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Drugs, sex and HIV: a mathematical model for New York City

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CONTENTS

SUMMARY

A data-based mathematical model was formulated to assess the epidemiological consequences of heterosexual, intravenous drug use (IVDU) and perinatal transmission in New York City (NYC). The model was analysed to clarify the relationship between heterosexual and IVDU transmission and to provide qualitative and quantitative insights into the HIV epidemic in NYC. The results demonstrated the significance of the dynamic interaction of heterosexual and IVDU transmission. Scenario analysis of the model was used to suggest a new explanation for the stabilization of the seroprevalence level that has been observed in the NYC IVDU community; the proposed explanation does not rely upon any IVDU or sexual behavioural changes. Gender-specific risks of heterosexual transmission in IVDUs were also explored by scenario analysis. The results showed that the effect of the heterosexual transmission risk factor on increasing the risk of HIV infection depends upon the level of IVDU. The model was used to predict future numbers of adult and pediatric AIDS cases; a sensitivity analysis of the model showed that the confidence intervals on these prediction estimates were extremely wide. This prediction variability was due to the uncertainty in estimating the values of the models' thirty variables (twenty biological-behavioural transmission parameters and the initial sizes of ten subgroups). However, the sensitivity analysis revealed that only a few key variables were significant in contributing to the AIDS case prediction variability; partial rank correlation coefficients were calculated and used to identify and to rank the importance of these key variables. The results suggest that long-term precise estimates of the future number of AIDS cases will only be possible once the values of these key variables have been evaluated accurately.

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1. INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is a major public health problem in New York City (NYC); as of September 1990 over 28000 adult AIDS cases and approximately 700 pediatric AIDS cases have been reported from the City (NYC Health Department 1990). Intravenous drug users (IVDUs) have become a significant risk group for the human immunodeficiency virus (HIV); IVDUs can acquire the virus through either heterosexual transmission or through IVDU (by the sharing of needles or other injecting equipment) (Curran *et al.* 1988; des Jarlais *et al.* 1989; Friedland & Klein 1987; Moss 1987). Seropositive IVDUs can heterosexually transmit HIV to their non-IVDU sex partners, and seropositive female IVDUs are the primary source for perinatal transmission in NYC (Curran *et al.* 1988; des Jarlais *et al.* 1989; Friedland & Klein 1987; Moss 1987). Consequently, IVDUs now play a major role in HIV transmission and disease in NYC. Furthermore, as it has been estimated that there are approximately 200000 addicts in the NYC IVDU community (Frank *et al.* 1978), large numbers of AIDS cases that are attributable to IVDU, heterosexual or perinatal transmission may be expected in the future.

Mathematical models may be conceptualized as thought experiments, and therefore models are useful when physical experiments are impossible to perform because of time, monetary or ethical constraints. As with physical experiments, the behaviour of the system is understood by altering the assumptions or parameter values and measuring the effect on the outcome variable. Thought experiments should be designed in the same manner as physical experiments, with only a few variables; the specific variables should be determined by the particular research objectives. In this study, only the epidemic of HIV that is due to IVDU, heterosexual and perinatal transmission is modelled, the effects of homosexual and bisexual transmission are excluded. Mathematical models may be used to make quantitative predictions; for example, models may be used to estimate the future number of AIDS cases. However, the precision of these predictions is often limited by the uncertainty in estimating both the sizes of the risk groups and the values of the biological-behavioural transmission parameters (Anderson & May 1988). Models may also be used to make qualitative predictions; for example, models may be used to explicate the mechanism that links specific risk behaviours of individuals with the seroprevalence level of a population. In this study, we formulate and analyse a model in order to generate both qualitative and quantitative predictions.

In this paper we present a data-based mathematical model that we have formulated and analysed to assess the epidemiological consequences of heterosexual, IVDU and perinatal HIV transmission. The model was designed to reflect the specific transmission dynamics of these three processes in New York City. It was used in two ways to understand HIV/AIDS epidemiology. First, the model was used to suggest a new explanation for the observed IVDU seroprevalence pattern in NYC and to explore the effect of the heterosexual transmission risk factor on increasing the risk of HIV infection in IVDUs. Second, the model was used to predict future numbers of adult and pediatric AIDS cases, to assess the variability in these predictions and to identify the key variables that contributed to this prediction imprecision. This paper is organized in the following manner: the model structure is described and justified, the model equations are presented, the qualitative behaviour of the model is explored through a specific scenario analysis, and finally the quantitative behaviour of the model is investigated by a sensitivity analysis.

2. JUSTIFICATION OF MODEL STRUCTURE

(*a*) *Basic structure*

The majority of IVDUs in NYC are heroin users (Hubbard *et al.* 1984; Joseph *et al.* 1981), many of whom became addicts in the late 1960s and the early 1970s when there was an increased availability of heroin (des Jarlais & Uppal 1980). Hence, the mathematical model presented in this paper is formulated for a fixed cohort of IVDUs; three transmission routes are modelled: IVDU (by sharing needles or other IVDU equipment), heterosexual and perinatal. IVDU behaviour and sexual behaviour are extremely heterogeneous and significant gender differences are found for these two types of behaviours (Chaisson *et al.* 1989; Coleman & Curtis 1988; des Jarlais & Friedman 1988*a*, *b*; des Jarlais *et al.* 1988*a*, *b*; Friedland *et al.* 1985; Schoenbaum *et al.* 1989, 1990); therefore, the model includes gender-specific behavioural heterogeneity.

Two predominant patterns of needle-sharing behaviour have been identified in NYC. IVDUs have been found to share needles and other IVDU equipment with either strangers in shooting galleries or with close friends and relatives in other social environments (des Jarlais *et al.* 1986*a*, *b*; Schoenbaum *et al.* 1989); these two types of IVDUs may be called stranger-users or buddy-users, respectively. Although both types of IVDUs share needles, they have significantly different risks of acquiring HIV. The risk of HIV infection in stranger-users depends upon the rate of sharing needles, the HIV transmission efficiency per injection and the seroprevalence in the subgroup of stranger-users. The risk of infection in buddy-users depends upon the stability of the buddy affiliations over time, the HIV transmission efficiency per buddy partnership and the seroprevalence in the subgroup of buddy-users. Stranger-users and buddy-users are not equally represented in the NYC IVDU community, only a small minority of IVDUs are stranger-users (Hartel *et al.* 1988; Hartel *et al.* submitted). Heterogeneity in IVDU behaviour was modelled by including both types of IVDUs. Gender-specific heterogeneity in IVDU behaviour was included by allowing the rate of sharing needles and the rate of change of buddy partners to differ between the sexes.

The model consists of thirty-four ordinary differential equations; the definitions of the parameters are given in table 1. There are ten interacting subgroups of

adults in the model; eight IVDU subgroups and two non-IVDU subgroups in the bridge community (male and female non-IVDU sex partners of the IVDUs). The eight IVDU subgroups are defined by a hierarchial stratification of the initial IVDU community at three levels: gender, IVDU behaviour (stranger-user or buddy-user) and sexual behaviour. At the sexual behaviour level, IVDUs are classified into two groups based upon whether they have any new sex partners over the time course of the epidemic. The two groups are 'no new sex partners' or 'X new sex partners', where X is assigned a specific data-based value for each IVDU behavioural group. This sexual behaviour dichotomy was devised because a certain proportion of IVDUs may be sexually inactive, due to a variety of causes including psychological dysfunction and heroin-related depressed libido (Kreek 1983). This hierarchial classification scheme of IVDUs incorporates gender-specific heterogeneity in both IVDU and sexual behaviour, and also ensures that the effects of the different risk factors can be independently assessed. Gender-specific heterogeneity in sexual behaviour is modelled by allowing the rate of change of sex partners to differ in each of the six sexually active subgroups.

(*b*) *IVDU and sexual mixing matrices*

The ten subgroups are linked by either IVDU (sharing needles and/or other IVDU equipment) and/or by sexual partner choice; these two mixing patterns are modelled by defining sexual and IVDU mixing matrices. The mixing matrices serve to allocate partnerships; they specify who has sex with whom and who shares needles with whom. Sexual mixing matrices are defined based upon particular assumptions as to how the different subgroups select sex partners. Three subgroups of each sex are sexually active: stranger-users, buddy-users and non-IVDUs. The three-by-three sexual mixing matrices are gender-specific; the coefficients of these matrices ($m_f(i,j;t)$ for females and $m_m(i,j;t)$ for males) are the probabilities that an individual in subgroup i has a sexual partnership with an individual of the opposite sex in subgroup j at time t; subgroups i and j are either sexually active stranger-users, buddy-users or non-IVDUs.

The sexual mixing matrices must meet the following four constraints:

(i) All of the coefficients ($m_f(i,j;t)$, $m_m(i,j;t)$) must be greater than or equal to zero and less than or equal to one.

(ii) The sum of every row in the mixing matrices must equal one or zero.

(iii) The number of male (m) partnerships at any time ($N_{mj}(t)\,c_{mj}(t)\,m_m(j,i;t)$) must equal the number of female (f) partnerships at that time ($N_{fi}(t)\,c_{fi}(t)\,m_f(i,j;t)$) for each subgroup; $c_i(t)$ is the rate of change of sex partners for group i at time t, N_i is the number of sexually active individuals (the sum of the susceptible, infected and AIDS individuals) in subgroup i at time t.

(iv) If the total number of partnerships of any subgroup is zero (either $N_{fi}(t)\,c_{fi}(t)$ or $N_{mj}(t)\,c_{mj}(t)$) then the corresponding mixing matrix coefficients ($m_f(i,j;t)$ and $m_m(j,i;t)$) are also zero.

Many different sexual mixing patterns are possible, because individuals can 'mix' with individuals in any of the three subgroups of the opposite sex. These possible sexual mixing patterns lie along a continuum; the extremes of this continuum are perfect positive and perfect negative assortative mixing. Perfect negative assortative mixing is defined as 'like individuals mix only with unalike individuals of the opposite sex', where individuals are one of the three types: stranger-users, buddy-users or non-IVDUs. Perfect positive assortative mixing is defined as 'like individuals mix only with like individuals of the opposite sex'. A perfect positive assortative sexual mixing matrix is equivalent to an identity matrix; the diagonal coefficients are ones and the off-diagonal coefficients are zeroes. Gender-specific perfect positive assortative sexual mixing matrices will only achieved if both the sex ratio and the gender-specific rates of sexual partner change are equal. If these conditions are not satisfied, then positive assortative mixing matrices can be generated, but these matrices are not equivalent to an identity matrix. This type of positive assortative mixing may be defined as 'like individuals mix mainly with like individuals of the opposite sex'. Proportional mixing lies between the extremes of perfect positive and perfect negative assortative mixing. Proportional mixing is defined as 'individuals mix with the opposite sex individuals in proportion to the frequency with which the opposite sex individuals are represented in the sexual community'.

The sex ratio in the NYC IVDU community is highly skewed (3 males:1 female) (des Jarlais *et al.* 1984; Drucker 1986) and the gender-specific rates of sexual partner change are heterogeneous. These observations and the available data suggest that the sexual mixing pattern in NYC may be characterized as 'like with mainly like' mixing†. Therefore, positive assortative sexual mixing matrices were generated for all of the numerical studies presented in this paper. A computer algorithm was developed to generate these matrices; this algorithm simultaneously maximized the amount of positive assortative mixing in both sexes in all three subgroups at all times throughout the numerical simulations. The epidemiological effects of other sexual mixing patterns (proportional mixing and negative assortative mixing) will be presented in a future paper.

In the model, a single IVDU mixing matrix is defined that specifies the needle-sharing mixing probabilities for both sexes; the coefficients of this matrix specify the probability that the needle-sharing partners practice the same type of IVDU (stranger-use or buddy-use). Therefore, the two-by-two IVDU mixing matrix is equivalent to the identity matrix, and stranger-users and buddy-users form mutually exclusive needle-sharing groups; consequently the only spread of the virus between these two groups is due to heterosexual transmission. This IVDU mixing pattern

† Montefiore Medical Center Group personal communication and unpublished data.

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is a simplification of the actual mixing pattern that occurs in the NYC IVDU community; IVDUs generally predominantly practice either stranger-user or buddy-user behaviour, although some individuals will practice both types of behaviour. The epidemiological consequences of more complex needle-sharing patterns that may occur between stranger-users and buddy-users will be presented in a future paper.

3. MODEL EQUATIONS

The following equations specify the model; the parameter definitions are listed in table 1. The rate of change of the population size of susceptible women (X_{1f}) who have the single IVDU risk factor (stranger-user) is:

$$\frac{dX_{1f}}{dt} = -X_{1f} i_f \lambda_i - X_{1f} a_{df}, \quad (1)$$

where i_f is the rate of sharing needles per female, λ_i is the female stranger-users IVDU transmission probability and a_{df} is the non-HIV mortality rate, calculated by assuming an average span for injecting drugs of 35 years. The per capita probability of acquiring HIV from a partner or a needle is the product of the transmission efficiency of the virus (given that the partner or the needle is infected) and the probability that the partner or needle is infected with the virus. The probability of acquiring HIV from sharing needles with strangers per female (λ_i) equals the transmission efficiency of acquiring HIV from injecting with one infected needle (β_{dn}) multiplied by the seroprevalence in the total group of male and female (sexually active and non-sexually active) stranger-users sharing needles at time $t(PS(t))$. It is assumed, throughout the model, that IVDUs with AIDS continue to inject drugs and to be sexually active.

The rate of change of the population size of susceptible women (X_{2f}) who have the single IVDU risk factor (buddy-user) is:

$$\frac{dX_{2f}}{dt} = -X_{2f} j_f \lambda_j - X_{2f}\, a_{df}, \quad (2)$$

where j_f is the rate of change of drug buddies per female and λ_j is the female buddy-users IVDU transmission probability. The probability of acquiring HIV from sharing needles with buddies per female (λ_j) equals the transmission efficiency of HIV during a buddy partnership (given that the buddy partner is infected) (β_{db}) multiplied by the seroprevalence in the total group of male and female (sexually active and non-sexually active) buddy-users sharing needles at time $t(PB(t))$.

The rate of change of the population size of susceptible women (X_{3f}) who have dual risk factors (sexually active stranger-users) is:

$$\frac{dX_{3f}}{dt} = -X_{3f}(i_f \lambda_i + c_{fs}(t)\, \lambda_{3f}) - X_{3f}\, a_{df}, \quad (3)$$

where $c_{fs}(t)$ is the rate of change of sex partners per female stranger-user and λ_{3f} is the probability of acquiring HIV from heterosexual transmission per female stranger-user; λ_{3f} equals the male to female heterosexual transmission efficiency per partnership (given that the male is infected) (β_{mf}) multiplied by the weighted seroprevalence $(\Sigma_i m_f(s,i;t)\, P_m(i,t)$; where $P_m(i,t)$ is the seroprevalence in sexually active males in subgroup i, where i equals stranger-user, buddy-users or non-IVDUs and $m_f(s,i;t)$ is the probability that a female stranger-user has a sexual partnership with a male in subgroup i at time t).

The rate of change of the population size of susceptible women (X_{4f}) who have dual risk factors (sexually active buddy-users) is:

$$\frac{dX_{4f}}{dt} = -X_{4f}(j_f \lambda_j + c_{fb}(t)\, \lambda_{4f}) - X_{4f}\, a_{df}, \quad (4)$$

where $c_{fb}(t)$ is the rate of change of sex partners per female buddy-user and λ_{4f} is the probability of acquiring HIV from heterosexual transmission per female buddy-user: λ_{4f} equals the male to female heterosexual transmission efficiency per partnership (given that the male is infected) (β_{mf}) multiplied by the weighted seroprevalence $(\Sigma_i m_f(b,i;t)\, P_m(i,t)$; where $m_f(b,i;t)$ is the probability that a female buddy-user has a sexual partnership with a male in subgroup i at time t).

The rate of change of the population size of susceptible women (X_{5f}) who have the single risk factor (heterosexual transmission) is:

$$\frac{dX_{5f}}{dt} = -X_{5f}\, c_{fn}(t)\, \lambda_{5f} - X_{5f}\, a_f, \quad (5)$$

where $c_{fn}(t)$ is the rate of change of sex partners per female non-IVDU, a_f is the non-HIV mortality rate (calculated by assuming an average sexually active span of 50 years; therefore non-IVDUs are assumed to live longer than IVDUs: $a_{df} > a_f$) and λ_{5f} is the probability of acquiring HIV from heterosexual transmission per female non-IVDU; λ_{5f} equals the male to female heterosexual transmission efficiency per partnership (given that the male is infected) (β_{mf}) multiplied by the weighted seroprevalence $(\Sigma_i m_f(n,i;t)\, P_m(i,t)$; where $m_f(n,i;t)$ is the probability that a female non-IVDU has a sexual partnership with a male in subgroup i at time t).

The rate of change of the population sizes of the five subgroups of infected/infectious women are given below (equations 6–10), where v_a is the average duration of stay in the infected/infectious class. A constant rate of progression to disease is assumed, as has been assumed in many other simple deterministic HIV/AIDS models (Anderson 1988; Anderson *et al.* 1986, 1988; May & Anderson 1987; May *et al.* 1989) and v_a is set equal to the average incubation time of the virus.

$$\frac{dY_{1f}}{dt} = X_{1f} i_f \lambda_i - Y_{1f}\left(\frac{1}{v_a}\right) - Y_{1f}\, a_{df}, \quad (6)$$

$$\frac{dY_{2f}}{dt} = X_{2f} j_f \lambda_j - Y_{2f}\left(\frac{1}{v_a}\right) - Y_{2f}\, a_{df}, \quad (7)$$

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$$\frac{dY_{3f}}{dt} = X_{3f}(i_f\lambda_i + c_{fs}(t)\lambda_{3f}) - Y_{3f}\left(\frac{1}{v_a}\right) - Y_{3f}a_{df}, \quad (8)$$

$$\frac{dY_{4f}}{dt} = X_{4f}(j_f\lambda_j + c_{fb}(t)\lambda_{4f}) - Y_{4f}\left(\frac{1}{v_a}\right) - Y_{4f}a_{df}, \quad (9)$$

$$\frac{dY_{5f}}{dt} = X_{5f}c_{fn}(t)\lambda_{5f} - Y_{5f}\left(\frac{1}{v_a}\right) - Y_{5f}a_f. \quad (10)$$

The rate of change of the population sizes of the five subgroups of AIDS women are given below (equations 11–15), where s_a is the average survival time from diagnosis of AIDS to death.

$$\frac{dA_{1f}}{dt} = Y_{1f}\left(\frac{1}{v_a}\right) - A_{1f}\left(\frac{1}{s_a}\right) - A_{1f}a_{df}, \quad (11)$$

$$\frac{dA_{2f}}{dt} = Y_{2f}\left(\frac{1}{v_a}\right) - A_{2f}\left(\frac{1}{s_a}\right) - A_{2f}a_{df}, \quad (12)$$

$$\frac{dA_{3f}}{dt} = Y_{3f}\left(\frac{1}{v_a}\right) - A_{3f}\left(\frac{1}{s_a}\right) - A_{3f}a_{df}, \quad (13)$$

$$\frac{dA_{4f}}{dt} = Y_{4f}\left(\frac{1}{v_a}\right) - A_{4f}\left(\frac{1}{s_a}\right) - A_{4f}a_{df}, \quad (14)$$

$$\frac{dA_{5f}}{dt} = Y_{5f}\left(\frac{1}{v_a}\right) - A_{5f}\left(\frac{1}{s_a}\right) - A_{5f}a_f. \quad (15)$$

The model also includes fifteen corresponding equations for males; these equations have the same structure as the equations for females, but contain male-specific values for the IVDU and sexual behaviour parameters (see table 1).

Since the model specifies the rate of change of sexual partnerships and the number of sexually active females ($N_f(t)$) and males ($N_m(t)$), the following heterosexual partnership sum rule has to be satisfied at all times:

$$\sum_i N_{fi}(t)\,c_{fi}(t) = \sum_i N_{mi}(t)\,c_{mi}(t), \quad (16)$$

where

$$N_{fi}(t) = X_{fi}(t) + Y_{fi}(t) + A_{fi}(t)$$

and

$$N_{mi}(t) = X_{mi}(t) + Y_{mi}(t) + A_{mi}(t)$$

and i = sexually active stranger-users, buddy-users and non-IVDUs.

During the course of an epidemic, the number of sexually active individuals will change due to non-AIDS and AIDS mortality; therefore, the rate of change of sex partners must vary with the population size to keep the equation balanced. The heterosexual partnership sum rule may be satisfied by specifying a variety of different mechanisms (Le Pont & Blower, submitted typescript). In the numerical analysis of the discrete version of the model, an algorithm was used that altered the rate of change of sex partners (for each of the three sexually active classes in both sexes) in proportion to the availability of the opposite sex, in the following manner:

$$c_{fi}(t) = c_{fi}(t-1)\,\frac{\sum_j N_{mj}(t)\,c_{mj}(t-1)\,m_m(j,i;t-1)}{\sum_j N_{mj}(t-1)\,c_{mj}(t-1)\,m_m(j,i;t-1)}, \quad (17)$$

where t is the time interval; time steps of one day were used in the simulations.

$$c_{mi}(t) = c_{mi}(t-1)\,\frac{\sum_j N_{fj}(t)\,c_{fj}(t-1)\,m_f(j,i;t-1)}{\sum_j N_{fj}(t-1)\,c_{fj}(t-1)\,m_f(j,i;t-1)}. \quad (18)$$

The rate of change of the population size of the infected babies born to IVDU mothers is:

$$\frac{dY_{BI}}{dt} = b_d[((Y_{3f}+Y_{4f})\,q_1) + ((A_{3f}+A_{4f})\,q_2)] - Y_{BI}\left(\frac{1}{v_b}\right), \quad (19)$$

where b_d is the birth rate of IVDU mothers, q_1 is the vertical transmission efficiency in mothers who are seropositive (but without AIDS), q_2 is the vertical transmission efficiency in mothers who have been diagnosed with AIDS and v_b is the average pediatric incubation time. A birth rate for NYC IVDUs of 110

Table 1. *Definitions of biological and behavioural parameters*

(All of the transmission efficiencies are conditional on the fact that the partner or needle is infected with HIV.)

β_{db}	HIV transmission efficiency per buddy partnership
β_{dn}	HIV transmission efficiency per needle injection
β_{fm}	heterosexual transmission efficiency per partnership (female to male)
β_{mf}	heterosexual transmission efficiency per partnership (male to female)
$c_{fb}(t)$	rate of change of sex partners per year (female buddy-users) at time t
$c_{fs}(t)$	rate of change of sex partners per year (female stranger-users) at time t
$c_{fn}(t)$	rate of change of sex partners per year (female non-IVDUs) at time t
$c_{mb}(t)$	rate of change of sex partners per year (male buddy-users) at time t
$c_{ms}(t)$	rate of change of sex partners per year (male stranger-users) at time t
$c_{mn}(t)$	rate of change of sex partners per year (male non-IVDUs) at time t
i_f	rate of sharing needles per year (for female stranger-users)
i_m	rate of sharing needles per year (for male stranger-users)
j_f	rate of change of buddy partners per year (for female buddy-users)
j_m	rate of change of buddy partners per year (for male buddy-users)
q_1	vertical transmission efficiency (seropositive mother, without AIDS)
q_2	vertical transmission efficiency (AIDS mother)
s_a	mean adult survival time (years)
s_b	mean pediatric survival time (years)
v_a	mean adult incubation time (years)
v_b	mean pediatric incubation time (years)

babies per 1000 females per year was used in all the numerical simulations (NYC Department of Health 1985).

The rate of change of the population size of the infected babies born to non-IVDU mothers is:

$$\frac{dY_{BN}}{dt} = b_r[(Y_{5f}\,q_1) + (A_{5f}\,q_2)] - Y_{BN}\left(\frac{1}{v_b}\right), \tag{20}$$

where b_r is the birth rate of non-IVDU mothers. A birth rate for NYC non-IVDUs of 147 babies per 1000 females per year was used in all the numerical simulations (NYC Department of Health 1985).

The rate of change of the population size of AIDS babies that are born to IVDU and non-IVDU mothers is:

$$\frac{dA_{BI}}{dt} = Y_{BI}\left(\frac{1}{v_b}\right) - A_{BI}\left(\frac{1}{s_b}\right), \tag{21}$$

$$\frac{dA_{BN}}{dt} = Y_{BN}\left(\frac{1}{v_b}\right) - A_{BN}\left(\frac{1}{s_b}\right), \tag{22}$$

where s_b is the average pediatric survival time from diagnosis to death.

4. SCENARIO ANALYSIS

The qualitative behaviour of the model was explored by generating particular scenarios; appropriate values for NYC for the biological-behavioural transmission parameters and the initial sizes of the subgroups were selected from the available data. These computer simulations illustrated that the model could generate a variety of different seroprevalence patterns in the IVDU community. The patterns ranged from a multi-peaked epidemic in the different IVDU subgroups, to a monotonically increasing seroprevalence curve; the particular seroprevalence pattern was dependent upon the values of the biological-behavioural transmission parameters and the (sexual and IVDU) mixing patterns.

A specific scenario is shown in figure 1; the values of the parameters and the initial sizes of the subgroups are given in the figure legend. Seroprevalence levels in the IVDU community rise dramatically, reach a plateau and then stabilize for several years before beginning to rise again (see fig. 1). This temporary stabilization of seroprevalence levels occurred without any change in IVDU or sexual behaviour; it was simply because of the heterogeneity of IVDU behaviour (the eight subgroups of IVDUs had different levels of drug use) and the loose degree of connection between some of the subgroups (i.e. the positive assortative sexual and IVDU mixing patterns). At the beginning of the epidemic, stranger-users were quickly infected by needle-sharing, then HIV slowly seeped into the buddy-user subgroups (due to heterosexual transmission), and finally the virus spread, by heterosexual and IVDU transmission, throughout the buddy subcommunity. In this particular scenario, at the end

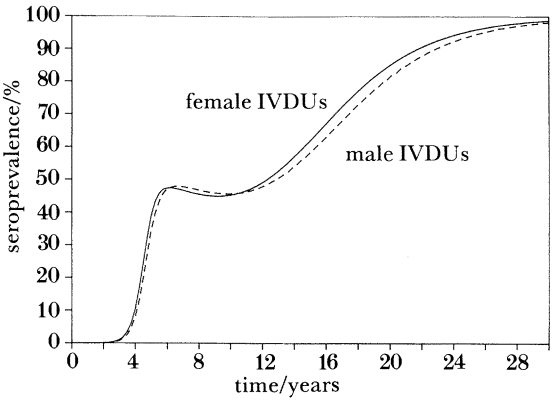

Figure 1. Seroprevalence levels (%) in male and female IVDUs are graphed. The epidemic was begun by introducing one infected male into the sexually active stranger-user category. The text includes a discussion of the estimation of the parameters and the initial subgroup sizes. The initial subgroup sizes, used in the scenario, were: $X_{1f} = 12\,500$, $X_{2f} = 8250$, $X_{3f} = 12\,500$, $X_{4f} = 16\,750$, $X_{5f} = 100\,000$, $X_{1m} = 63\,750$, $X_{2m} = 37\,500$, $X_{3m} = 11\,250$, $X_4 = 37\,500$, $X_{5m} = 50\,000$. The parameter values were estimated from the available data: $\beta_{db} = 0.5$, $\beta_{dn} = 0.01$, $\beta_{fm} = 0.08$, $\beta_{mf} = 0.24$, $c_{fb}(t) = 1.0$, $c_{fs}(t) = 2.0$, $c_{fn}(t) = 0.57$, $c_{mb}(t) = 1.0$, $c_{ms}(t) = 1.0$, $c_{mn}(t) = 1.0$, $i_f = 300$, $i_m = 230$, $j_f = 0.75$, $j_m = 0.75$, $s_a = 1.0$, $v_a = 8.0$.

of 30 years, only 0.03% of non-IVDU women and 0.01% of non-IVDU men were infected. The low amount of heterosexual transmission among the non-IVDUs was the result of the positive assortative sexual mixing pattern. This scenario also generated many more cumulative AIDS cases, at the end of thirty years, in non-IVDU females (3596) than in non-IVDU males (483). This asymmetry in the sex ratio of non-IVDU AIDS cases was due to the asymmetry in the heterosexual transmission efficiencies, the gender-specific differences in sexual behaviour and the asymmetric sex ratio in the IVDU community, (the majority of IVDUs are males, consequently the majority of their sex partners were non-IVDU females).

The history of the HIV epidemic in the NYC IVDU community has been constructed by using a series of seroprevalence surveys (des Jarlais *et al.* 1989). This reconstruction suggests that the epidemic in IVDUs has occurred in three distinct stages: an initial stage when the virus was first introduced and transmission was slow, a secondary stage when the seroprevalence level in IVDUs rose extremely rapidly within a few years, and a tertiary stage when the seroprevalence level stabilized between 50–60% (des Jarlais *et al.* 1989; des Jarlais & Friedman 1988*a*, *b*). Sexual and IVDU behaviour changes have been reported to have occurred in NYC (Chaisson *et al.* 1989; Cox *et al.* 1986; des Jarlais *et al.* 1985; Friedman *et al.* 1987; Selwyn *et al.* 1985) and it has been proposed that IVDU behaviour changes may have effected this stabilization (des Jarlais *et al.* 1989; des Jarlais & Friedman 1988*a*, *b*). However, the epidemiological consequences of behaviour changes cannot be evaluated without a dynamic analysis. Many alternative explanations can explain the stabilization of the seroprevalence level.

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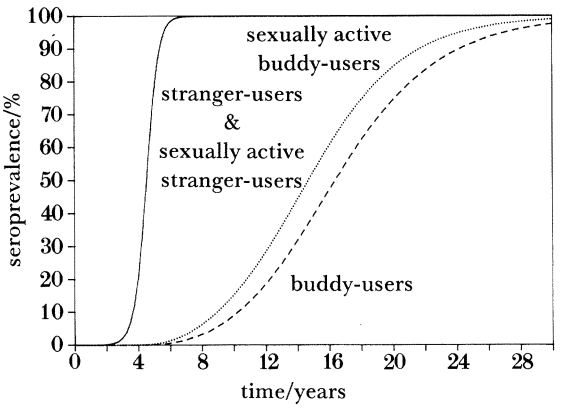

Figure 2. This figure shows the relative effects of heterosexual transmission versus IVDU transmission in female IVDUs. The seroprevalence levels in four groups of IVDUs (stranger-users, buddy-users, sexually active stranger-users and sexually active buddy-users) are graphed. The seroprevalence levels ris at exactly the same rate in both subgroups of stranger-users, but the seroprevalence levels in the two subgroups of buddy-users increase at different rates. The values of the initial subgroup sizes and the biological-behavioural parameter values are given in figure legend 1.

The simulated epidemic in figure 1 closely mirrors the observed seroprevalence pattern in the NYC IVDU community. The simulation results demonstrate that seroprevalence stabilization can occur without any change in IVDU or sexual behaviour; the stabilization of the seroprevalence levels in the simulated epidemic is simply due to the heterogeneity in IVDU behaviour and the (sexual & IVDU) mixing patterns. The simulation results imply that although seroprevalence patterns can be deduced from the transmission dynamics, the causal processes which alter the transmission dynamics should not be inferred from the seroprevalence patterns. If the model provides an adequate explanation of the observed stabilization of the seroprevalence level in the NYC IVDU community, then the simulation results suggest that the current stabilization period may be only temporary and seroprevalence levels may begin to increase.

The computer simulation of the specific scenario shown in figure 1 was also used to examine the gender-specific risks of heterosexual transmission in IVDUs. The results for females are graphed in figure 2 (the results for males were similar, but are not shown); figure 2 was generated by the same set of values for the initial subgroup sizes and the biological-behavioural transmission parameters that were used to generate figure 1. Figure 2 shows that the effect that the heterosexual transmission risk factor has on increasing the risk of HIV infection is dependent upon the level of IVDU. The results for this scenario demonstrate that the addition of the heterosexual transmission risk factor to an individual with a very high risk activity (stranger-IVDU) does not increase the individuals risk of HIV infection. However, the addition of the same risk factor to an individual with a lower risk activity (buddy-IVDU) can significantly increase the individual's risk of HIV infection. These theoretical results are in agreement with the results from a cohort study of IVDUs in NYC, this study has determined that the heterosexual transmission risk is greatest in female IVDUs with the lowest cumulative drug use (Schoenbaum *et al.* 1989).

5. SENSITIVITY ANALYSIS

There is considerable uncertainty in estimating the values of the models' 30 variables: the initial population sizes of the ten subgroups and the twenty biological-behavioural transmission parameters. This degree of estimation uncertainty in the input values ensures that there will be significant variability in the models predictions of the future number of adult and pediatric AIDS cases. Consequently, we performed a sensitivity analysis to assess the variability in these case predictions (i.e. to determine the confidence intervals of the predictions) and to evaluate which were the key variables in contributing to the prediction imprecision. The parameter space of the model is defined by thirty dimensions; each dimension specifies a different variable (initial subgroup size or biological-behavioural transmission parameter), the length of each dimension is determined by the range in the estimates of the value for the particular variable. The Latin Hypercube Sampling/Partial Rank Correlation Coefficient (LHS/PRCC) technique was used, because it is an extremely efficient type of sensitivity analysis that enables the exploration of the entire parameter space of the model, with a minimum number of computer simulations (Blower & Dowlatabadi, submitted typescript). This study is the first application of the LHS/PRCC technique to the analysis of a biological or an epidemiological model; the methodology, advantages and further applications of the technique are described in detail elsewhere (Blower & Dowlatabadi, submitted typescript).

(*a*) *Sensitivity analysis methodology*

The LHS/PRCC sensitivity analysis involved the repeated evaluation of the previously described deterministic model, with all of the variable values varied in each of one hundred runs. The estimation uncertainty for the variables was investigated by specifying a probability density/distribution function (pdf) for each variable; hence, the variability in the pdf was used as a direct measure of the estimation uncertainty for each variable. Each specified pdf described the range of possible values and the probability of occurrence of any specific value for the variable; specific pdfs will be described in detail in a later section of the paper. The model contains 30 variables (10 subgroup sizes and 20 biological-behavioural transmission parameters), however only 24 (5 subgroup sizes and 19 biological-behavioural transmission parameters) were sampled. Only 5 subgroups were sampled, because each of these 5 subgroups was perfectly inversely correlated with one of the remaining 5 subgroups, due to the nature of the subgroup classification scheme. Only 19 parameters were sampled as two parameters were constrained to have the same

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value ($\beta_{mf} = \beta_{fm}$), the reason for this constraint will be discussed in a later section of the paper.

A stratified Latin Hypercube sampling scheme was used to select the input values (the values of the variables) for each of the one hundred numerical simulations. To sample the values for each variable, each pdf was divided into one hundred equiprobable intervals; consequently, the sampling distribution of the values for each variable reflected the shape of the particular pdf. Every equiprobable interval of each variable was randomly sampled one hundred times, without replacement. The sampling scheme ensured that the complete range of each variable was sampled (without bias), that every equiprobable interval was used only once, and that the frequency of the selection of the possible values of each variable were determined by their probability of occurrence in the pdf. Furthermore, all of the 24 sampled variables were uncorrelated, because they were sampled by selecting sampling indices along orthogonal vector spaces (see Blower & Dowlatabadi (submitted typescript) for further methodological details). Three biological assumptions were included as constraints at the sampling stage: $q_2 > q_1, \beta_{db} > \beta_{dn}$ and $\beta_{mf} = \beta_{fm}$; these assumptions will be discussed in detail in a later section of the paper, further methodological details of sampling with constraints is given in Blower & Dowlatabadi (submitted typescript). Sampled values were then used as input values for the numerical simulations of the model; the Runga-Kutta 4th order numerical method was used for the simulations. After one hundred simulations had been completed, frequency histograms and descriptive statistics were calculated from two of the model outputs: the cumulative number of adult and pediatric AIDS cases at the end of thirty years.

Non-parametric partial rank correlation coefficients (PRCCs) were then calculated between the input values for each of the 24 sampled variables and the two model outputs. Calculation of these PRCCs enabled the determination of the statistical relationship between each input variable and the specific output variable; these calculations assume that the relationship between each input variable and each output variable is monotonic. The PRCCs allowed the independent effects of each variable to be determined, as they statistically adjusted for the variation produced by all of the other variables; furthermore the PRCCs were not inflated or deflated due to inter-correlations among the variables, because all of the variables had initially been sampled along orthogonal axes.

(*b*) *Estimation of pdfs for the input variables*

Uniform probability density functions were defined for the initial sizes of the ten subgroups; therefore, each interval in the pdf had an equal probability of being sampled. Upper and lower bounds on these pdfs were assigned based upon the available data in the following manner. For each numerical simulation both the initial size and the sex ratio of the IVDU community was kept constant, but the sizes of the IVDU subgroups at the secondary level (type of IVDU behaviour) and the tertiary level (sexual behaviour) were varied. The NYC IVDU community has been estimated to be composed of 50000 women and 150000 men (Frank *et al.* 1978; des Jarlais & Friedman 1988*a*, *b*; des Jarlais *et al.* 1984); hence these values were used to set the initial sex ratio and IVDU community size. Data also suggest that the majority of NYC IVDUs share needles with friends or relatives rather than with strangers in shooting galleries (Hartel *et al.* 1988; Hartel *et al.*, submitted typescript); therefore, the proportion of stranger-users (s) was varied between 0.0 and 0.5 and the proportion of buddy-users (b; $b = 1 - s$) was varied between 0.5 and 1.0. The relative proportions of these types of IVDU behaviour were varied independently in men and women. At the tertiary level of sexual behaviour, the proportion of each of the eight IVDU subgroups in the sexually active category was varied between 0.0 and 1.0.

The size of the bridge group has only been crudely estimated; this crude estimate suggests that the size of the bridge group is at least sixty per cent of the size of the IVDU community and may be much greater (des Jarlais *et al.* 1984). In the numerical analysis of the model we assumed that the bridge group was the same size as the IVDU community (200000 individuals). The sex ratio in the bridge community is female-biased (des Jarlais *et al.* 1984), because the sex ratio in the IVDU community is male-biased and hence male IVDUs are more likely than female IVDUs to have non-IVDU sex partners. Therefore, we varied the sex ratio of the bridge community (from 1:1 to 3:1 female-biased) in every run, but we maintained the initial size of the bridge community at 200000 non-IVDUs: therefore, the number of non-IVDU males ranged from 50000 to 100000 and the number of non-IVDU females ranged from 100000 to 150000.

Probability density/distribution functions (pdfs) (with upper and lower bounds) were defined for the biological-behavioural transmission parameters; see table 2 for a full description of these pdfs. It was necessary to construct pdfs for the average values of the adult and pediatric survival times and incubation periods. If a large number of unbiased studies of IVDUs had been conducted, with long-term follow-up periods, then the pdfs could have been constructed simply by plotting out the average values from these studies. However, the few studies that have been conducted have focused on homosexual, haemophiliac-associated or transfusion-associated AIDS cases. Only a few studies have been conducted on the natural history of HIV infection in IVDUs (des Jarlais *et al.* 1987; Fernandez-Cruz *et al.* 1988, 1990; Galli *et al.* 1989; Goedert *et al.* 1986; Rezza *et al.* 1989; Vaccher *et al.* 1989). The results from these natural history studies should be interpreted with caution, due to the small sample sizes and the short follow-up periods. However, the preliminary results from some of these studies suggest that there may be significant differences between IVDUs and other risk groups in the rates of disease progression (Fernandez-Cruz *et al.* 1988, 1990; Galli *et al.* 1989; Schoenbaum *et al.* 1990); other studies have identified an expanded spectrum of HIV-related illness in IVDUs (Schoenbaum *et al.* 1990; Stoneburner *et al.* 1988). These results suggest that there may exist

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Table 2. *Parameter density /distribution functions*

Parameter	Min.	Max.	Median	Standard deviation	Function shape
β_{db}	β_{dn}	1	0.56	0.23	triangular (peak at β_{dn})
β_{dn}	0	1	0.28	0.23	triangular (peak at 0.0)
β_{fm}	0	0.5	0.25	0.15	uniform
β_{mf}	0	0.5	0.25	0.15	uniform
$c_{fb}(t)$	1	11	1	1.74	left skewed
$c_{fn}(t)$	1	20	2.19	2.46	left skewed
$c_{fs}(t)$	1	100	2	20.99	left skewed
$c_{mb}(t)$	1	20	1	3.02	left skewed
$c_{mn}(t)$	1	38	2	4.98	left skewed
$c_{ms}(t)$	1	15	1	2.94	left skewed
i_f	13	5265	299	1201	left skewed
i_m	13	3120	228	738	left skewed
j_f	0	4	1.8	0.77	triangular (peak at 1.0)
j_m	0	4	1.8	0.76	triangular (peak at 1.0)
q_1	0	1	0.28	0.23	triangular (peak at 0.0)
q_2	q_1	1	0.56	0.23	triangular (peak at q_1)
s_a	1.0	5.0	1.0	0.85	left skewed
s_b	0.21	4.8	1.04	1.09	left skewed
v_a	1.36	20	8	3.71	Weibull
v_b	0.1	20	0.33 and 5.5	4.99	mixture of two Weibulls

significant differences in the pattern and progression of HIV infection between IVDUs and the previously studied risk groups; these differences may translate into a difference in the average incubation period of HIV in IVDUs. Furthermore, since survival time is related to the clinical manifestation of AIDS, and IVDUs have a different distribution of presenting conditions for AIDS than the distribution that has been found for homosexual men (Schoenbaum *et al.* 1990; Stoneburner *et al.* 1988), then the average survival time in IVDU AIDS cases may differ from the average survival time that has been estimated from homosexual AIDS cases. Therefore, since the appropriate data have not been collected, we used the published data merely as a guide in constructing the necessary pdfs.

The median survival time of adult AIDS cases (estimated from studies of homosexuals and transfusion-associated cases) ranges from 9–13 months (Anderson & Medley 1988; Jason *et al.* 1989; Lemp *et al.* 1990; Harris 1990; Rothenberg *et al.* 1987; Stehr-Green *et al.* 1989; Volberding *et al.* 1990), although some individuals have survived for several years after an AIDS diagnosis. The only published study of survival time of AIDS in IVDUs is based upon 289 spanish IVDUs, the results show that the survival time of IVDU-related AIDS is slightly longer than the estimated survival times calculated for other risk groups (Batalla *et al.* 1989). Consequently, we defined the pdf for the average adult survival time to be left-skewed, with a minimum value of one year and a maximum value of five years; this pdf ensured that there was a much greater probability of shorter than longer survival times, but it also enabled us to investigate the effects of longer survival times. Results of published studies indicate that pediatric survival time may be significantly shorter than adult survival time, although some pediatric cases have survived for several years after an AIDS diagnosis (Anderson & Medley 1988; Rogers *et al.* 1987; Scott *et al.* 1989). Consequently, we defined the pdf for the average pediatric survival time to be left-skewed, with a minimum value of two to three months and a maximum value of approximately five years.

Unfortunately, there are no published studies estimating the average incubation period of HIV in IVDUs. The majority of studies (of transfusion-associated or homosexual AIDS cases) estimate that the average incubation period is in the range of seven to twelve years, but all of these estimates have very wide confidence intervals (Anderson & Medley 1988; Bacchetti & Moss 1989; Hessol *et al.* 1989; Jason *et al.* 1989; Kalbfleisch & Lawless 1988; Lemp *et al.* 1990; Lui *et al.* 1988; Medley *et al.* 1987; Medley *et al.* 1988*a*, *b*). Since the average incubation period in IVDUs may be shorter or longer than in the other risk groups, we used a Weibull distribution for the pdf of the average incubation period. The Weibull that we used ensured that the great majority of selected values were in the seven to twelve year range, but that a few shorter and longer average incubation periods were also investigated. The results of published studies suggest that the incubation period in HIV-infected children is shorter than in HIV-infected adults (Anderson & Medley 1988; Auger *et al.* 1988; Rogers *et al.* 1987; Scott *et al.* 1989). A recent study of the pediatric incubation period suggests that two subgroups of cases may exist: a small subgroup which develops AIDS very quickly and a second much larger subgroup which has an adult-like incubation period (Auger *et al.* 1988). We defined the pdf for the average pediatric incubation period to be bimodal, by adding two Weibull distributions, the two peaks of this function occurred at four months and at five to six years. This pdf enabled us to explore the effects of both short and long average incubation periods; the majority of the probabilities were selected from the

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second Weibull. The pdfs for the six remaining biological parameters: IVDU (β_{dn} & β_{db}), heterosexual (β_{mf} & β_{fm}) and vertical transmission efficiencies (q_1 & q_2) are discussed in the biological constraints section.

The calculation of pdfs for the sexual and IVDU behavioural parameters was limited by the availability of the data. Data have not been collected on sexual and IVDU behaviour from large random or representative samples of male and female IVDUs (and their non-IVDU male and female sex partners); such data are necessary to capture adequately all of the gender-specific behavioural heterogeneity. However, the Montefiore Medical Center Group (MMCG) has collected behavioural data from a selected group of IVDUs in NYC, and these data were used to estimate sexual and IVDU behavioural parameters. The MMCG are currently studying a cohort of over 700 IVDUs at a methadone maintenance clinic in a high AIDS incidence area in the Bronx, New York (Hartel *et al.* 1988; Hartel *et al.* submitted; Selwyn *et al.* 1985, 1987, 1988*a*, *b*, 1989*a–d*; Schoenbaum *et al.* 1987*a*, *b*, 1989). Data from the MMCG's study may be fairly representative of a large fraction of the NYC IVDU community, because surveys have shown that the majority of opiate addicts in NYC have had some experience with treatment clinics (Drucker & Vermund 1981). Many of the MMCG's selected IVDUs were in drug treatment at the time of their interview, but their pre-treatment history was obtained. The MMCG data capture a heterogeneous sample of risk behaviours, the MMCG's study participants are current and former opiate addicts; 95% have used heroin intravenously and 70% have also used cocaine. Most patients (89%) have injected drugs for at least two years during the period 1978 to 1987, and approximately 55% of them are still injecting. The median age of the study population is 34 years old (75% are between 30 and 45 years old). There is no evident selection bias between the study participants and other patients as the methadone maintenance clinic; no statistically significant differences were found on the basis of socio-economic class, IVDU behaviour, time in treatment and AIDS incidence (D. Hartel, unpublished data).

The MMCG's study, initiated in 1985, examines subjects at six month intervals to determine the rates of HIV seroconversion, and the development of AIDS and HIV-related disease; data are collected on sexual behaviour and needle-sharing practices since 1978. The needle use data appears reliable (measured by reproducibility in repeat interviews and internal consistency) as well as valid (measured by urine toxicology testing) (D. Hartel, unpublished data). Distribution functions derived directly from the data were used to define the pdfs for the gender-specific rates of needle-sharing and the rates of sexual partner change for the six subgroups of sexually active IVDUs (former IVDUs were used to assess the rates for non-IVDUs). Data had not been collected on the gender-specific rate of change of buddy-users; therefore pdfs were defined for these two variables on the basis of qualitative patterns (MMCG, personal communication). The pdfs for the rate of change of buddy-users were defined to be triangular distribution functions; such functions reflect the expectation that values close to the peak of the triangle are those considered most likely to occur.

(*c*) *Biological constraints*

Three constraints were incorporated at the Latin Hypercube sampling stage of the sensitivity analysis, in order to include the following three biological assumptions: (i) $q_2 > q_1$, (ii) $\beta_{db} > \beta_{dn}$ and (iii) $\beta_{mf} = \beta_{fm}$. These three assumptions are discussed below:

(i) $q_2 > q_1$

Vertical transmission studies are currently being conducted to estimate the probability that the baby of a seropositive woman will be born infected with HIV. Data from these studies suggest that the vertical transmission efficiency in a mother with AIDS (q_2) is greater than in a mother who is seropositive, but without AIDS (q_1) (Anderson & Medley 1988; Goedart *et al.* 1989; Mayers *et al.* 1989; Thomas *et al.* 1989). The vertical transmission studies have produced a wide range of estimates (0.0–0.73) (Anderson & Medley 1988; Blanche *et al.* 1989; Boylan & Stein 1990; Douard *et al.* 1989; European Collaborative Study 1988; Goedart *et al.* 1989; Mayers *et al.* 1989; Ryder & Hassig 1988; Thomas *et al.* 1989). The variability in the results of these studies may be due to the differences in study methodology, the small sample sizes, the heterogeneity in the infectivity of the mother, the biological cofactors, the length of follow-up, the passage of maternal antibodies and the criteria used to define HIV infection. The results from the majority of these studies imply that the vertical transmission efficiency is skewed towards the lower end of the probability scale. Therefore a triangular pdf was used for q_1. The peak of the function was set at zero and the values of q_1 were varied between zero and one; this pdf ensured that the majority of the randomly selected values of q_1 were in the lower end of the probability scale, although some high values were also selected. The pdf for q_2 was conditional on the value for q_1, in order to satisfy the biological constraint $q_2 > q_1$. A triangular pdf was also used for q_2; however, the peak of the function was set at q_1 and the values of q_2 were varied between q_1 and one.

(ii) $\beta_{db} > \beta_{dn}$

By definition, the HIV transmission efficiency through IVDU in a buddy-user partnership (where many needles are shared and given that the buddy partner is infected) (β_{db}) has to be greater than the HIV transmission efficiency for a single injection of drugs with an infected needle (β_{dn}). The values of the transmission efficiencies of HIV through IVDU are hard to determine; β_{dn} has been estimated from the available data on HIV needle-stick studies (Friedland & Klein 1987; Marcus *et al.* 1988), but there are no data from which to estimate β_{db}. The needle-stick studies have assessed the probability of individuals becoming infected with HIV due to accidental needle-

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stick injuries; these studies have estimated the transmission efficiency of such needle-stick injuries to be very low (0.0–0.008) (Friedland & Klein 1987; Marcus *et al.* 1988). These needle-stick studies are useful for evaluating the lower bound of β_{dn}, however the actual value of β_{dn} may be significantly greater than the lower bound estimate, due to certain IVDU behaviours that facilitate HIV transmission. IVDUs inject directly into veins and may also deliberately share blood or 'boot' (i.e. draw blood up into a syringe to flush out any of the drug that remains in the syringe from the previous injection, and then re-inject) (des Jarlais *et al.* 1986*a*, *b*). The frequent use of these practices suggest that the transmission efficiency from a single injection of drugs with an infected needle will be significantly greater than the transmission efficiency due to a needle stick injury. Furthermore, the volume of blood that is shared by 'booting' (or 'flushing') can often be a hundred or a thousand times greater than the volume of blood that is transferred due to an accidental needlestick injury (Ho *et al.* 1989; Hoffman *et al.* 1989). Consequently, a triangular pdf was used for β_{dn}; the peak of the function was set at zero and the values of β_{dn} were varied between zero and one. This pdf ensured that high values of β_{dn} were sampled, but that the majority of the sampled values of β_{dn} were at the lower end of the probability scale. The pdf for β_{db} was conditional on the value for β_{dn}, to satisfy the biological constraint $\beta_{db} > \beta_{dn}$. A triangular pdf was also used for β_{db}; the peak of the function was set at β_{dn} and the values of β_{db} were varied between β_{dn} and one.

(iii) $\beta_{mf} = \beta_{fm}$

Sexual partnership studies are being conducted to estimate the values of the heterosexual transmission efficiency per partnership (β_{mf} and β_{fm}) (Anderson & May 1988; Anderson & Medley 1988; Anderson *et al.* 1989; European Study Group 1989; Holmes & Kreiss 1988; Johnson 1988; Johnson & Laga 1988; Padian *et al.* 1987; Peterman *et al.* 1988). These studies generally involve monitoring monogamous couples in which only one partner is infected with the virus and neither partner is exposed to the virus through other risk factors. These sexual partnership studies are the only means to evaluate the heterosexual transmission efficiences; estimates of these efficiencies are extremely heterogeneous (0.03–0.71) (Anderson & May 1988; Anderson & Medley 1988; Anderson *et al.* 1989; European Study Group; Holmes & Kreiss 1988; Johnson 1988; Johnson & Laga 1988; Padian *et al.* 1987; Peterman *et al.* 1988). The variability in the results of these studies may be due to the differences in the study methodology, the small sample sizes, the heterogeneity in sexual practices, the behavioural-biological cofactors, the partnership duration and the specific sexual behaviour changes (e.g. condom use) that occur in the different studies. The results of the studies (that have been conducted in developed countries) imply that the value of the heterosexual transmission efficiency (β) is almost always below 0.5; studies of non-IVDUs suggest that the value of β is skewed towards the low end of the probability scale, but studies of heterosexual transmission in IVDUs suggest that the value of β may be much higher than in non-IVDUs. Furthermore, sexual partnership studies also suffer from a bias in their selection of participants, this bias could result in an under-estimate of the value of β; for example, partnerships in which the index case very quickly infects the partner (i.e. the β is high) will often not be included in partnership studies. Therefore, we used uniform distribution functions for β_{mf} and β_{fm} and we varied the values between zero and 0.5. The results of the sexual partnership studies also conflicts in their conclusion as to whether the efficiency of male to female transmission is greater than or equal to female to male transmission. However, in many of the studies, male to female transmission has been more readily apparent than female to male transmission, because the majority of the index cases have been males. Therefore, both the values of β_{mf} and β_{fm} and the degree of the difference between the two transmission efficiencies remains uncertain. In the sensitivity analysis the two heterosexual transmission efficiencies were set to be equal (future studies will evaluate the epidemiological effects of asymmetric heterosexual transmission).

(*d*) *Results: frequency distributions and descriptive statistics*

The size of the NYC IVDU community has only been assessed once and was very crudely estimated to be 200000 addicts (Frank *et al.* 1978); consequently, we used this estimate in every numerical simulation in the sensitivity analysis. However, because this estimate of the IVDU community was derived by using a flawed methodology and a biased data-base, the estimate of 200000 addicts is probably inaccurate (Blower & Hartel 1989). We also wish to stress that the current model does not contain any IVDU or sexual behaviour changes and that such behaviour changes would probably result in significantly fewer numbers of AIDS cases. Hence, we wish to stress that the qualitative insights that the sensitivity analysis produces are of much greater significance than any of the specific numerical values that are predicted for the future number of AIDS cases.

The frequency distributions of the probable number of cumulative AIDS cases (adult and pediatric) produced by the sensitivity analysis are shown in figure 3. The maximum and minimum of these distributions (see table 3) reflect the likely ranges of possible outcomes, rather than the absolute upper and lower bounds of the system; it is unlikely that any one run in the sensitivity analysis would have the specific combination of parameters to produce the absolute extreme values. The frequency distribution of adult AIDS cases is skewed slightly to the right and the frequency distribution of pediatric AIDS cases is skewed to the left (see figure 3). A scatterplot that relates the cumulative number of adult AIDS cases to the cumulative number of pediatric AIDS cases is shown in figure 4; it may be seen that the variance in the number of pediatric AIDS cases increases as the number of adult cases increases. This pattern is the result of the LHS sampling design: if only a few adults

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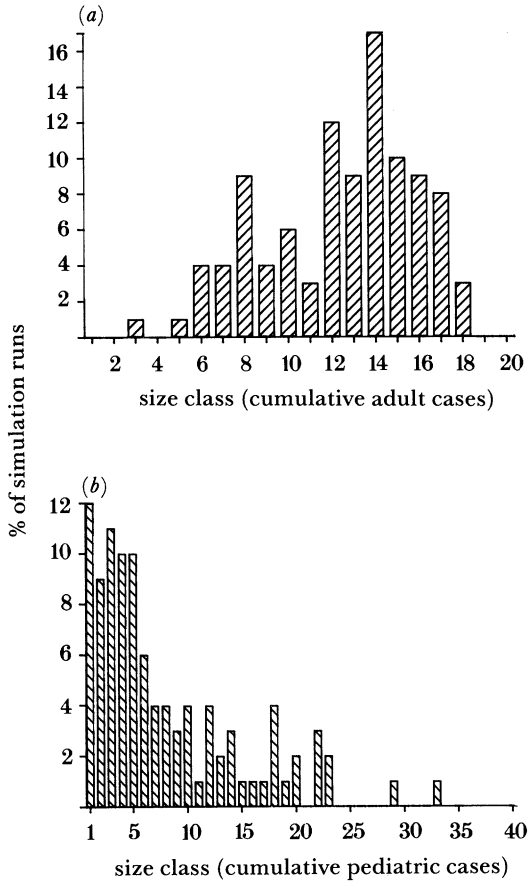

Figure 3. The frequency distributions of the cumulative number of AIDS cases, after 30 years, produced by 100 numerical simulations in the LHS/PRCC sensitivity analysis are graphed for adults (*a*) and pediatrics (*b*). The size class intervals are 20000 AIDS cases in the adult graph; size class 1 contains runs that fall in the range 0–20000. The size class intervals are 5000 AIDS cases in the pediatric graph; size class 1 contains runs that fall in the range 0 to 5000.

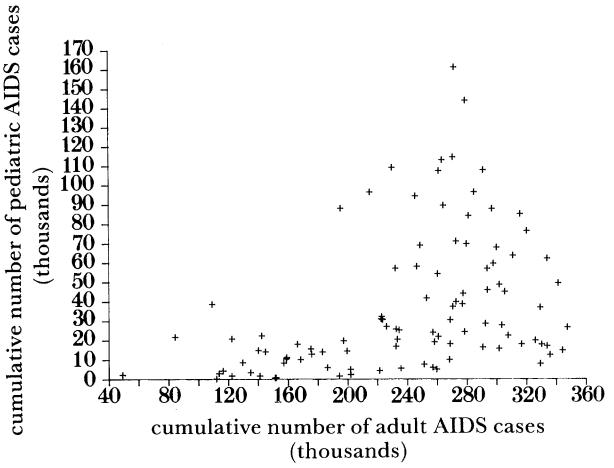

Figure 4. The scatterplot reveals the relationship between the cumulative number of adult and pediatric AIDS cases produced by the 100 numerical simulations for the LHS/PRCC sensitivity analysis.

Table 3. *Descriptive statistics from the sensitivity analysis*

	Cumulative number of aids cases in 30 years	
	Adult cases	Pediatric cases
Minimum	49134	246
Maximum	347420	161615
Mean	238571	37330
Median	257085	22663
Variance	$4.7*10^9$	$1.2*10^9$
90% confidence intervals	116422–333932	1780–108173

are infected, the number of pediatric AIDS cases are constrained to be low, however, if a large number of adults are infected, the number of pediatric AIDS cases may be either high or low (because the input variables to the model are sampled independently). The frequency distributions of the cumulative number of AIDS cases can be used to assess the probabilities of specific outcomes.

For example, the probability is 0.99 that 30 years after the introduction of the virus, at least 49000 adults with have contracted AIDS, due to either IVDU or heterosexual transmission. The descriptive statistics of the frequency distributions of the cumulative number of adult and pediatric AIDS cases are given in table 3. These statistics and the frequency distributions in figure 3 show that the model can predict a wide range of estimates for the future number of AIDS cases. For example, the 90% confidence interval for cumulative adult AIDS cases is 116422 to 333932. This prediction imprecision is due to the uncertainty in estimating the values of the models' variables. These descriptive statistics and the frequency distributions can not be used to identify which of the input variables are the most important in contributing to the prediction imprecision; consequently, partial rank correlation coefficients (which will be presented in the next section) were calculated in order to identify these key variables.

Approximately 12500 cumulative adult AIDS cases and approximately 550 cumulative pediatric AIDS cases (that are attributed to either IVDU or heterosexual transmission) have been reported to the AIDS surveillance unit in NYC (NYC Health Department 1990). These actual numbers of reported cases can be compared with the number of AIDS cases that are predicted by the model (see table 3)). However, two facts should be considered when the predicted and actual numbers are compared: (*a*) it has been inferred from the reports of the initial AIDS cases that HIV was introduced into the NYC IVDU community in the mid to late seventies (des Jarlais *et al.* 1989; Thomas *et al.* 1988), consequently the actual epidemic is at a considerably earlier stage than the 30 year simulated epidemic. (*b*) The reported AIDS cases may reflect only a fraction of the true HIV morbidity and mortality in NYC IVDUs, due to under-reporting errors and the high non-AIDS mortality rate in IVDUs (Schoenbaum *et al.* 1990; Stoneburner *et al.* 1988). The AIDS case definition was originally devised based upon AIDS cases in homosexual men. It became apparent that IVDUs appear to present with a larger spectrum of HIV-related infections than other risk groups and that therefore the AIDS cases in NYC's

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IVDUs were being under-reported (Schoenbaum *et al.* 1990; Stoneburner *et al.* 1988); the AIDS case definition was expanded in 1987. The magnitude of the under-reporting error has recently been assessed by a reevaluation of approximately eight thousand narcotic-related deaths that occurred between 1978 and 1986 (Stoneburner *et al.* 1988). This analysis revealed that narcotic-related mortality due to endocarditis, tuberculosis and pneumonia had significantly increased, concurrently with the HIV epidemic; but that drug-overdose deaths had remained constant. These results were used to suggest a causal association between these diseases and HIV and to propose that the actual HIV-related death rates in IVDUs in NYC may have been twice as high as the reported death rates (Stoneburner *et al.* 1988). Therefore the reported AIDS cases may be expected to be far fewer than the predicted cases due to under-reporting and to the shorter duration of the epidemic; however, it should be noted that the reported number of pediatric AIDS cases (approximately 550) has already exceeded the minimum 30 year predicted value of 246 pediatric cases.

(*e*) *Results: partial rank correlation coefficients* (*PRCCs*)

The PRCCs were used to identify which were the key variables in contributing to the imprecision in predicting the future number of adult and pediatric AIDS cases; the PRCC results are presented in table 4. The magnitude of the PRCC indicates the importance of the uncertainty in estimating the value of the specific variable in contributing to the prediction imprecision. The sign of the PRCC indicates the qualitative relationship between the input variable and the output variable (cumulative number of adult or pediatric AIDS cases). The order of the ranking of the variables in table 4 indicates the relative importance of the key variables. Different subsets of key variables were identified for the adult and pediatric cases (see table 4).

The PRCCs of eleven of the twenty biological-behavioural transmission parameters and none of the ten initial subgroup sizes are statistically significant ($p < 0.05$) for the adult cases. The values and the rankings of the PRCCs (see table 4) suggest that the uncertainties in estimating the values of three biological-behavioural transmission parameters are the most critical in affecting the prediction imprecision of the future number of adult AIDS cases; these three parameters are the two heterosexual trnsmission efficiencies and the average adult incubation period. The uncertainties in estimating the values of the remaining eight IVDU and sexual behavioural transmission parameters (see table 4) are statistically significant, but are of lesser importance (PRCC $\leqslant 0.35$) in contributing to the prediction imprecision for the adult AIDS cases. These eight parameters are: the IVDU transmission efficiency per buddy partnership, the rates of sex partner change in specific subgroups (female and male non-IVDUs, male buddy-users and male stranger-users, female stranger-users), the rate of sharing needles (for male stranger-users) and the HIV transmission efficiency of a single injection with an infected needle. These results show that sexual and IVDU behavioural parameters, as well as biological parameters are important in prediction imprecision for adult AIDS cases.

The PRCC of eight of the twenty biological-behavioural transmission parameters and two of the initial sizes of the ten subgroups are statistically significant ($p < 0.05$) for the pediatric cases. The values and the rankings of the PRCCs (see table 4) suggest that the uncertainty in estimating the values of four of the biological-behavioural transmission parameters are the most critical in affecting the prediction imprecision of the future number of pediatric AIDS cases; these four parameters are the vertical transmission efficiency, the two heterosexual transmission efficiencies and the average adult incubation period. The uncertainties in the values of six other variables are statistically significant, but are of lesser importance (PRCC $\leqslant 0.36$) in contributing to prediction imprecision for pediatric AIDS cases; these six variables are the average adult survival time, the initial population size of the sexually active female IVDUs (stranger-users and buddy-users), the rate of sex partner change in specific sub-groups (male buddy-users and male stranger-users) and the average pediatric incubation period. These results demonstrate that sexual behavioural and biological parameters, as well as the initial population sizes of the two groups of sexually active female IVDUs are important in prediction imprecision for pediatric AIDS cases.

The sign of the PRCC identifies the specific qualitative relationship between the input and the output variable; the qualitative relationship is the same for all of the key variables, except the average incubation periods. The positive value of the PRCC for the majority of the variable implies that when the value of the input variable increases, the future number of AIDS cases will also increase. The future number of AIDS cases decreases as the average incubation period lengthens, because even though individuals remain infectious for a longer period and consequently can

Table 4. *Partial rank correlation coefficients* (*PRCCs*) *calculated from the sensitivity analysis*

(The PRCCs are between the input values of the biological-behavioural transmission parameters and the output values (the cumulative number of adult and pediatric AIDS cases in 30 years). The results are significant at the 0.05 level (*), the 0.01 level (**) or the 0.001 level (***).

Adult cases		Pediatric cases	
Parameter	PRCC	Parameter	PRCC
β_{mf} and β_{fm}	0.84 ***	q_1	0.77 ***
v_a	−0.72 ***	β_{mf} and β_{fm}	0.77 ***
β_{db}	0.35 ***	v_a	0.51 ***
$c_{fn}(0)$	0.29 **	X_{4f}	0.36 ***
$c_{mn}(0)$	0.29 **	$c_{mb}(0)$	0.36 ***
$c_{mb}(0)$	0.25 *	s_a	0.35 ***
$c_{ms}(0)$	0.23 *	v_b	−0.30 **
i_m	0.22 *	$c_{ms}(0)$	0.28 **
$c_{fs}(0)$	0.21 *	$X_{3f}(0)$	0.20 *
β_{dn}	0.20 *	—	—

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infect more individuals, the rate of progression to disease decreases. Epidemiological implications may be inferred from the qualitative PRCC relationships for the key biological parameters, but not for the key behavioural parameters. For example, it may be inferred if average adult survival time is increased, at any time throughout the epidemic, the number of pediatric AIDS cases will increase. This result is of epidemiological relevance, because pregnancy decisions are often independent of HIV sero-status (Selwyn *et al.* 1989*d*), and average adult survival time may now be increasing because of the administration of prophylactic aerosolized pentamidine and other therapeutic drugs, such as AZT and ddI (Cooley *et al.* 1990; Fischl *et al.* 1987; Gail *et al.* 1990; Golden *et al.* 1989; Harris 1990; Lambert *et al.* 1990; Lemp *et al.* 1990; Yarchoan *et al.* 1986). However, decreasing the rate of change of sex partners for male stranger-users, at any time throughout the epidemic, may or may not significantly decrease the future number of adult AIDS cases. The key biological parameters apply to all subgroups, throughout the epidemic; however, the behavioural parameters apply to specific subgroups and may have a time dependent effect by only exerting a significant effect at a specific stage of the epidemic. Consequently, deducing the epidemiological effects of reducing specific behavioural parameters at a midpoint in the epidemic, may lead to erroneous conclusions. The epidemiological effects of behavioural change will be dependent upon both the magnitude, the type and the timing of the behaviour change, and should be investigated through a time-dependent analysis.

6. EPIDEMIOLOGICAL IMPLICATIONS AND CONCLUSIONS

The sensitivity analysis results have significant epidemiological implications. The analysis revealed that the confidence intervals on the prediction estimates of future cumulative numbers of AIDS cases are extremely wide. However, only a few key variables are important in contributing to this prediction imprecision; PRCCs were used to identify and rank the importance of these key variables. Therefore, the results suggest that it is most important to quantify accurately these key variables, and hence the results can be used to suggest a strategic agenda to focus data collection efforts. Reducing the estimation uncertainty in the key biological-behavioural transmission parameters will have a much greater effect on increasing the prediction precision of adult AIDS cases than accurately estimating any of the subgroup sizes. Reducing the estimation uncertainty in the key biological-behavioural transmission parameters will also increase the precision in estimating the future number of pediatric AIDS cases. However, for pediatric AIDS case prediction it is also important to determine the number of sexually active female IVDUs. The PRCC results for pediatric cases highlight the significance of sexually active female IVDUs in the epidemiology of pediatric AIDS in NYC. The magnitude of the effect that reducing the estimation uncertainty of the key variables has on prediction precision will be presented in a subsequent paper.

The model presented in this paper is a simplistic and deterministic model of heterosexual, IVDU and perinatal transmission in NYC. The model was used to provide qualitative insights into HIV epidemiology in NYC and to clarify the relationship between heterosexual and IVDU transmission. Results of the sensitivity and the scenario analysis demonstrated the significance of the dynamic interaction of heterosexual and IVDU transmission. In the early stages of the epidemic, IVDU transmission is often more important than heterosexual transmission; however, the relative importance of heterosexual transmission increases, as the epidemic spreads from the IVDU to the bridge community. The model results suggested a new explanation for the stabilization of the seroprevalence level that has been observed in the NYC IVDU community; the proposed explanation does not rely upon any IVDU or sexual behavioural changes. A computer simulation of a specific scenario was used to examine the gender-specific risks of heterosexual transmission in IVDUs. The results showed that the effect of the heterosexual transmission risk factor on increasing the risk of HIV infection depends upon the level of IVDU. The sensitivity analysis of the model revealed extremely wide confidence intervals in predicting future numbers of adult and pediatric AIDS cases. The analysis revealed that the prediction imprecision was mainly due to the estimation uncertainty of the values of a few key variables; these key variables were identified and ranked by their importance in contributing to prediction imprecision. Long-term precise predictions of AIDS cases will not be possible until these key variables have been determined accurately; however, it is also necessary to develop more realistic mathematical models. Behavioural changes and additional biological complexities, (such as recruitment, more complicated incubation functions, variable transmission efficiencies, age structure and ethnicity) should be included in future models. In the analyses in this paper, we have only investigated the effects of parameter estimation uncertainty for a specified model structure, we assumed positive assortative (sexual and IVDU) mixing patterns. We are currently investigating the sensitivity of our scenario and sensitivity results to the structure of the model (i.e. the specific mixing patterns). In this future analysis, the epidemiological consequences of model structure uncertainty (i.e. the uncertainty in specifying the sexual and IVDU mixing matrices) will be explored and the relative effects of parameter estimation uncertainty and model structure uncertainty will be compared. We hope that this paper has shown the utility of data-based mathematical models in understanding HIV epidemiology and that it may lead to other close collaborations between field epidemiologists and theoreticians. Such collaborations are necessary in order to develop realistic mathematical models that link specific risk behaviours of individuals with the seroprevalence level of a population; the formulation of such models is essential to assess the

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epidemiological significance of behavioural intervention strategies.

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