Mathematical models for HIV among a group of intravenous drug users in one Canadian city

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Contents

Abstract

Since the discovery of HIV in the early 1980's there has been a vast amount of research conducted on HIV. A topic of particular interest has been the investigation of possible prevention methods to halt or slow down the spread of HIV. In this paper, we develop two models which examine the effectiveness of education and treatment methods for HIV-infected individuals on the spread of HIV. The first model developed is a population-based system of ordinary differential equations. We show that under certain conditions, the disease-free equilibrium is globally-asymptotically stable. Through numerical simulations it is shown that education and treatment maybe effective but further research is required. In particular, our model identified the critical parameters as the number of needles the average injection drug user comes in contact with before and after the introduction of an education program as well as the proportion of individuals reached by the program. The other model we developed was an individual-based model; the goal was to compare results of this model with the population-based model. We outline the difficulties in implementing an individual-based model for HIV, as well as, discuss why we are interested in developing this model and its usefulness.

1 Introduction

A 2002 national study estimated that 30% of new HIV infections which occurred in Canada were among injection drug users [3]. That same year, HIV prevalence among injection drug users (IDU) in Ottawa was estimated at 19.7% [3]. The sharing of needles is relatively common among this population and poses an efficient mode of transmission for the HIV virus [3]. In cities with more mature HIV epidemics, such as New York and Milan, HIV prevalence levels are reportedly as high as 50% [7]. As such, the spread of HIV among the Canadian injection-drug user population merits serious and immediate attention.

From an economic perspective, the total medical cost of one HIV infection is estimated at $150,000 Canadian [7]. It clearly makes financial sense to fund effective public health interventions that can decrease the number of infections acquired by the Canadian IDU population. Kuyper et al. estimated total expected medical expenditures in Vancouver, based on their current HIV prevalence of 31% among IDUs at $215,852,613 [7]. However, forecasts show that, should the prevalence rise to 50%, as in other major urban centres, the medical costs of treating HIV among IDUs in Vancouver would skyrocket to $348,935,865.

Here, we attempt to model HIV/AIDS disease progression within the IDU community of one Canadian city. Treatment strategies involving education programs and/or anti-retroviral programs are considered, with varying uptake and retention rates. There is evidence to support the hypothesis that by educating injection drug users about HIV transmission and providing them with clean needles, risky needle-sharing behaviour will decrease resulting in a decreased HIV transmission rate [4]. We consider the inclusion of anti-retroviral treatment as

this is known to lower viral load, and thus, decrease transmission rates. The outcome of interest in this analysis is the prevalence of HIV/AIDS. We expect that these results could be useful from a policy-making perspective in order to determine the most effective treatment strategy.

2 Mathematical model

The objectives of the models developed in this paper are to evaluate the effectiveness of education and treatment on the HIV epidemic among a group of IDU in one Canadian city. For this study, we use preliminary data from Ottawa, Ontario as an example. The education program examines the effect of having a fraction of the population enter a program that reduces the risk they use a "bad" needle and contract HIV. The treatment model considers how effective treating HIV-infected individuals is on lowering prevalence and incidence rates. The two strategies are also combined in one model to determine if it is more beneficial to consider only one strategy at a time, or both.

The main challenge in meeting these objectives is the lack of data available for IDU in Ottawa. The lack of data makes precise quantitative results impossible. Hence, models focus on theoretical frameworks, qualitative results and uncertainty analysis over a broad range of parameter values. These theoretical results can identify important model parameters which can be used to guide future research in this area.

2.1 Model assumptions

A yearly time scale is used to model population dynamics, which includes calculating the fraction of the population entering an education program, becoming infected with HIV, entering or leaving treatment, developing AIDS and succumbing to mortality.

First, we define some notation:

- let $S(t)$ denote the number of individuals in the IDU group who have not contracted HIV;

- $S_e(t)$ be the number of individuals who entered an education program;

- $I_u(t)$ be the number of untreated individuals who are HIV-infected;

- $I_T(t)$ the number of HIV-infected individuals in treatment;

- and $A(t)$ the number of individuals who have AIDS.

We assume that there is a constant recruitment rate into $S(t)$, denoted by π, regardless of interventions implemented and individuals leave due to natural death a rate μ. Individuals enter an education program at a rate $\psi\epsilon$ (units 1/time) which reduces their chance of being infected (see text below). Thus, the term $\psi\epsilon S$ is the number of people per year that enter an education program and $(1 - \psi\epsilon)S$ is the number of individuals who chose not to enter a program.

Individual's in the IDU group will use c infected needles per year. The probability that this use leads to infection depends on whether the needle was previously used by an individual who has HIV, HIV-infected and in treatment or infected with AIDS, denoted by β_1, β_2 and β_3, respectively. For this paper, we assume that each β is constant so that the incidence term is referred to as standard incidence [6]. So, the contact rate does not vary with population size which is a reasonable assumption for a HIV model. Now consider, for example, the term $\frac{(1-\psi\epsilon)Sc\beta_1 I_u}{N}$ which is the incidence of new infections due to a bad needle being contaminated by a untreated, HIV-infected individual. Thus, the incidence of new infections due to contact with an infected individual is given by

$$\lambda_s = \frac{(1-\psi\epsilon)Sc(\beta_1 I_u + \beta_2 I_T + \beta_3 A)}{N}. \tag{1}$$

Note that the probability of infection is highest when the needle was previously used by an AIDS-infected individual, followed by untreated HIV-infected individuals and treated HIV-infected individuals. This reflects that fact that an individual who has AIDS will have more virus present in their blood then either of two HIV-infected groups.

Individuals who chose to enter an education program have a reduced probability of becoming infected. We assume that these individuals will use a lower number of infected needles per year, denoted by c_{se}. Thus, the incidence of infection among educated susceptibles is given by

$$\lambda_{se} = \frac{\psi S_e c_{se}(\beta_1 I_u + \beta_2 I_T + \beta_3 A)}{N}. \tag{2}$$

Since there is a delay between HIV and the appearance of symptoms, individuals who become infected with HIV are initially untreated. A fraction of individuals, p, enter a treatment program. Since treatment can result in harsh side effects we assume that individuals leave treatment at some rate α.

After initial symptomatic infection, HIV enters a dormant stage which lasts approximately 10 years. We assume that individuals who have HIV but have not taken treatment will develop AIDS at a rate ν. Individuals in treatment will progress to AIDS at a slower rate denoted by θ. Upon development of AIDS, individuals succumb to the disease at a rate γ.

From these assumptions, we obtain the following system of five ODEs:

$$\dot{S} = \pi - (\mu + \psi\epsilon)S - (1 - \psi\epsilon)\lambda_s$$
$$\dot{S_E} = \psi\epsilon S - \mu S_E - \lambda_{Se}$$
$$\dot{I_u} = (1 - \psi\epsilon)\lambda_s + \lambda_{se} + \alpha I_T - (p + \theta + \mu)I_u$$
$$\dot{I_T} = p I_u - (\alpha + \mu + \nu)I_T$$
$$\dot{A} = \theta I_u + \nu I_T - (\mu + \gamma)A, \tag{3}$$

with positive initial conditions $(S_0, S_{e0}, I_{u0}, I_{T0}, A_0)$. If we let $\psi\epsilon = 0$ then the model is for treatment only and if $p = \alpha = \nu = 0$ then the model is for education only.

2.2 Results

In this subsection we present analysis of model 3 as well as some numerical simulations of the model. The analysis of the model will show that upon certain conditions that the disease-free equilibrium (DFE) is globally asymptotically using a Lyapunov function. For numerical results, we generated a large sample of parameter space using Latin hypercube sampling. The ranges used for each parameter are shown below in Table (1). In this paper, the results presented are from subsets of the Latin hypercube sample.

2.2.1 Disease-free equilibrium

The disease-free equilibrium for model 3 is found by setting $I_u = I_T = A = 0$, as well as time derivatives and solving for $\bar{S}$ and $\bar{S}_e$. For model 3 the DFE is given by

$$\left(\bar{S}, \bar{S}_e, 0, 0, 0\right) = \left(\frac{\pi}{\mu + \psi\epsilon}, \frac{\psi\epsilon}{\mu}\frac{\pi}{\mu + \psi\epsilon}, 0, 0, 0\right),$$

where, for example, $\frac{\pi}{\mu+\psi\epsilon}$ is the mean time an individual spends in S. The stability of the DFE is determined using the next-generation method technique of Watmough and van den Driessche [12]. The quantity that determines stability is known as the basic reproduction number (R_0) which is the number of secondary infections caused by the introduction of one infectious individual into a totally susceptible population. For model 3, one can find the following matrices F, V for the next generation method:

$$F = \begin{bmatrix} \beta_1((1-\psi\epsilon)S_0c_s + S_{E0}c_{Se}) & 0 & 0 \\ 0 & \beta_2((1-\psi\epsilon)S_0c_s + S_{E0}c_{Se}) & 0 \\ 0 & 0 & \beta_3((1-\psi\epsilon)S_0c_s + S_{E0}c_{Se}) \end{bmatrix}$$

and

$$V = \begin{bmatrix} p + \theta + \mu & 0 & 0 \\ 0 & \mu + \gamma & 0 \\ 0 & 0 & \alpha + \mu + \nu \end{bmatrix}.$$

Therefore, since R_0 is given by the largest eigenvalue of FV^{-1} we have

$$R_0 = \max_{i \in \{1,2,3\}} R_i, \tag{4}$$

where, for example, $R_1 = R_{I_u} = \frac{\beta_1 c(S_0(1-\psi) + S_{e0}\phi)}{p+\theta+\mu}$ and R_{I_T}, R_A are similar in form. Thus, the reproduction number is the maximum of the number of infections caused by the introduction of a untreated HIV-infected individual, a treated HIV-infected individual or an AIDS-infected individual into a totally susceptible population. We now show that the DFE is globally asymptotically stable whenever $R_0 < 1$.

Theorem 1. *The DFE is globally-asymptotically stable whenever $R_0 < 1$.*

Proof. First, one can easily show that the system of equations given in 3 with positive initial conditions are well-posed (e.g. there exists a non-negative solution for all time). Now, let

$$D = \{(S, S_e, I_u, I_T, A) \in R_+^5 | S, S_e, I_u, I_T, A \geqslant 0, S + S_e + I_u + I_T + A \leqslant N_0\},$$

and summing the 5 ODEs in 3 we obtain

$$\dot{N} = N_0 - \mu N - \gamma A \leqslant N_0 - \mu N.$$

Therefore, N is bounded below by N_0 and above by $N_0 \exp\{-\mu t\} + \frac{\pi}{\mu}(1 - \exp\{\mu t\})$ and D is attracting and positively invariant.

Let $F(I, A) = (1 - \psi\epsilon)R_I I + R_T I_T + R_A A$; we claim F is a Lyapunov function on D. First, it is obvious that $F(0, 0) = 0$ and $F(I, A) > 0$ for all I_u, I_T and A not equal to 0.

Now, we must show that $\dot{F}(I_u, I_T, A) < 0$ for all I_u, I_T and A. We have

$$\begin{aligned}
\dot{F}(I_u, I_T, A) &= (1 - \psi\epsilon)R_I \dot{I} + R_T \dot{I_T} + R_A \dot{A} \\
&= I_u(p + \theta + \mu)(R_I - 1) + I_T(\alpha + \mu + \nu)(R_{I_T} - 1) + A(\mu + \gamma)(R_A - 1) \\
&< 0,
\end{aligned}$$

which is less than 0 because all parameters are positive and we assume that $R_0 < 1$ so all partial reproductions numbers must also be less than 1. Therefore F is a Lyapunov function on D, which implies $I(t)$ and $A(t)$ go to 0 as t approaches ∞. From this, we get that the limit of $S(t)$ as t approaches ∞ is N_0 and the DFE is GAS. □

2.3 Numerical Results

The Latin hypercube sampling technique was first developed by McKay et al. [8] and more recently by Blower and Dowlatabadi [1]. It is a modified Monte Carlo, or random sampling technique in which each parameter is treated as a random variable and is assigned a probability density function. Each distribution is then divided into n sub-intervals and randomly sampled creating input vectors of length n for each parameter. In this study, each parameter was assigned a continuous uniform probability density function, with ranges shown in Table 1, to generate parameter sets. We chose a continuous uniform distribution for several reasons. First, data are equally likely to be sampled which is important because of the uncertainty in the data. Secondly, choosing other distributions leads to other assumptions, which may or may not be true and thus we chose to use a simple distribution until more data becomes available.

For this study, thousands of simulations were run and the figures focus on some key results. It should be noted that some parameters were assumed to be constant as reasonable estimates were available. For this study, π, μ, θ, ν and γ were set to 1000, .0195, 1/10, 1/15 and 1/5. For example, we assumed that the average time to develop AIDS was 10 years and if an individual was in treatment this time would be extended to, on average, 15 years.

Table 1: Parameter ranges for Latin hypercube sample

parameter
$0 \leqslant \psi \epsilon \leqslant 1$
$0.003 \leqslant \beta_1 \leqslant 0.05$
$.0003 \leqslant \beta_2 \leqslant .005$
$.05 \leqslant \beta_3 \leqslant .5$
$10 \leqslant c_s \leqslant 100$
$1 \leqslant c_{se} \leqslant 10$
$0 \leqslant p \leqslant 1$
$0 \leqslant \alpha \leqslant 1$

Before presenting numerical results we discuss the initial conditions for model 3. A usual choice for many models is to set initial conditions as the DFE. However, given that the HIV epidemic is almost 30 years old now, we chose to use a different approach. The initial conditions were chosen to reasonably represent current numbers in Ottawa based on the crude estimates available [2, 5, 9]; from [2, 5, 9] we have

$$(S_0, S_{e0}, I_{u0}, I_{T0}, A_{T0}) = (2000, 0, 300, 0, 50)$$

Thus, the goal of these simulations was to evaluate the effectiveness of introducing education and treatment on the current epidemic in Ottawa and predicting future prevalence rates. More specifically, we wondered if an outreach-based HIV prevention program should be put in place in a community with a (approximately) 20% HIV/AIDS prevalence. Our model predicts that the results are dependent on a number of factors:

- The number of infected needles the average injection drug user comes in contact with in a year, prior to the program;

- the number of infected needles the average injection drug user comes in contact with in a year, after to the program;

- the proportion of susceptible injection drug users reached by the program.

Before considering results of the full model, we examined the effectiveness of education-only and treatment-only intervention methods. For simulations of the treatment-only model we did not notice any interesting results. In all simulations, treatment was ineffective in lowering the prevalence rates of HIV and AIDS. One possible reason for this is that the treatment model is too simple; see Section 4 for a further discussion of this point.

Figures 1-2 show two simulations of the education-only model when 80 % of susceptible individuals enter a education program and it would lower the number of infected needles they encounter by a factor of 10. Over the first 20 years (see Figure (1)) we see that the education program is effective as prevalence rates for
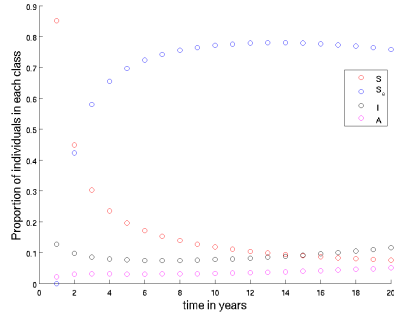
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Figure 1: Numerical solutions of the model for $c_s = 30$, $c_{se} = 3$ and $\psi\epsilon = .8$. This figure shows that prevalence rates are approximately 20 % after 20 years. Other parameter values were $\beta_1 = .025$, $\beta_2 = .0025$, $\beta_3 = .25$
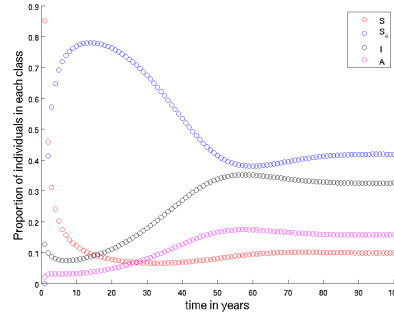
Figure 2: Numerical solutions of the model for $c_s = 30$, $c_{se} = 3$ and $\psi\epsilon = .8$. This figure shows that prevalence rates are approximately 45 % after 100 years. Other parameter values were $\beta_1 = .025$, $\beta_2 = .0025$, $\beta_3 = .25$

HIV and AIDS reach a level of 20 % after 20 years. After 100 years, we see that prevalence rates reach levels of approximately 45%. This means that education programs are not effective in combating the HIV epidemic for the parameters in this scenario. Figures 3-4 show two simulations where the number of needles used by educated and un-educated individuals was increased (see figure caption for values). These figures show that, even after 20 years, education programs were ineffective in stabilizing current prevalence rates or lowering them. In fact, prevalence rates increase immediately and sharply, reaching 30% HIV prevalence in just 10 years.

There are two conclusions that can be drawn from these figures. First, education-only programs maybe effective in stabilizing current prevalence rates for 30 years, thus providing additional time for the discovery of other prevention methods. Secondly, all results indicated that the important model parameters were c_s and c_{se}. Thus, future research projects need to determine reasonable estimates of these parameters so that there is less uncertainty in our theoretical model.

An outreach-based HIV prevention program could provide effective and anonymous HIV testing and treatment facilities. We considered that 50% of HIV-infected IDUs would take treatment were it made available to them. As the viral load among treated HIV-infecteds is lower, we decreased the transmission rate from the mean value of 0.05 to the lower limit of 0.025. The trends are similar to the scenarios considered previously, but the climb in HIV prevalence is more gradual. Figures 5-6 show a simulation of this scenario after 20 years and 100 years, respectively. After 20 years, one can see that the combination of both programs has been effective as prevalence rates have been lowered to approximately 10 %, down from the current level of 20 %. However, after 100
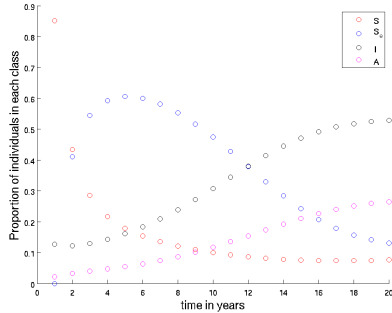
Figure 3: Numerical solutions of the model for $c_s = 50$, $c_{se} = 5$ and $\psi\epsilon = .8$. This figure shows that prevalence rates are approximately 45 % after 100 years. Other parameter values were $\beta_1 = .025$, $\beta_2 = .0025$, $\beta_3 = .25$
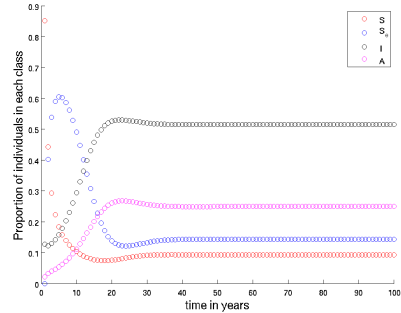
Figure 4: Numerical solutions of the model for $c_s = 50$, $c_{se} = 5$ and $\psi\epsilon = .8$. This figure shows that prevalence rates are approximately 45 % after 100 years. Other parameter values were $\beta_1 = .025$, $\beta_2 = .0025$, $\beta_3 = .25$

years it can be seen in Figure 6 that the combination of both programs are not efficient to keep the prevalence rates lowered long-term. After approximately 50 years, prevalence rates are approximately 45 %. Figures 7-8 show that prevalence rates reach levels of approximately 80 % after 20 years if $c_s = 50$ and $c_{se} = 5$. Figures 5-6 show that the combined prevention method of education and treatment can be effective in lowering prevalence rates, however, over a long-time period they are ineffective. However, the combined effort will provide some additional time to develop other prevention methods. We also once again found that the important model parameters were c_s and c_{se}. Thus, it is imperative that future research projects attempt to estimate the number of dirty needles individuals are using as these estimates would greatly improve this theoretical model.

3   Individual-based model

Individual-based models (IBM) have seen applications in many areas such as ecology and forestry. However, to the best our knowledge, no IBM has been developed to model the dynamics of HIV. In this section, we present some results on the IBM developed in this paper and discuss some of the complications we faced in implementing this model.

The IBM developed follows the same assumptions as the ODE model developed in Section 2. However, there are some distinctions between the two models that must be discussed. First, the ODEs of model 3 are replaced by difference equations which keep track of the number of individuals in each class. Each individual is assigned a different value for each model parameter although this value is not necessarily unique. That is, it is possible to have two individuals
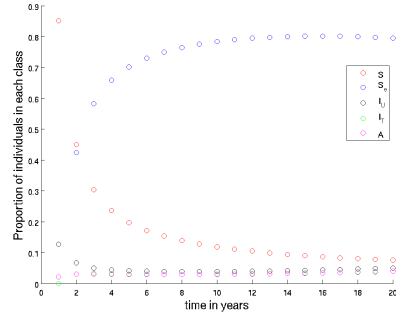
Figure 5: Numerical solutions of the model for $c_s = 30$, $c_{se} = 3$, $\psi\epsilon = .8$, $p = .5$ and $\alpha = .25$. This figure shows that prevalence rates are approximately 10 % after 20 years. Other parameter values were $\beta_1 = .025$, $\beta_2 = .0025$, $\beta_3 = .25$
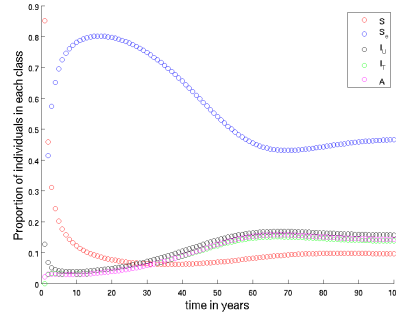

Figure 6: Numerical solutions of the model for $c_s = 30$, $c_{se} = 3$, $\psi\epsilon = .8$, $p = .5$ and $\alpha = .25$. This figure shows that prevalence rates are approximately 40 % after 100 years. Other parameter values were $\beta_1 = .025$, $\beta_2 = .0025$, $\beta_3 = .25$
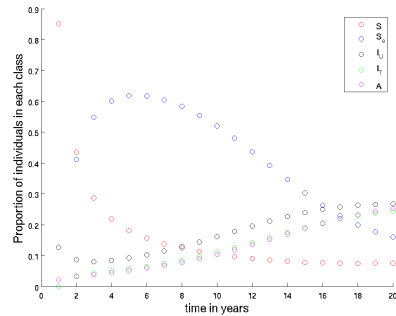

Figure 7: Numerical solutions of the model for $c_s = 50$, $c_{se} = 5$, $\psi\epsilon = .8$, $p = .5$ and $\alpha = .25$. This figure shows that prevalence rates are approximately 60 % after 20 years. Other parameter values were $\beta_1 = .025$, $\beta_2 = .0025$, $\beta_3 = .25$

Figure 8: Numerical solutions of the model for $c_s = 50$, $c_{se} = 5$, $\psi\epsilon = .8$, $p = .5$ and $\alpha = .25$. This figure shows that prevalence rates are approximately 70 % after 100 years. Other parameter values were $\beta_1 = .025$, $\beta_2 = .0025$, $\beta_3 = .25$
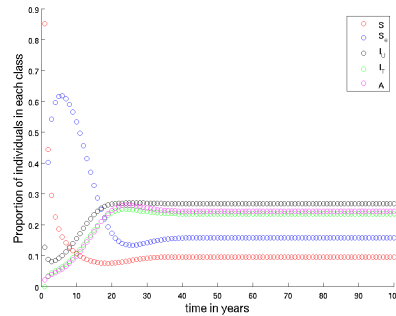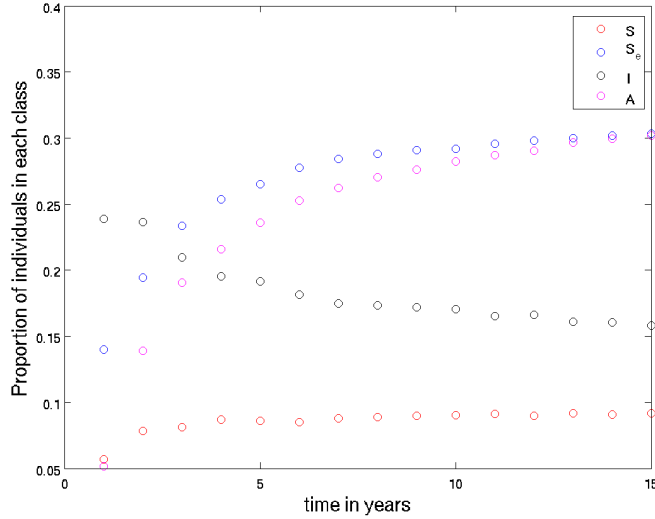
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Figure 9: Numerical simulation of the IBM for the same parameter set as Figure 3

in the population who have the same value of, for example, β_1. Below, we first present a result from the IBM for education-only and then discuss some difficulties we faced in implementing further models.

Figure 9 shows a simulation of the IBM for $c_s = 50$, $c_{se} = 5$ and other parameters the same as in Figure 3. Comparing this figure with Figure 3 we can see that in the IBM that we have similar proportions for the number of individuals in the educated and uneducated susceptibles. It appears that the proportion of individuals in the HIV class and AIDS class have switched for these two figures. It is hard to say anything more as the IBM is expensive computationally as discussed below.

There were many difficulties in implementing the individual-based model proposed in this paper. The most important was the computational time required to run the model. For example, let's assume the population begin with 1000 individuals with $c_s = 20$ and $c_{se} = 5$. Even in this case where individuals are exposed a small number of dirty needles, the computational time required is large. This is because for each of the 1000 individuals, we must check each of the 20 dirty needles for individuals in S and 5 for individuals in S_e. As the population increases from year to year this results in an extraordinary number of calculations. Secondly, it is difficult to parameterize the model; for example, since it individual is unique it is difficult to determine the likelihood each individual would enter an education program or take treatment. Lastly, further uncertainties are introduced because of the stochastic nature of the IBM. However, once the model is implemented more efficiently, we feel it will make an

important contribution to HIV research as discussed in Section 4.

4   Discussion and conclusion

The current HIV prevalence among injection drug users in major Canadian cities is alarming. Prevalence estimates from American and European cities are even more so. It is clear that something needs to be done in order to curb HIV transmission among Canadian injection drug users. Even those who argue that injection drug users are knowingly putting their health and their lives at risk must understand that the implications of this epidemic stretch far beyond the IDU community. The costs of treating this disease among this population are astronomical. The Canadian health care budget will suffer by hundreds of millions of dollars if we cannot control this epidemic.

The results of our analysis indicate that beating the current Canadian HIV epidemic among the injection drug using population is not an easily achievable goal. However, with education and treatment strategies in place, we can buy some time, in the hopes that a cure may be found within the coming decades. Our recommendation would be to implement a treatment + education program, aiming for 80% uptake of prevention, and 50% treatment uptake, until that time when more effective prevention and/or treatment strategies are available.

As mentioned in Section 2.3, one possible explanation for the results of our treatment model is that it is far too simple. This model does not include drug levels in the body, development of drug resistance and other important factors identified in [10, 11]. Thus, if the treatment model in this paper was changed to a similar model was [10, 11], we may see improved results for the treatment-only model and the combined model as well.

Although we were not able to get many interesting results from the individual-based model, we still feel it will be useful contribution to research on HIV once it is working efficiently. IBMs can investigate questions that the population-based models cannot; for example, examining the effect of individual variability in entering an education program or accepting treatment. However, IBMs can also become quite complex rather quickly making the results difficult to interpret. These models can also be difficult to parameterize as it is challenging to obtain sufficient individual-based data from HIV studies. Thus, one must be careful when interpreting the results and putting any emphasis on future policies. These models should be treated as theoretical in nature and used to aid future research studies.

The greatest limitation of our model is that we were unable to find estimates of the frequency with which HIV-susceptible injection drug users inject from HIV-infected needles. There are obvious challenges involved in the estimation of this variable. A well-designed, anonymous survey of the IDU population could determine an approximate number of needles shared in a year, and perhaps the number of people with whom the average IDU shares needles. At that point, contact network modeling techniques could be used to determine the number of infected needles the average HIV-susceptible IDU contacts in a year. Once

this has been done, we can then develop a bio-economic model to determine the most cost-effective strategy for combating HIV.

References

[1] S. M. Blower and H. Dowlatabadi. Sensitivity and uncertainity analysis of complex models of disease transmission: an HIV model, as an example. *International Statistical Review*, 2:229–243, 1994.

[2] Julie Bruneau, Francois Lamothe, Julio Soto, Nathalie Lachance, Jean Vincelette, Anne Vassal, and Eduardo L. Franco. Sex-specific determinants of HIV infection among injection drug users in montreal. *Canadian Medical Assocation Journal*, 164:767–773, 2001.

[3] Health Canada: Hepatitis C and Injection Drug Use. Ottawa: 2001. www.phacaspc.gc.ca/hepc/hepatitis_c/pdf/aboutFactsSheet1.pdf.

[4] SL. Coyle, RH. Needle, and J. Normand. Outreach-based HIV prevention for injection drug users: a review of published outcome data. *Public Health Rep.*, 113:19–30, 1998.

[5] Catherine Hankins, Michel Alary, Raymond Parent, Caty Blanchette, Christianne Claessens, and The SurvUDI Working Group. Continuing HIV transmission among injection drug users in eastern central canada: the survUDI study, 1995 to 2000. *Journal of Acquired Immune Deficiency Syndromes*, 30:514–521, 2002.

[6] H. Hethcote. The mathematics of infectious diseases. *SIAM Review*, 42:599–653, 2000.

[7] LM. Kuyper, RS. Hogg, JSG. Montaner, MT. Schechter, and E. Wood. The cost of inaction of HIV transmission among injection drug users and the potential for effective interventions. *Journal of Urban Health: Bulletin of the New York Academy of Medicine*, 81, 2004.

[8] M. D. Mckay, W. J. Conover, and R. J. Beckman. A comparison of three models for selecting values of input variables in the analysis of output from a computer code. *Technometrics*, pages 239–245, 1979.

[9] University of Ottawa: Individual and Population Health. www.med.uottawa.ca/curriculum/iph/data/HIV_Ottawa_e.htm.

[10] R.J. Smith? and L.M. Wahl. Distinct effects of protease and reverse transcriptase inhibition in an immunological model of HIV-1 infection with implusive drug effects. *Bulletin of mathematical biology*, 66:1259–1283, 2004.

[11] Robert J. Smith? Explicit accounting for antiretroviral drug uptake in theoretical HIV models predicts long-term failure of protease-only therapy. *Journal of Theoretical Biology*, 251:227–237, 2007.

[12] Pauline van den Driessche and James Watmough. Reproduction numbers and sub-threshold endemic equilibrium for compartmental models of disease transmission. *Mathematical Biosciences*, 180:29–48, 2002.