\beta_1}{M}, \tag{6}
$$

where

$$
\begin{aligned}
M &= q+p_1+\mu+\delta-Qp_2, \\
Q &= \frac{q}{\mu+\delta+p_2+p_3}.
\end{aligned}
$$

Here, $1/M$ represents the average length of the time period during which an injection-addiction individual can transmit the behavior of needle-sharing.

Injection-Addiction Free Equilibrium

For this model, we consider the injection-addiction free equilibrium as the point at which there are no IDUs within a susceptible population of addicts. The injection-addiction free equilibrium point is obtained by setting the left-hand side of (1)-(5) equal to zero and setting $U_S = 0$ and $U_E = 0$. Thus, we obtain the injection-addiction free equilibrium point $(\frac{\Lambda}{\mu}, 0, 0, 0)'$ where "*prime*" denotes vector transpose. To test the stability of the injection-addiction-free equilibrium, we consider the Jacobian matrix evaluated at $(\frac{\Lambda}{\mu}, 0, 0, 0)'$.

$$J_{(\frac{\Lambda}{\mu},0,0,0)} = \begin{pmatrix} -\mu & -\beta_1 & 0 & 0 \\ 0 & \beta_1 - (q + p_1 + \mu + \delta) & p_2 & 0 \\ 0 & q & -(\mu + \delta + p_2 + p_3) & 0 \\ 0 & p_1 & p_3 & -(\mu + \delta) \end{pmatrix} \tag{7}$$

Two of the eigenvalues for this Jacobian (7) are given by

$$\lambda_1 = -\mu, \lambda_2 = -(\mu + \delta) < 0$$

while the other two correspond to the eigenvalues of the sub-Jacobian

$$J_2 = \begin{pmatrix} \beta_1 - (q + p_1 + \mu + \delta) & p_2 \\ q & -(\mu + \delta + p_2 + p_3) \end{pmatrix}$$

In order for the matrix J_2 to have negative eigenvalues, we must have $\text{tr}(J_2) < 0$ and $\det(J_2) > 0$. The second condition holds if and only if $R_0 < 1$ and this condition ensures that the first condition is satisfied, where R_0 is the basic reduction number and is given by (6). Thus, we show the following proposition.

Proposition 1. *The injection-addiction free equilibrium* $E_0 = (\frac{\Lambda}{\mu}, 0, 0, 0)'$ *is locally asymptotically*

stable if and only if $R_0 < 1$.

Endemic Equilibrium and Stability

On putting the derivatives in the left-hand side of equations (1)-(5) equal to zero and solving the resulting system with respect to the model states, we arrive at the proportions of subpopulations in the endemic state as

$$\begin{aligned} x = \frac{A^*}{N^*} &= \frac{\mu+\delta}{\delta+\mu+\beta_1 y_s}, \\ y_e = \frac{U_E^*}{N^*} &= \frac{q y_s}{\mu+\delta+p_2+p_3}, \\ z = \frac{T^*}{N^*} &= \frac{y_s}{\delta+\mu+\beta_3 y_s}\left(p_1 + \frac{p_3 q}{\mu+\delta+p_2+p_3}\right), \end{aligned} \tag{8}$$

where y_s is given by

$$\beta_1\beta_3(1+Q)y_s^2 + (\beta_1 M + \beta_3[(1+Q)(\mu+\delta) - \beta_1])y_s + (\mu+\delta)[M-\beta_1] = 0 \tag{9}$$

and

$$\begin{aligned} Q &= \frac{q}{\mu+\delta+p_2+p_3}, \\ M &= q + p_1 + \mu + \delta - p_2 Q. \end{aligned}$$

Equation (9) can have up to two feasible solutions. It has a unique solution if $\beta_1 > M$. However, if $\beta_1 < M$ and $\beta_3 > \frac{M^2}{p_3 Q + p_1}$, it can have two solutions. The condition $\beta_3 > \frac{M^2}{p_3 Q + p_1}$ is necessary but not sufficient for the existence of two solutions. In fact, it is the condition for the existence of backward bifurcations, which means that the needle-sharing problem persists in the population even if R_0 is reduced to below one.

Since the analytical stability is difficult to establish, we consider the numerical stability of the endemic equilibrium. We use the parameter values given in Table 4 with the exception of β_1 and β_3, which are manipulated to fit the conditions of the following two cases.

Case 1: $\beta_1 > M$

For the case where $\beta_1 > M$, there is a unique solution for Equation (9) and therefore there is a unique endemic equilibrium for the model (1)-(5). For $\beta_1 = 0.0168$ and $\beta_3 = 0.023145$, the endemic equilibrium is

$$E_1 = (6272.6657, 4016.26855, 6608.98791, 1695.4217)'$$

which produces the following characteristic polynomial

$$\lambda^4 + 2.78 * 10^{-3}\lambda^3 + 1.90 * 10^{-3}\lambda^2 + 1.1 * 10^{-5}\lambda + 6.9 * 10^{-7} = 0.$$

The above characteristic polynomial has the eigenvalues

$$\lambda_1 = -0.0092, \lambda_2 = -0.0092, \lambda_3 = -0.0072, \lambda_4 = -0.0022.$$

Since all eigenvalues are negative, the endemic equilibrium point E_1 is stable when $\beta_1 > M$.

Case 2: $\beta_1 < M$ *and* $\beta_3 > \dfrac{M^2}{p_3 Q + p_1}$

If we choose β_1 to be slightly less than M and $\beta_3 > \dfrac{M^2}{p_3 Q + p_1}$, there are two possible endemic equilibria. For example, if $\beta_1 = 0.00505996$ and $\beta_3 = 0.110154$, the two endemic equilibria are given by E_{11} and E_{12} where

$$E_{11} = (28584.9, 5071.85, 1091.82, 513.813)', E_{12} = (58618, 99.0248, 21.3171, 34.3771)'.$$

Thus, the corresponding characteristic polynomials are given by

$$P_{E11} = \lambda^4 + 0.0864\lambda^3 + 0.0014\lambda^2 + 1.7 * 10^{-6}\lambda + 8.89119 * 10^{-11} = 0,$$

$$P_{E12} = \lambda^4 + 0.0699\lambda^3 + 2.7246 * 10^{-4}\lambda^2 + 1.4425 * 10^{-7}\lambda - 6.1783 * 10^{-12} = 0.$$

The characteristic polynomials have the eigenvalues

$$\lambda_{11} = -0.01945, \lambda_{12} = -0.06568, \lambda_{13} = -0.0006439 + 0.0005305\mathbf{i}, \lambda_{14} = -0.0006439 - 0.0005305\mathbf{i},$$

and

$$\lambda_{21} = -0.0658, \lambda_{22} = -0.00346, \lambda_{23} = -0.00068, \lambda_{24} = 0.0000398.$$

The eigenvalues generated from E_{11} have all negative real parts. Therefore, E_{11} is locally asymptotically stable. However, the eigenvalues generated by E_{12} contain one with a positive value, which implies that E_{12} is unstable.

From Case 1, we see that when $\beta_1 > M$, there exists a unique endemic equilibrium point that is stable. Therefore, when R_0 is greater than one, there exists a unique equilibrium point that is locally asymptotically stable. From Case 2, we see two endemic equilibrium points although the basic reproductive number is less than one. Only one of these two points is locally asymptotically stable.

3 Analysis of a perfect-treatment model

We consider the case where treatment is effective and the rate of relapse, $\beta_3 = 0$. The system of differential equations governing this model is given in Appendix 9.3.

Analysis of equilibria

The relapse-free model has the same injection-addiction-addiction free equilibrium and stability $E_0 = (\frac{\Lambda}{\mu}, 0, 0, 0)'$ outlined in Proposition 1 and the same basic reproduction number, R_0 shown in Equation (6). Now, we consider the case in which U_S and U_E do not equal zero in order to obtain the injection-addiction endemic equilibrium point. The endemic equilibrium (A^*, U_S^*, U_E^*, T^*) is unique and is given by the following equations

$$
\begin{aligned}
X^* &= \frac{\mu+\delta}{\delta+\mu+\beta_1 Y_S^*}, \\
Y_S^* &= \frac{(\mu+\delta)(\beta_1-M)}{\beta_1 M}, \\
Y_E^* &= QY_S^*, \\
Z^* &= \frac{(p_1+Qp_3)}{\delta+\mu} Y_S^*, \\
N^* &= \frac{\Lambda}{\left[\mu+\delta-\frac{\delta}{R_0}\right]},
\end{aligned} \tag{10}
$$

where

$$
X^* = \frac{A^*}{N^*}, \quad Y_S^* = \frac{U_S^*}{N^*}, \quad Y_E^* = \frac{U_E^*}{N^*}, \quad Z^* = \frac{T^*}{N^*}.
$$

To determine the stability of the endemic equilibrium, we consider the Jacobian matrix evaluated at

$$
\begin{aligned}
A^* &= \frac{\Lambda}{(\mu+\delta)R_0-\delta}, \\
U_S^* &= \frac{\Lambda(\mu+\delta)}{M} \frac{(1-\frac{1}{R_0})}{\mu+\delta(1-\frac{1}{R_0})}, \\
U_E^* &= \frac{\Lambda(\mu+\delta)Q}{M} \frac{(1-\frac{1}{R_0})}{\mu+\delta(1-\frac{1}{R_0}))}, \\
T^* &= \frac{\Lambda(p_1+p_3Q)}{M} \frac{1-\frac{1}{R_0}}{\mu+\delta(1-\frac{1}{R_0})},
\end{aligned}
$$

which can be viewed in Appendix 9.2. It is clear that the endemic equilibrium exists if and only if $R_0 > 1$. By substituting the parameter values from Table 4, we determine the unique endemic equilibrium point

$$
(1931.036, 6755.86, 2999.42, 3991.40),
$$

which produces the characteristic polynomial given by

$$
\lambda^4 + 0.425\lambda^3 + 0.00648\lambda^2 - 0.000635\lambda - 610^{-8} = 0.
$$

The eigenvalues associated with the Jacobian at the endemic equilibrium are

$$\lambda_1 = -0.00323, \lambda_2 = -0.00536507, \lambda_3 = -0.0376654 - 0.0144795\mathbf{i}, \lambda_4 = -0.0376654 + 0.0144795\mathbf{i}.$$

Since the real part of all eigenvalues are negative, the endemic equilibrium is locally asymptotically stable.

4 Normalized Sensitivity Analysis

Normalized Sensitivity Analysis of R_0

In considering the dynamics of the injection-addiction system, we conduct normalized sensitivity analysis on R_0 and the endemic proportions of subpopulations to determine the impact of parameter perturbations on the dynamics of the system. The normalized sensitivity indices given by Equation (8) are useful to understand which parameters impact the basic reproduction number as well as the endemic equilibrium points. By computing the normalized sensitivity indices, we consider the percent change in the output with respect to a percent change in the parameter input. Those parameters with the largest magnitude of change impact the compartment the most; the sign indicates whether the change produces an increase or decrease.

We first consider the normalized sensitivity indices for R_0 by taking the partial derivative of R_0 with respect to each parameter and multiply the derivative with the ratio of the parameter to R_0. For example, to determine the sensitivity of R_0 with respect to β_1, we compute the following:

$$S_{\beta_1} = \frac{\beta_1}{R_0}\frac{\partial R_0}{\partial \beta_1} = \frac{\beta_1 M}{\beta_1}\frac{1}{M} = 1. \tag{11}$$

This value represents the percent change in R_0 with respect to a 1% change in the parameter value β_1. Similarly to Equation (11), we compute the following sensitivity indices for R_0.

Analyzing the percent change in R_0 with respect to the percent change in q, p_1, p_2, p_3, μ, and δ,

respectively, we obtain the following sensitivity indices:

$$\begin{aligned}
\frac{q}{R_0}\frac{\partial R_0}{\partial q} &= -\frac{Q}{M}(p_3+\mu+\delta),\\
\frac{p_1}{R_0}\frac{\partial R_0}{\partial p_1} &= -\frac{p_1}{M},\\
\frac{p_2}{R_0}\frac{\partial R_0}{\partial p_2} &= \frac{p_2Q^2}{qM}(p_3+\mu+\delta),\\
\frac{p_3}{R_0}\frac{\partial R_0}{\partial p_3} &= \frac{-p_2p_3Q^2}{qM},\\
\frac{\mu}{R_0}\frac{\partial R_0}{\partial \mu} &= -\frac{\mu}{M}(1+\frac{p_2}{q}Q^2),\\
\frac{\delta}{R_0}\frac{\partial R_0}{\partial \delta} &= -\frac{\delta}{M}(1+\frac{p_2}{q}Q^2).
\end{aligned}$$

We use the parameters values from Table 4 to study the sensitivity of R_0 to each parameter. We compute normalized sensitivity analysis on all parameters, but we are only concerned with analyzing the impact of parameters that we are able to control: p_1, p_2, p_3 and q. The numerical solutions to the sensitivity of R_0 with respect to each parameter are given by Table 2 and a graphical depiction is given by Figure 2.

Table 2: Percent Change in R_0 with respect to parameters

Parameter	p_1	p_2	p_3	q	μ	δ	β_1
% change	-0.12%	0.29%	-0.12%	-0.32%	-0.15%	-0.58%	1%

Although we cannot control the successful contact rate, it is important to note that R_0 is most sensitive to perturbations in β_1. Of parameters that are within our control, R_0 is most sensitive to changes in q and p_2. As q increases, R_0 decreases by 0.32%, while an increase in p_2 increases R_0. Thus, as people enter the NEP, there are less people in the population to spread needle-sharing behavior, and thus R_0 decreases. However, as people abandon the NEP, there are more people in the population that are sharing needles, and therefore the basic reproductive number increases.

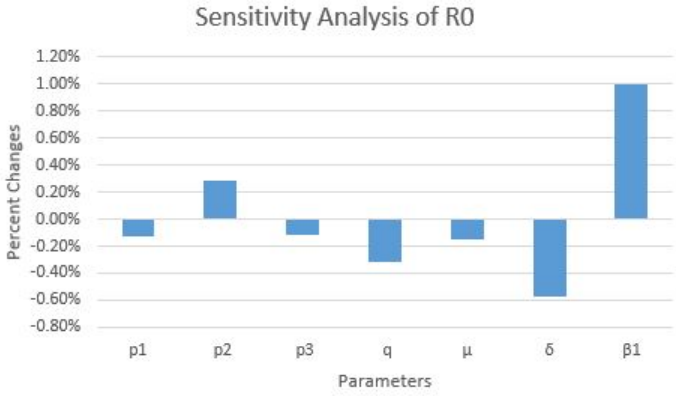

Figure 2: Change in R_0 with respect to change in parameters

Normalized Sensitivity Analysis of Endemic Proportions of Subpopulations

We consider the normalized sensitivity indices of the endemic proportions of each subpopulation represented in the compartments of Equation (10). Recall that in the endemic steady state, X^* represents the proportion of the population susceptible to begin IV drug use, Y_S^* represents the proportion of the population sharing needles, Y_E^* represents the proportion of the population using an NEP, and Z^* represents the proportion of the population in treatment. We are interested in studying which parameter values have the greatest impact on the system overall; therefore, we study the normalized sensitivity indices for X^*, Y_E^*, Y_S^*, and Z^*, following the same process described in Equation (11). We further examine the parameters that have the greatest impact on Z^* in order to study how the NEP impacts the endemic proportion of the subpopulation that seeks treatment. From the resulting equations, we substituted the numerical parameter values from Table 4 into the equations to determine the sensitivity of each endemic proportion of the subpopulations with respect to $\beta_1, p_1, p_2, p_3, q, \mu$, and δ. To analyze the sensitivity, we only consider those parameters that we are able to control: p_1, p_2, p_3, and q. The analytical results are available in Appendix 9.1, and the numerical results are represented in Table 3 and Figures (3)-(6).

Figure 3 describes the sensitivity of X^* with respect to each parameter. Among parameters we can control, X^* is most sensitive to perturbations in p_2 and q. When q increases, X^* increases by

Table 3: Percent Change of Endemic Proportions of Subpopulations with Respect to Parameters

Parameter	p_1	p_2	p_3	q	μ	δ	β_1
Change in X^*	0.12%	-0.29%	0.12%	0.32%	0.15%	0.58%	-1%
Change in Y_S^*	-0.14%	0.33%	-0.14%	-0.37%	0.03%	0.12%	0.16%
Change in Y_E^*	-0.14%	-8.65%	0.18%	0.63%	0.02%	0.08%	0.16%
Change in Z^*	0.34%	-0.13%	0.36%	0.14%	-0.18%	0.69%	0.16%

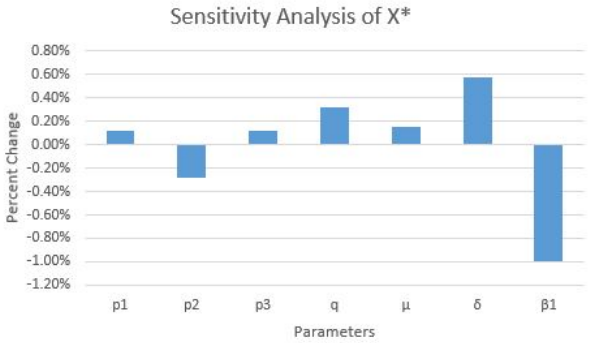

Figure 3: Change in X^* with respect to change in parameters

0.32%. In contrast, as p_2 increases, X^* decreases by 0.29%. Thus, as people join the NEP, the endemic subpopulation available to spread needle-sharing behavior decreases, and the subpopulation susceptible to beginning IV drug use increases. However, as more people abandon the NEP, the endemic subpopulation of people who are capable of spreading needle-sharing behavior increases and the endemic subpopulation susceptible to beginning IV drugs decreases.

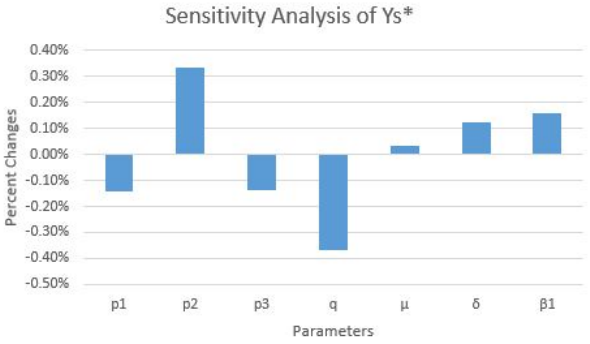

Figure 4: Change in Y_S^* with respect to change in parameters

Figure 4 describes the sensitivity of Y_S^* with respect to each parameter. Among parameters we can control, Y_S^* is most sensitive to perturbations in q and p_2. As q increases, Y_S^* decreases by 0.37%, while an increase in p_2 causes Y_S^* to increase by 0.33%. Thus, as more people join the NEP, the endemic subpopulation sharing needles decreases, while as people abandon the NEP, the endemic subpopulation sharing needles increases.

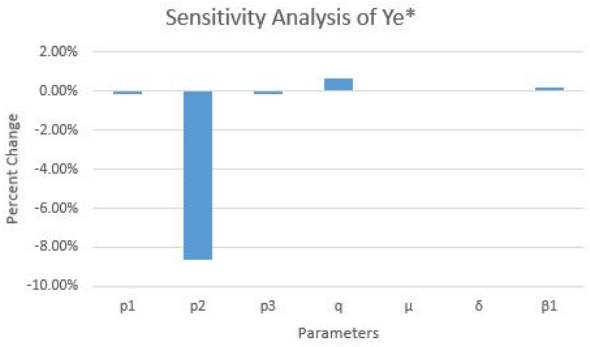

Figure 5: Change in Y_E^* with respect to change in parameters

Figure 5 describes the sensitivity of Y_E^* with respect to each parameter. Among parameters we can control, Y_E^* is most sensitive to perturbations in q and p_2. As q increases, Y_E^* increases by 0.63%. However, as p_2 increases, Y_E^* decreases by 8.65%. Thus, as people join the NEP, the endemic subpopulation not sharing needles increases. However, as people abandon the NEP, the endemic subpopulation not sharing needles dramatically decreases.

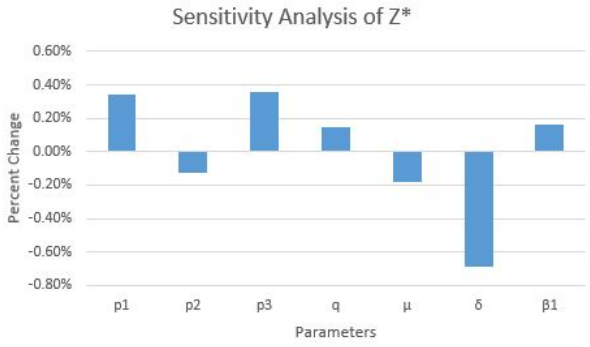

Figure 6: Change in Z^* with respect to change in parameters

Figure 6 describes the sensitivity of Z^* with respect to each parameter. Among parameters we can control, Z^* is most sensitive to perturbations in p_1 and p_3. As p_1 and p_3 increases, the population in treatment increases by 0.34% and 0.36%, respectively. Thus, as people seek treatment for IV drug addiction, the endemic subpopulation in treatment increases.

5 Numerical Simulations

Impact of NEP on R_0

Through sensitivity analysis, we determined that the basic reproductive number is impacted by changes in both the rate at which people join the NEP and the rate at which people leave the NEP. We also noted that the average number of new needle-sharing cases caused by one needle-sharing individual is most sensitive to changes in the successful contact rate. In the construction of the model, Equation (6) defines the ineffectiveness of the NEP as the ratio of rates of people leaving the NEP to return to needle sharing behavior over the sum of people leaving the NEP program for treatment and needle-sharing behavior; that is,

$$\alpha = \frac{p_2}{p_2 + p_3}.$$

Figure (7) graphically represents the impact of the ineffectiveness of the NEP on the basic reproduction number.

As the ineffectiveness of the NEP increases, we observe a slow increase in the basic reproduction number until $\alpha \approx 0.7$, or 70% ineffective. At that threshold, we observe a sharp incline in R_0, which implies that when approximately 70% of NEP participants leave the program to return to needle-sharing behavior, the NEP does not help control the spread of injection drug use behavior.

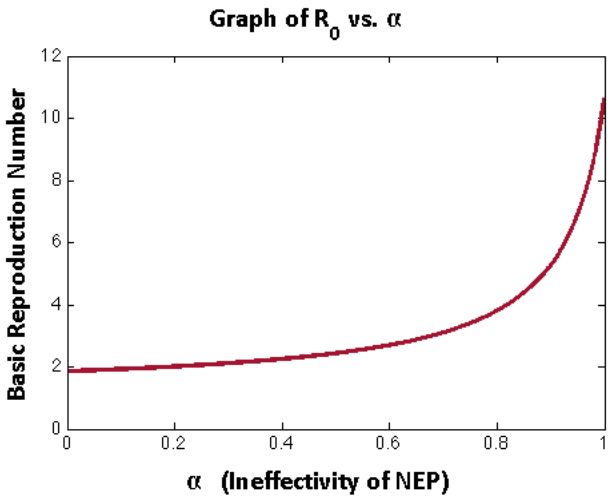

Figure 7: Change in Basic Reproduction Number as ineffectiveness of NEP increases

The Impact of an NEP on the endemic equilibrium without relapse

To further study the relationship between the ineffectiveness of an NEP and IDUs seeking treatment, we consider the numerical plots of the treatment and needle-sharing compartments with respect to α. When the ineffectiveness if closer to zero, the NEP is more effective; however, when the ineffectiveness approaches 1, the program is less effective in getting IDUs to seek treatment.
First, we consider the impact of the ineffectiveness of the NEP on those in a population that shares needles, shown in Figure (8). We note that a certain level of ineffectiveness does not have a signficant impact on the needle-sharing population, although there is a slight increase as the NEP becomes less effective. However, we note a threshold at which the ineffectiveness of the NEP causes a steep increase in the needle-sharing population.

Next, we consider the relationship between the endemic point, T^*, and the ineffectiveness of the NEP, α, shown in Figure (9).

Figure (7) corresponds to Figures (8) and (9), showing a similar critical point in ineffectiveness of the NEP. We note a critical ineffectiveness point, occuring approximately at $\alpha = 0.7$. Prior to this threshold, the ineffectiveness of an NEP does not discourage IDUs from seeking treatment. However, if the NEP program is less than 30% effective, IDUs seeking treatment dramatically

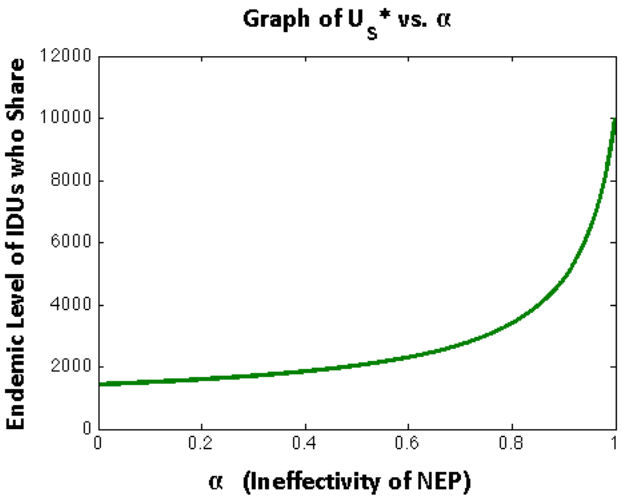

Figure 8: The interaction between U_S^* and α

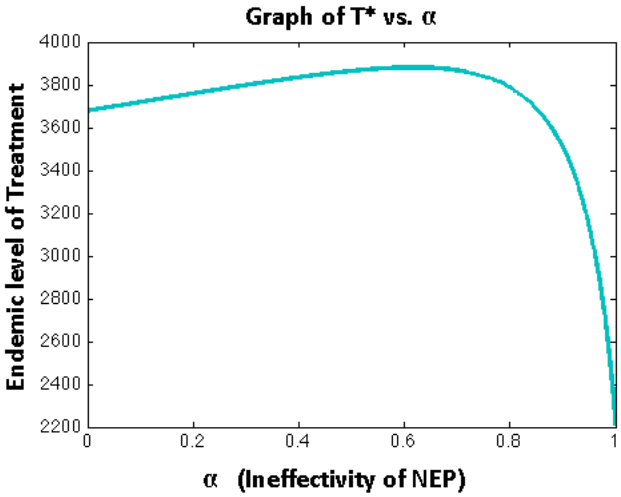

Figure 9: The interaction between T^* and α

decreases.

Injection-Addiction Model Simulations

In order to understand the dynamics of the injection-addiction system, we plotted the state variables over short and long time periods using numerical values for the parameters in Table 1. The

numerical values for the parameters defined in Table 1 are outlined in Tables 4 and 5. Due to scarcity of data, as well as the unpredictability of IDU populations, it is crucial to recognize the limitations of generalizing IDU populations and behaviors. Our population and parameter estimates were based on data from Baltimore, Maryland, and some of the values were available through literature. Those that were were not directly available were determined through algebraic manipulation, which provided the estimates available in Tables 4 and 5. For more information about parameter estimation, see Appendix 9.4.

Table 4: Simulation Parameter Values

Parameters	Λ	β_1	β_3	p_1	p_2	p_3	q	μ	δ
Values	40.36	0.042	0.05875	0.00071	0.0497	0.00221	0.0187	0.0187	0.00255

Table 5: Simulation Initial Conditions

Parameter	Value	Reference
A_0	58,783	[1, 10, 4, 6]
U_{S0}	9574	[6, 10]
U_{E0}	1030	[6, 10]
T_0	325	[4]

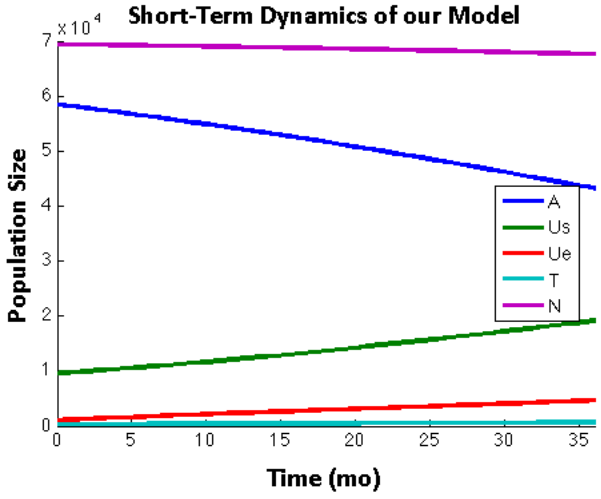

Figure 10: Short-term system dynamics

Figure 10 represents the dynamics of the system over the course of three years. During this time period, the dynamics of the system appear linear. There is some interaction occurring as the susceptible class visibly decreases and the injection-addiction population slowly increases. Over the course of three years, however, we do not observe a significant change in the treatment compartment, and we cannot see the full dynamics of the compartment interactions.

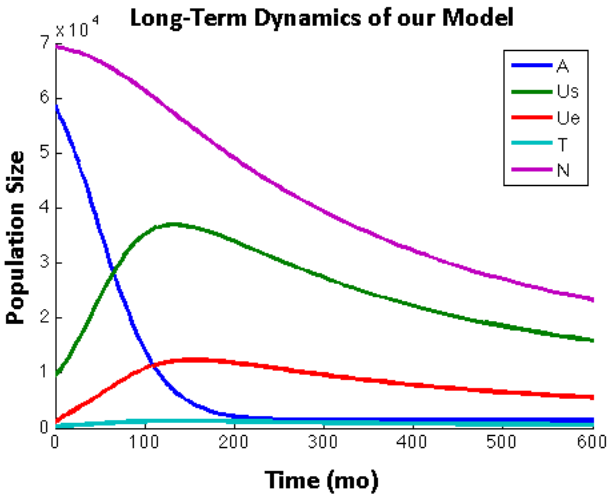

Figure 11: Long-term system dynamics

Figure (11) represents the dynamics of the system over fifty years. In Figure (11), we are able to observe the fluctuation in the compartments over time. Under the assumption that the associated parameters are applicable to a long-term model, we see that the treatment state increases slowly, ultimately reaching a steady state. We note that the greatest increase in the treatment state appears to coincide with the increase in the U_E state. We also note that the susceptible state rapidly drops near the beginning, but slowly increases over time and ultimately reaches a steady state.

While it's important to consider the long-term dynamics of the model, it is also important to note that IDU populations are unpredictable. Therefore, Figures (10) and (11) are not good predictors for the long-term dynamics of the IDU population, although they do describe the stability of the model.

6 Controlling the Problem of Needle-Sharing Behavior

With the analysis of this model, we are able to address several questions raised at the beginning of this paper. First, we considered at what minimum rate people must begin utilizing an NEP to create a population free from needle-sharing behavior. To determine this, we consider what conditions are necessary on q such that $R_0 < 1$. By setting $R_0 < 1$ and solving for q, we are able to determine the following condition:

$$q > \frac{\beta_1 - (p_1 + \mu + \delta)(\mu + \delta + p_2 + p_3)}{\mu + \delta + p_3}.$$

To understand this condition, we consider the implications with respect to β_1, the rate of successful contact between U_S and U_E classes and conclude the following:

Proposition 2.

- *If* $\beta_1 < p_1 + \mu + \delta$, *then* $R_0 < 1$ *holds* $\forall\ q$.
- *If* $\beta_1 > p_1 + \mu + \delta$, *then* $R_0 < 1$ *when* $q > q^*$ *where* q^* *is given by*

$$\frac{\beta_1 - (p_1 + \mu + \delta)(\mu + \delta + p_2 + p_3)}{\mu + \delta + p_3}.$$

Next, we considered at what maximum rate people may abandon the NEP and still maintain addiction-injection free population dynamics. We again set $R_0 < 1$ and solved for p_2, coming to the following result:

$$p_2 < \frac{(\mu + \delta + p_3)(q + p_1 + \mu + \delta - \beta_1)}{\beta_1 - (p_1 + \mu + \delta)}.$$

We consider this result in terms of β_1 and come to the following conclusion:

Proposition 3.

- *If* $\beta_1 > p_1 + \mu + \delta + q$, *then* $\nexists$ *a minimum* p_2.

- *If* $p_1 + \mu + \delta < \beta_1 < p_1 + \mu + \delta + q$, *then* $R_0 < 1$ *when* $p_2 < p_2^*$ *where* p_2^* *given by*

$$\frac{(\mu + \delta + p_3)(q + p_1 + \mu + \delta - \beta_1)}{\beta_1 - (p_1 + \mu + \delta)}.$$

- *If* $\beta_1 < p_1 + \mu + \delta$, *then* $R_0 < 1$ *holds* $\forall\ p_2$.

By Proposition 2 and 3, we conclude that, if the successful contact rate β_1 is relatively small, then any solutions for q and p_2 will satisfy the conditions, and the population will ultimately reach an injection-addiction free equilibrium. If the successful contact rate is within a certain range, then $q > q^*$ and $p_2 > p_2^*$ to achieve an injection-addiction free equilibrium. If the successful contact rate is high enough, however, there is no minimum value for p_2 such that injection-addiction equilibrium can ever be achieved; that is, the population will never be free from injection drug behavior.
Next we considered what conditions on α, the ineffectiveness of the NEP, were necessary to maintain an injection-addiction free equilibrium. To determine this, we consider $p_2 = \frac{\alpha}{(1-\alpha)}p_3$ and $R_0 = \frac{\beta_1}{M}$. By substituting $p_2 = \frac{\alpha}{(1-\alpha)}p_3$, we determine that $R_0 < 1$ when $\alpha^* > \alpha$.

Proposition 4.

- *If* $\beta_1 < q + \mu + \delta + p_1$, *then* $R_0 < 1\ \forall\ \alpha$.

- *If* $\mu + \delta + p_1 < \beta_1 < q + \mu + \delta + p_1$, *then* $\alpha^* > \alpha$ *where* α^* *is given by*

$$\alpha^* = \frac{(\mu + \delta + p_3)(q + \mu + \delta + p_1 - \beta_1)}{qp_3 + (\mu + \delta)(q + \mu + \delta + p_1 - \beta_1).}$$

- *If* $q + \mu + \delta + p_1 < \beta_1$, *then* $\nexists$ *condition on* α *such that* $R_0 < 1$.

By Proposition 4, we conclude that if the successful contact rate is relatively small, then the system will reach an injection-addiction free equilibrium regardless of the ineffectiveness of the NEP. For a slightly larger successful contact rate, the effectiveness of the NEP, given as E_{NEP}, is given as follows

$$E_{NEP} = (1 - \alpha) = \frac{p_3[\beta_1 - (\mu + \delta + p_1)]}{qp_3 + (\mu + \delta)(q + \mu + \delta + p_1 - \beta_1)}$$

Finally, for a successful contact rate that is relatively large, the injection-addiction process cannot be controlled by the effectiveness of the NEP.

7 Discussion

The analysis of model (1)-(5) is sufficient to answer the questions posed at the beginning of this paper. We constructed a model to examine the dynamics of a population of addicts and IDUs with the presence of an NEP. Within that model, we determined the basic reproduction number and developed a biological interpretation of that number. Furthermore, we numerically established the stability of the injection-addiction free equilibrium, and determined the endemic equilibria for two cases of the model. We showed that, when relapse is taken into account, we have two cases for the endemic equilibrium. When the basic reproduction number is larger than one, then there is one stable endemic equilibrium. However, when the basic reproduction number is less than one, we showed that there are two possible endemic equilibria, one stable and one unstable. The behavior of the endemic equilibria is determined by the numerical value of the relapse rate. When relapse is not considered, however, we numerically determined that there is one stable equilibrium.

To address our research questions, we determined that, if the successful contact rate between the IDU and non-IDU population is small enough, the system will ultimately reach an injection-addiction free equilibrium regardless of the presence of an NEP. If the successful contact rate is bounded between two established conditions, then an injection-addiction free equilibrium is possible given a certain level of effectiveness of the NEP. If the successful contact rate is high enough, however, the NEP is not sufficient to contain the injection-addiction behavior. Based on the successful contact rate, we made several propositions on the maximum rate that people may abandon the NEP and the minimum rate at which people much join an NEP in order to maintain an injection-addiction free equilibrium. Furthermore, we showed that an NEP can be ineffective to a certain degree without significantly impacting the endemic dynamics. However, if an NEP is significantly ineffective, the treatment compartment dramatically decreases.

Through sensitivity analysis, we focused on those parameters within our control that impact

the entire system. Therefore, we note that the rate at which an IDU begins using an NEP has an impact on dynamics of the system each proportion of the endemic subpopulations, with the exception of the non-IDU population. We also note that the rate at which people abandon the NEP impacts each subpopulation, especially the endemic proportion of the subpopulation utilizing the NEP.

From the research and analysis, it is clear that the presence of an NEP impacts the dynamics of an IDU population. Although the results from this research provide insight to the impact of NEPs on injection-addiction behavior, more research is needed to explore the factors that impact an IDU population seeking treatment.

8 Future Study

This model is constrained by limited data and the difficult nature of quantifying IDU dynamics. As a result, this is a generalized model that explores possible interactions, but does not fully capture the dynamics of an IDU population or the role of NEPs within these communities. Further research is needed to consider what additional factors may contribute to an IDU population choosing to utilize an NEP, and what effect those factors may have on an IDU ultimately choosing to seek treatment for addiction. Furthermore, much of the data available for numerical solutions was from the late 1990's. Much of this data was collected in order to understand the spread of HIV within IDU communities at that time. Future research includes investigating more recent data to understand how IDU dynamics have changed in the past twenty years as knowledge of HIV has continued to expand.

Acknowledgments

We would like to thank Dr. Carlos Castillo-Chavez, Executive Director of the Mathematical and Theoretical Biology Institute (MTBI), for giving us this opportunity to participate in this research program. We would also like to thank Co-Executive Summer Directors Dr. Omayra Ortega and

Dr. Baojun Song for their efforts in planning and executing the day to day activities of MTBI. This research was conducted in MTBI at the Simon A. Levin Mathematical, Computational and Modeling Sciences Center (SAL MCMSC) at Arizona State University (ASU). This project has been partially supported by grants from the National Science Foundation (DMS-1263374 and DUE-1101782), the National Security Agency (H98230-14-1-0157), the Office of the President of ASU, and the Office of the Provost of ASU.

References

[1] Substance Abuse and Mental Health Services Administration. National household survey on drug abuse: Main findings 1998. *Department of Health and Human Services*, 1998.

[2] Bryon Adinoff, Chelsea Talmadge, Mark J Williams, Erica Schreffler, Patricia K Jackley, and Steven R Krebaum. Time to relapse questionnaire (trq): A measure of sudden relapse in substance dependence. *The American journal of drug and alcohol abuse*, 36(3):140–149, 2010.

[3] Priti Arun, BS Chavan, and Harprit Kaur. A study of reasons for not seeking treatment for substance abuse in community. *Indian journal of psychiatry*, 46(3):256, 2004.

[4] Robert Brooner, Michael Kidorf, Van King, Peter Beilenson, Dace Svikis, and David Vlahov. Drug abuse treatment success among needle exchange participants. *Public Health Reports*, 113(Suppl 1):129, 1998.

[5] Centers for Disease Control, Prevention (CDC, et al. Syringe exchange programs—united states, 2008. *MMWR. Morbidity and mortality weekly report*, 59(45):1488, 2010.

[6] Samuel R Friedman, Barbara Tempalski, Hannah Cooper, Theresa Perlis, Marie Keem, Risa Friedman, and Peter L Flom. Estimating numbers of injecting drug users in metropolitan areas for structural analyses of community vulnerability and for assessing relative degrees of service provision for injecting drug users. *Journal of Urban Health*, 81(3):385, 2004.

[7] Becky L Genberg, Stephen J Gange, Vivian F Go, David D Celentano, Gregory D Kirk, and Shruti H Mehta. Trajectories of injection drug use over 20 years (1988–2008) in baltimore, maryland. *American journal of epidemiology*, page kwq441, 2011.

[8] David Greenhalgh and Fraser Lewis. The general mixing of addicts and needles in a variable-infectivity needle-sharing environment. *Journal of mathematical biology*, 44(6):561–598, 2002.

[9] James A. Inciardi and Lana D. Harrison. *Harm Reduction*, chapter 1. Sage Publications, Inc., 2000.

[10] Robert Hayman Isabelle Horon, Estelle Apelberg. Maryland vital statistics annual report. page page, YEAR.

[11] Edward H Kaplan. Needles that kill: modeling human immunodeficiency virus transmission via shared drug injection equipment in shooting galleries. *Review of Infectious Diseases*, 11(2):289–298, 1989.

[12] Edward H Kaplan and Robert Heimer. A model-based estimate of hiv infectivity via needle sharing. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, 5(11):1116–1118, 1992.

[13] Edward H Kaplan and Robert Heimer. A circulation theory of needle exchange. *Aids*, 8(5):567–574, 1994.

[14] Edward H Kaplan and Elaine O'Keefe. Let the needles do the talking! evaluating the new haven needle exchange. *Interfaces*, 23(1):7–26, 1993.

[15] National Institute on Drug Abuse. Drug facts: Nationwide trends, 2014.

[16] Harold Pollack and Robert Heimer. The impact and cost-effectiveness of methadone maintenance treatment in preventing hiv and hepatitis c. *MONOGRAPHS*, page 8, 2004.

[17] Drug Strategies. Smart steps: Treating baltimore's drug problem. page 3, 2000.

[18] Thomas W Valente, Mr Robert K Foreman, Mr Benjamin Junge, and David Vlahov. Needle-exchange participation, effectiveness, and policy: syringe relay, gender, and the paradox of public health. *Journal of urban health*, 78(2):342, 2001.

[19] Emma White and Catherine Comiskey. Heroin epidemics, treatment and ode modelling. *Mathematical biosciences*, 208(1):312–324, 2007.

9 Appendix

9.1 Appendix 1

We compute the partial derivatives with respect to each parameter for X^*, Y_S^*, Y_E^*, Z^* and multiply that partial derivative by the parameter divided by the compartment. The following are the analytical results used to generate the numerical sensitivity analysis.

Sensitivity Indices for X^*

$$\begin{aligned}
\frac{p_1}{X^*}\frac{\partial X^*}{\partial p_1} &= \frac{p_1}{M} \\
\frac{p_2}{X^*}\frac{\partial X^*}{\partial p_2} &= -\frac{p_2 Q^2}{Mq}(\mu + \delta + p_3) \\
\frac{p_3}{X^*}\frac{\partial X^*}{\partial p_3} &= \frac{p_2 p_3 Q^2}{qM} \\
\frac{q}{X^*}\frac{\partial X^*}{\partial q} &= \frac{Q}{M}(\mu + \delta + p_3) \\
\frac{\mu}{X^*}\frac{\partial X^*}{\partial \mu} &= \frac{\mu}{M}\left[1 + \frac{p_2 Q^2}{q}\right] \\
\frac{\delta}{X^*}\frac{\partial X^*}{\partial \delta} &= \frac{\delta}{M}\left[1 + \frac{p_2 Q^2}{q}\right] \\
\frac{\beta_1}{X^*}\frac{\partial X^*}{\partial \beta_1} &= -1
\end{aligned}$$

Sensitivity Indices for Y_S^*

$$\begin{aligned}
\frac{p_1}{Y_S^*}\frac{\partial Y_S^*}{\partial p_1} &= \frac{-p_1\beta_1}{(\beta_1 - M)M} \\
\frac{p_2}{Y_S^*}\frac{\partial Y_S^*}{\partial p_2} &= \frac{p_2\beta_1}{(\beta_1 - M)M}\left(\frac{Q^2}{q}(\mu + \delta + p_3)\right) \\
\frac{p_3}{Y_S^*}\frac{\partial Y_S^*}{\partial p_3} &= \frac{-p_2 p_3 Q^2\beta_1}{(\beta_1 - M)Mq} \\
\frac{q}{Y_S^*}\frac{\partial Y_S^*}{\partial q} &= -\frac{\beta_1 Q}{(\beta_1 - M)M}(\mu + \delta + p_3) \\
\frac{\mu}{Y_S^*}\frac{\partial Y_S^*}{\partial \mu} &= \frac{\mu}{\mu + \delta} - \frac{\mu\beta_1}{(\beta_1 - M)M}\left(1 + \frac{p_2}{q}Q^2\right) \\
\frac{\delta}{Y_S^*}\frac{\partial Y_S^*}{\partial \delta} &= \frac{\delta}{\mu + \delta} - \frac{\delta\beta_1}{(\beta_1 - M)M}\left(1 + \frac{p_2}{q}Q^2\right) \\
\frac{\beta_1}{Y_S^*}\frac{\partial Y_S^*}{\partial \beta_1} &= \frac{M}{\beta_1 - M}
\end{aligned}$$

Sensitivity Indices for Y_E^*

$$\begin{aligned}
\frac{p_1}{Y_E^*}\frac{\partial Y_E^*}{\partial p_1} &= \frac{-p_1\beta_1}{M(\beta_1 - M)} \\
\frac{p_2}{Y_E^*}\frac{\partial Y_E^*}{\partial p_2} &= \frac{p_2\beta_1}{(\beta_1 - M)M}\left[\frac{Q^2}{q}(\mu + \delta + p_3) - \frac{p_2 Q}{q}\right] \\
\frac{p_3}{Y_E^*}\frac{\partial Y_E^*}{\partial p_3} &= -\frac{p_3 Q}{q}\left[1 + \frac{p_2 Q}{M^2(\frac{1}{M} - \frac{1}{\beta_1})}\right] \\
\frac{q}{Y_E^*}\frac{\partial Y_E^*}{\partial q} &= 1 - \frac{\beta_1 q}{M(\beta_1 - M)}\left[1 - \frac{p_2 Q}{q}\right] \\
\frac{\mu}{Y_E^*}\frac{\partial Y_E^*}{\partial \mu} &= \mu\left[-\frac{Q}{q} + \frac{1}{\mu + \delta} - \frac{\beta_1}{(\beta_1 - M)M}\left(1 + \frac{p_2 Q^2}{q}\right)\right] \\
\frac{\delta}{Y_E^*}\frac{\partial Y_E^*}{\partial \delta} &= \delta\left[-\frac{Q}{q} + \frac{1}{\mu + \delta} - \frac{\beta_1}{(\beta_1 - M)M}\left(1 + \frac{p_2 Q^2}{q}\right)\right] \\
\frac{\beta_1}{Y_E^*}\frac{\partial Y_E^*}{\partial \beta_1} &= \frac{M}{\beta_1 - M}
\end{aligned}$$

Sensitivity Indices for Z^*

$$\begin{aligned}
\frac{p_1}{Z^*}\frac{\partial Z^*}{\partial p_1} &= \frac{p_1}{p_1+Qp_3} - \frac{\beta_1 p_1}{M(\beta_1 - M)} \\
\frac{p_2}{Z^*}\frac{\partial Z^*}{\partial p_2} &= \frac{p_2 Q^2}{q}\left[\frac{-p_3}{(p_1+Qp_3)} + \frac{\beta_1(\mu+\delta+p_3)}{M(\beta_1-M)}\right] \\
\frac{p_3}{Z^*}\frac{\partial Z^*}{\partial p_3} &= \frac{Q^2 p_3}{q}\left[\frac{(\mu+\delta+p_2)}{(p_1+Qp_3)} - \frac{p_2\beta_1}{M(\beta_1-M)}\right] \\
\frac{q}{Z^*}\frac{\partial Z^*}{\partial q} &= \frac{p_3 Q}{p_1+Qp_3} - \frac{q\beta_1}{(\beta_1-M)M}\left[1 - \frac{p_2 Q}{q}\right] \\
\frac{\mu}{Z^*}\frac{\partial Z^*}{\partial \mu} &= \frac{-\mu p_3 Q^2}{q(p_1+Qp_3)} - \frac{\mu\beta_1}{(\beta_1-M)M}\left[1 + \frac{p_2 Q^2}{q}\right] \\
\frac{\delta}{Z^*}\frac{\partial Z^*}{\partial \delta} &= \frac{-\delta p_3 Q^2}{q(p_1+Qp_3)} - \frac{\delta\beta_1}{(\beta_1-M)M}\left[1 + \frac{p_2 Q^2}{q}\right] \\
\frac{\beta_1}{Z^*}\frac{\partial Z^*}{\partial \beta_1} &= \frac{M}{\beta_1 - M}
\end{aligned}$$

Sensitivity Indices for R_0

$$\begin{aligned}
\frac{q}{R_0}\frac{\partial R_0}{\partial q} &= -\frac{Q}{M}(p_3+\mu+\delta) \\
\frac{p_1}{R_0}\frac{\partial R_0}{\partial p_1} &= -\frac{p_1}{M} \\
\frac{p_2}{R_0}\frac{\partial R_0}{\partial p_2} &= \frac{p_2 Q^2}{qM}(p_3+\mu+\delta) \\
\frac{p_3}{R_0}\frac{\partial R_0}{\partial p_3} &= \frac{-p_2 p_3 Q^2}{qM} \\
\frac{\mu}{R_0}\frac{\partial R_0}{\partial \mu} &= -\frac{\mu}{M}(1+\frac{p_2}{q}Q^2) \\
\frac{\delta}{R_0}\frac{\partial R_0}{\partial \delta} &= -\frac{\delta}{M}(1+\frac{p_2}{q}Q^2) \\
\frac{\beta_1}{R_0}\frac{\partial R_0}{\partial \beta_1} &= 1
\end{aligned}$$

9.2 Appendix 2

The Jacobian matrix evaluated at the endemic equilibrium point for the case where $\beta_3 = 0$ is given by the following:

$$J_{EE} = \begin{pmatrix} -\frac{\beta_1}{M}(\mu+\delta)\left[1-\frac{1}{R_0}\right]^2 - \mu & \frac{-\beta_1}{R_0}\left[1-\frac{(\mu+\delta)(1-\frac{1}{R_0})}{M}\right] & \frac{\beta_1(\mu+\delta)}{R_0 M}\left[1-\frac{1}{R_0}\right] & \frac{\beta_1(\mu+\delta)}{R_0 M}\left[1-\frac{1}{R_0}\right] \\ \frac{\beta_1}{M}(\mu+\delta)\left[1-\frac{1}{R_0}\right]^2 & \frac{-\beta_1}{R_0}\left[1-\frac{(\mu+\delta)(1-\frac{1}{R_0})}{M}\right] - (q+p_1+\mu+\delta) & \frac{\beta_1(\mu+\delta)}{R_0 M}\left[1-\frac{1}{R_0}\right] + p_2 & -\frac{\beta_1(\mu+\delta)}{R_0 M}\left[1-\frac{1}{R_0}\right] \\ 0 & q & -(\mu+\delta+p_2+p_3) & 0 \\ 0 & p_1 & p_3 & -(\mu+\delta) \end{pmatrix}$$

9.3 Appendix 3

$$\begin{aligned} \dot{A} &= \Lambda - \beta_1 A\frac{U_S}{N} - \mu A, \\ \dot{U_S} &= \beta_1 A\frac{U_S}{N} - (q+p_1+\mu+\delta)U_S + p_2 U_E, \\ \dot{U_E} &= qU_S - (\delta+\mu+p_2+p_3)U_E, \\ \dot{T} &= p_1 U_S + p_3 U_E - (\delta+\mu)T, \\ \dot{N} &= \Lambda - \mu N - \delta(U_S+U_E+T), \end{aligned} \tag{12}$$

where

$$N = A(t) + U_S(t) + U_E(t) + T(t).$$

9.4 Appendix 4

Estimating parameters is necessary for running simulations to show behavior of our model, as well as necessary for sensitivity analysis. Unfortunately, given the uncertainty regarding the population we have studied with regards to numbers and behaviors, it was very difficult to find the parameters we needed in the literature. Therefore, all of our parameters are approximations. Due to the brevity of our model, a decision based on the inability to model an unpredictable population of drug addicts, our parameters are measured per month with the exception of initial conditions. An

important note is that our parameters and approximations are based on Baltimore, MD (the city) in the year 1998, and years around that time period, as well as state or national data in or around that time.

Table 6: Our Estimated Initial Population Sizes

Population	Population of the City	N_0	U_{E0}	U_{S0}	T_0	A_0
People	654,590	69,387	1,030	9,574	325	58,458

Table 7: Our Estimated Parameters

Parameter	μ	δ	Λ	q	p_1	p_2	p_3	β_1	β_3
Values	0.00068	0.00255	40.36	0.0169	0.00071	0.00483	0.00221	0.042	0.05875

Estimation of Initial Population Sizes

For the Population of the City: Throughout our research we became interested in Baltimore, Maryland in or around 1998 as a location and time frame to base our model on. We found *Maryland Vital Statistics: Annual Report 1998* from the Division of Health Statistics that provided us with the population size of Baltimore city in 1998, 654,590 people.[10]

For the Total Population of Illicit Drug Users (N_0): The Substance Abuse and Mental Health Services Administration (SAMHSA) has conducted the National Household Survey on Drug Abuse (NHSDA) across the years, and throughout research we came across their *Main Findings 1998* which provided us with a percentage of the total population of the United States that used illicit drugs in the past year (for 1998). This percentage was 10.6%[1], and using this we approximated how many people of our total population of Baltimore, MD[10] had used illicit drugs within the past year :

$$\begin{aligned} \text{Pop'n of Baltimore in } 1998 \times 10.6\% &= \text{Pop'n of Illicit Drug Users} \\ 654,590 \text{ people} \times 0.106 &\approx 69,387 \text{ people} \end{aligned}$$

Therefore, our initial population of total drug users is 69,387 people. [10, 1]

For the Population of IDUs using an Exchange Program (U_{E0}): In *Needle-Exchange Participation, Effectiveness, and Policy: Syringe Relay, Gender, and the Paradox of Public Health*, in the section where they go over their sample size and exchange program participation, we gathered that 2,574 people over a 30mo period visited and participated in the needle-exchange program more than one time.[18] To find a per-month number of people actively using a needle exchange program we get:

$$\begin{aligned} \frac{2,574 \text{ people}}{30 \text{ mo}} &= 85.8 \text{ people/mo} \\ 85.8 \text{ people/mo} \times 12 \text{ mo} &\approx 1,030 \text{ people for the year of 1998} \end{aligned}$$

Therefore, our initial population of IDUs using an NEP is 1,030 people. [**?**]

For the Population of IDUs who are Sharing Needles (U_{S0}): To find the number of IDUs who are not using a needle-exchange program, and therefore we assume are sharing, we needed to estimate the total number of IDUs in Baltimore in 1998. We found *Estimating Numbers of Injecting Drug Users in Metropolitan Areas for Structural Analyses of Community Vulnerability and for Assessing Relative Degrees of Service Provision for Injecting Drug Users*, which provided estimations for the total population of IDUs in Baltimore in 1998. Although they provided a variety of estimations (using different techniques) we chose the one that provided us with ≈ 162 IDUS per 10,000 people in a population, giving us[6]:

$$\begin{aligned} \frac{162 \text{ people}}{10,000 \text{ people}} &= \frac{x \text{ people}}{654,590 \text{ people}} \\ \frac{162 \text{ people}}{10,000 \text{ people}} \times 654,590 \text{ people} &= x \text{ people} \\ 0.0162 \times 654,590 \text{ people} &\approx 10,604 \text{ IDUs for Baltimore, MD 1998} \end{aligned}$$

Therefore, 10,604 people is our initial total population size of IDUs in Baltimore, MD 1998. [6, 10] From this, we can find the number of IDUs who are sharing by subtracting the number of IDUs

using the exchange program:

$$10,604 \text{ people} - 1,030 \text{ people} \quad = \quad 9,574 \text{ IDUs who share for Baltimore, MD 1998 [18, 10, 6]}$$

For the Population of IV Drug Addicts in Treatment (T_0): In *Drug Abuse Treatment Success and Needle Exchange Participants*, they grouped the individuals who entered based on how they were referred either via NEP, or via Standard Referral. In total they had 325 in treatment, and we use this number as our initial population size for the Treatment compartment. [4] ***For the Drug Users not using IV Drugs (A_0):*** Using the information gathered regarding population sizes, we can calculate the number of illicit drug users not using IV drugs. We assume that people who are using illicit drugs in Baltimore, MD 1998 minus the total IDU population would be the population of drug users who are not IV drug addicts.

$$69,387 \text{ people} - 10,604 \text{ IDUs} - 325 \text{ those in treatment for IV drug addiction} \quad = \quad 58,793 \text{ people}$$

Thus, the number of illicit drug users who are not addicted to IV drugs is 58,793 which represents the initial at-risk population of our model. [1, 10, 6, 4] [18, 10, 6]

Estimation of Parameters

For the Natural Death Rate (μ): In *Maryland Vital Statistics: Annual Report 1998* a crude death rate for the state of Maryland in 1998 was given as 817.4/100,000 died per year. Thus, we found that 0.008174 divided by 12 months gave us a monthly natural death rate of 0.00068/mo for μ. [10]

For the IV Drug Related Death Rate (δ): In *Smart Steps: Treating Baltimore's Drug Problem* we found that 324 individuals had died from overdose in 1999.[17] If we assume the rate at which people die due to overdose is similar to the rate at which people die to withdrawal we can say generally that δ is the death due to IV drug-related death:

$$\begin{aligned}\frac{324 \text{ people die}}{10,604 \text{ IDU pop'n}} &= 3.06\% \text{ IDUs die a year due to overdose} \\ \frac{3.06\%}{12 \text{ mo}} &= 0.00255/\text{mo}\end{aligned}$$

Thus, the rate at which IV drug addicts die due to IV drug-related death is $\delta = 0.00255$/mo. [17, 6, 10]

For the Number of People Who Enter the At-Risk Population (Λ): In our search to find a Λ value, we discovered in SAMHSA's *Main Findings 1998* that between the years 1997 and 1998 there was a 0.6% *decrease* in the proportion of the total population that used illicit drugs, which is a 0.05% decrease per month. Thus, our Λ rate must have less people entering the illicit drug user population than leaving the population. Notice that the only exit from our model is via death (natural or IV drug-related), and that because people in A do not die due to IV drug-related death:

$$\begin{aligned}\Lambda - (\mu + \delta)N + \delta A &= -0.0005N. \\ \Lambda &= (\mu + \delta)N - 0.0005N - \delta A \\ \Lambda &= (0.00068 + 0.00255)N - 0.0005N - (0.00255)A \\ \Lambda &= 0.00323(654,590) - 0.0005(654,590) - 0.00255(654,590) \\ \Lambda &\approx 40.36\end{aligned}$$

Thus, approximately 40 people enter the at-risk (A) population per month.[6, 10] From this, we can find the number of IDUs who are sharing by subtracting the number of IDUs using the exchange program:

$$10,604 \text{ people} - 1,030 \text{ people} = 9,574 \text{ IDUs who share for Baltimore, MD 1998 [18, 10, 6]}$$

For the rate at which People Move to NEP (q): In *Needle-Exchange Participation, Ef-*

fectiveness, and Policy: Syringe Relay, Gender, and the Paradox of Public Health we found the information we could use to find the number of people who began using a needle exchange program per month. In this paper they said 5,369/30mo visited the Baltimore Needle Exchange Program, which would be ≈ 178.97 IDUs/mo, visited out of the U_S population. [18] Then

$$\frac{178.97 \text{ people/mo}}{9,574 \ U_S \text{ IDU pop'n}} = 0.0187 \text{ begin using NEP/mo}$$

Thus, the rate at which IDUs who share begin to use an NEP is $q = 0.0187$/mo. [17, 6, 10]

For the Rate at which People in U_S go to Treatment (p_1): In *Drug Abuse Treatment Success and Needle Exchange Participants*, they grouped the individuals who entered based on how they were referred either via NEP, or via Standard Referral. We assume that because 82 were IDUs going into treatment via NEP referral, that standard referrals would be IDUs not in a needle exchange program. Therefore we find that 243 IDUs from U_S went into treatment out of the 325 total participants. [4]

$$\begin{aligned} \frac{243 \text{ people}}{3 \text{ years}} &= 81 \text{ people/yr via standard referral} \\ \frac{81 \text{ people/yr}}{9,574 \text{ pop'n of } U_S} &= 0.00846/\text{year} \\ \frac{0.00846/\text{year}}{12\text{mo}} &= 0.00071/\text{mo} \end{aligned}$$

Thus, the rate at which IDUs who share go to treatment (T) is $p_1 = 0.00071$/mo. [4, 18, 10, 6]

For the rate at which People in U_E return to U_S (p_2): In *Needle-Exchange Participation, Effectiveness, and Policy: Syringe Relay, Gender, and the Paradox of Public Health* we found the information we could use to find the number of people who began using a needle exchange program per month. In this paper they said 1,190/30mo visited the Baltimore Needle Exchange Program

only once, and that 873/30mo did not return the needles they had obtained from the NEP. We interpreted this as 1,910 visited once and of those 1,910, 873 did not even return their needles after their initial visits (thus meaning they did not even use the program for one full needle exchange). Recall that 2,574/30mo had used the program more than once, thus:[18]

$$\begin{aligned} \frac{2,574 \text{ use NEP} - (1910 \text{ used only once} - 873 \text{ did not return})}{30 \text{ mo}} &\approx 51.23 \text{ stop using NEP/mo} \\ \frac{51.23 \text{ stop using/mo}}{1,030 \text{ pop'n of } U_E} &\approx 0.0497 \end{aligned}$$

Thus, the rate at which IDUs in an NEP returning to a population of IDUs who share is $p_2 = 0.0497$/mo. [17, 6, 10]

For the Rate at which People in U_E go to Treatment (p_3): In *Drug Abuse Treatment Success and Needle Exchange Participants*, they grouped the individuals who entered based on how they were referred either via NEP, or via Standard Referral. There were 82 IDUs going into treatment via NEP referral, giving us: [4]

$$\begin{aligned} \frac{82 \text{ people}}{3 \text{ years}} &\approx 27.33 \text{ people/yr via NEP referral} \\ \frac{27.33 \text{ people/yr}}{1,030 \text{ pop'n of } U_E} &= 0.0265/\text{year} \\ \frac{0.0256/\text{year}}{12\text{mo}} &= 0.00221/\text{mo} \end{aligned}$$

Thus, the rate at which IDUs who use a needle exchange program go to treatment (T) is $p_3 = 0.00221$/mo. [4, 18, 10, 6]

For the Rate of At-Risk Individuals Becoming IDUs (β_1): We found a paper, *The Impact and Cost-Effectiveness of Methadone Maintenance Treatment in Preventing HIV and Hep-*

atitis C, which provided the rate of 0.5 of becoming an IDU with successful contact per year. Thus, getting a monthly rate of ≈ 0.042/mo. [16]

For the Rate of People in Treatment Relapsing back into the U_S population (β_3): We found a paper, *Time to Relapse Questionnaire (TQR): A Measure of Sudden Relapse in Substance Dependence*, which provided a relapse rate of $66\% - 75\%$ per year going back into the IDU population that shares needles (U_S). Thus, on average we get a monthly rate of $\beta_3 = 0.05875$/mo.[2]