The Basic Reproduction Ratio of HIV among Intravenous Drug Users

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ABSTRACT

A new approach for the estimation of the Basic Reproduction Ratio R_0 for HIV among intravenous drug users (IVDU) is proposed. This approach is based in an adaptation of the models proposed by Ross and Macdonald for vector-borne infections. A straightforward adaptation of Macdonald's model is presented first: biological vectors are replaced by needles and syringes and we consider a homogeneous population of IVDUs; next we present a modified model where several heterogeneities are considered. Some of those heterogeneities are due to intrinsic differences between needles and syringes and biological vectors; others, such as those related to movements of individuals between communities, should apply to both biological vectors and injection apparatuses. An example of the calculations of R_0 for a real IVDUs community is presented.

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1. INTRODUCTION

In 1990 an outbreak of malaria was observed among a group of intravenous drug users (IVDU) in the city of Bauru, São Paulo, Brazil [5]. This outbreak was attributed to needle sharing, since it occurred only among the IVDUs. It is true that a small amount of *Anopheles albitarsis*, a vector of secondary importance in malaria transmission [27], was identified in the region, but this was not sufficient to explain neither the number of cases found nor the fact that only the IVDUs were affected.

Actually, many of the so-called vector-borne infections of humans can be eventually acquired through transfusion of blood or blood products. Occasionally these infections can be transmitted by accidents with contaminated material and/or intravenous drug usage [7]. In fact several epidemic outbreaks of such infections have been reported in the literature [7].

The current AIDS pandemic is the most dramatic example of the importance of such a transmission route.

Among IVDUs, HIV is transmitted by parenteral exposure to HIV-contaminated needles and other equipment used for injection. The social structure of IVDUs' communities promotes the sharing of needles and syringes [22]. The ethic of cooperation within small groups is applied to the sharing of equipment for injecting drugs. To refuse to share the needles without a socially legitimate reason would call into question the reliability of the person with respect to other cooperative actions [22]. Also, the relatively high prices and limited supplies of drug injection equipment can lead to sharing among casual acquaintances or even complete strangers. In addition, it has been verified that one of the most important reason for using drugs in group is the fear of overdose [22].

Although current laboratory and epidemiological data continue to provide no support for insect transmission of HIV [18], among IVDUs the drug injection equipment (called for the sake of simplicity from now on needles) can be faced as inanimate "vectors." Interestingly enough, prostitutes from the harbor city of Santos, Brazil, and who are regular IVD users are called "dengue" by their mates, after dengue fever, showing that the notion of needles acting as vectors may be even intuitive.

The basic difference between a biological vector and needles is that a vector is a true intermediate host, in the sense that the parasite undergoes a phase of obligatory development (and often reproduction) within the arthropod, while needles and syringes are merely carriers of the pathogen [6].

In spite of these differences, concepts developed for the quantification of transmission of vector-borne infections can be useful for the understanding of the transmission dynamics of these diseases when acquired via transfusion, or, of particular interest in the context of this paper, via intravenous drug usage.

This paper presents new uses of old ideas and concepts related to blood-borne infections, in particular an adaptation of the malaria transmission developments of Macdonald, as applied to HIV among IVDUs.

The idea of considering needles as vectors is conceptually new, although the resulting formalism has been around for some time. In fact, Kaplan [11, 12] thoroughly discusses the dynamics of the interaction between HIV and the injection equipment in IVDUs communities. He also discussed the results of interventions at this level.

After this introduction, we present in Section 2 an adaptation of Macdonald's formalisms for vector-borne infections to the transmission of HIV among IVDUs. The contents of this section is very similar to Kaplan's work [11]. It is included here to fix the notation for the rest of the paper and to introduce the mathematical methods used in a simple context.

Section 3 modifies the simple models of Section 2 by including heterogeneities in it. This is the core of the paper and the following types of heterogeneities are considered: first, heterogeneities in the density of viraemia in the population of HIV positive IVDUs; second, heterogeneities in the habits as regards frequency of use and sharing habits; and third, the problem of the interaction between communities of IVDUs.

Finally, Section 4 presents a preliminary estimation of the basic reproduction ration for HIV, the proportion of infective needles, and the prevalence of HIV infection expected at equilibrium, for a community of IVDUs from the city of Santos, Brazil.

Concluding remarks are the contents of Section 5.

2. AIDS AMONG INTRAVENOUS DRUG USERS: WHEN A NEEDLE CAN BE A VECTOR

The quantification of transmission of infectious agents through biological vectors have been studied for several decades since the seminal work by Sir Ronald Ross at the beginning of this century [23–25], culminating with the developments of George Macdonald in the mid-fifties [19–21].

The central concept related to transmission quantification is the so-called basic reproduction ratio of the parasite, R_0. This parameter was defined by Macdonald as the number of secondary infections

produced by a single infective individual in an entirely susceptible population [20]. So the total number of infections due to the primary case would be

$$R_0 = \frac{ma^2bp^n}{-r\ln(p)}, \tag{1}$$

where m is the density of mosquitoes as related to the human population; a is the average daily biting rate of mosquitoes; b is the proportion of mosquitoes with sporozoites (the infective stage of the malaria parasite) in their salivary glands and who are actually infective; p is the daily survival probability of the mosquito population; and r is the daily recovery rate of parasitaemia in the human population.

The sporozoite rate S, defined by Macdonald [20] as the proportion of mosquitoes with sporozoites in their salivary glands, is another crucial parameter related to transmission. It was defined by Macdonald as [20]

$$S = \frac{p^n ay}{ay - \ln(p)}, \tag{2}$$

where y is the prevalence of the infection among humans, and a and p are as above.

Another central parameter related to malaria transmission is the inoculation rate h defined for the first time by Sir Ronald Ross as the number of new infections which should occur in one tunit of time [19] as

$$h = mabS = \frac{ma^2byp^n}{ay - \ln(p)}. \tag{3}$$

As mentioned in the introduction, syringes and needles can replace biological vectors acting as vehicles of parenterally transmitted infections. It is therefore natural to extend the concepts and parameters for malaria by Macdonald and others [9, 19–21] to those inanimate vectors that characterize new epidemiological scenarios. However, some of the basic assumptions ought to be adapted to face this new approach.

For HIV, R_0 is essentially a product of three factors [3]: the average probability that an infected person will infect a partner over the duration of the partnership, the average number of partners acquired per unit of time, and the average duration of the infectiousness. Let us

now see how Macdonald's derivations can be applied to HIV transmission among IVDUs.

We begin by stating the basic assumptions related to needle mediated transmission.

Let $1/\alpha$ be the average period of time a needle remain circulating among the IVDUs population. However, infected needles remain infective for a shorter period of time $1/\mu$. Although HIV remains viable inside the needle for a period of time ranging from hours to days after drying, residual blood tends to coagulate inside the needle after few minutes, preventing reusing of the needle, unless it is cleaned. Therefore the "expectation of life" of infective needle is $1/(\mu + \alpha)$. Before proceeding with the definition of R_0 for needles, let us state some basic differences between biological vectors, as described by Macdonald [19], and needles:

a. All vectors which bite an infective host become infected (although some recent publications explicitly assume that only a fraction of those bites are infective to the vector [2, 8]). In contrast we consider that only a fraction δ of the needles which bite infective individuals becomes infected.

b. Only a fraction b of the infected vectors is considered to be infective. In contrast we assume that all infected needles are infectious, although for a limited period of time $1/\mu$.

c. For the biological vectors the infective period is their whole remaining life after the extrinsic incubation period. In contrast, there is no extrinsic incubation period of the virus in the needle. This implies the absence of a time lag between infection and infectiousness of the needle. Therefore, for needles, the infectious period begins immediately after the biting and lasts for $1/(\mu + \alpha)$, where $1/\alpha$ is the needle life expectancy.

So, for needles, let m be the average number of needles per human IVD user; a be the average daily number of bites a needle inflicts in the human population (so ma is the average daily number of bites an individual receives); $1/(\mu + \alpha)$ be the life expectancy of a needle in the infective condition; $a\delta/(\mu + \alpha)$ be the average number of infective bites needles inflict during the infectious period; and $1/r$ be the average period a human host remains infective for the needles. This will be considered as the average period of time an IVDU remains sharing needles in a specific community.

Therefore, the expression for R_0 for needles is

$$R_0 = \frac{ma^2\delta}{r(\mu + \alpha)}. \tag{4}$$

By the same token, we can deduce the equivalent to the sporozoite rate for the needles S_n, which assumes the form

$$S_n = \frac{\delta a y}{(\delta a y + \mu + \alpha)}. \tag{5}$$

It should be mentioned that the sporozoite rate, as defined by Macdonald, is the proportion of *infected* mosquitoes. The corresponding concept for needles would be (5) with $\mu = 0$. This quantity represents the proportion of *infected* needles, regardless of the fact of their being *infective* or not.

The corresponding inoculation rate for needles is now

$$h = \frac{m a^2 \delta y}{(\delta a y + \mu + \alpha)}, \tag{6}$$

which in terms of R_0 assumes the form

$$h = \frac{R_0 r(\mu + \alpha) y}{(\delta a y + \mu + \alpha)}. \tag{7}$$

Let us now see how the expression for R_0 in the case of HIV transmission by needles can be deduced from a system of differential equations which takes into account the dynamic of three populations, namely: individuals susceptible to infection, denoted $X(t)$; individuals infected with HIV, denoted $Y(t)$; and the number of infected needles, denoted $P^i(s,t)$. It should be noted that the latter varies as a function of the age s of the needle and also as a function of time t. Therefore the differential equation for $P^i(s,t)$ is

$$\frac{\partial P^i(s,t)}{\partial s} + \frac{\partial P^i(s,t)}{\partial t} = \delta a y(t)\left[N(s,t) - P^i(s,t)\right] - (\mu + \alpha) P^i(s,t), \tag{8}$$

where $N(s,t)$ is the total number of needles in the population, δ, μ, α, and a as above, and $y(t)$ is the proportion of infected individuals in the community. Integrating (8) from 0 to ∞ with respect to age (s) of the needles and defining

$$\int_0^\infty P^i(s,t)\, ds = P^i(t) \tag{9}$$

and

$$\int_0^\infty N(s,t)\, ds = N(t), \tag{10}$$

we also have

$$\int_0^\infty \frac{\partial P^i(s,t)}{\partial s}\, ds = 0. \tag{11}$$

Substituting (9)–(11) in (8) and dividing by the total number of individuals of the human host population (considered constant) we get

$$\frac{dp^i(t)}{dt} = \delta a y(t) m - [\delta a y(t) + (\mu + \alpha)] p^i(t), \tag{12}$$

where $p^i(t)$ is the number of infected needles divided by the total human populations and m is the total number of needles (considered as a constant) divided by the total human population. So, the system of equations, written for the proportions as related to the human population $x(t)$, $y(t)$, and $p^i(t)$, is

$$\frac{dx(t)}{dt} = ry(t) - p^i(t) a x(t) \tag{13}$$

$$\frac{dy(t)}{dt} = p^i(t) a x(t) - ry(t) \tag{14}$$

$$\frac{dp^i(t)}{dt} = \delta a y(t) m - [\delta a y(t) + (\mu + \alpha)] p^i(t). \tag{15}$$

It should be mentioned that the term $ry(t)$ represents the mortality attributable to AIDS and has been added in (13) in order to keep the total population constant.

The trivial solutions for the system above is $x = 1$, $y = p^i = 0$, that is, absence of infection. Applying the principle of linearized stability [28] we can analyze the stability of the equilibrium around the trivial solution and find a threshold that makes such equilibrium unstable, that is, the relationship between the parameters that allows the installing of the disease.

The threshold can be obtained when the stability of the trivial solution is broken and this occurs when

$$\delta a^2 m = r(\mu + \alpha). \tag{16}$$

Therefore if

$$R_0 = \frac{\delta a^2 m}{r(\mu + \alpha)} > 1, \tag{17}$$

the stability of the trivial solution is broken and the disease prevails. Equation (17) is exactly the same as (4), the definition of R_0 for the needles.

The above deduction of R_0 shall be used in the next section.

3. HETEROGENEITIES

We now consider how to modify the model of the previous section in order to taken into account some of the heterogeneities which determine the risk of acquiring HIV infection by IVD usage.

3.1. *HETEROGENEITY IN THE SOURCE OF INFECTION*

The first heterogeneity to be considered refers to the proper calculation of the chance a needle has of becoming infected after biting an infective individual denoted as δ.

We consider that this chance δ depends on the statistical distribution of HIV serus titre in the host population. The mean titers of HIV in the blood of contaminated individuals is quantified in the literature as tissue culture infective doses (also called by some authors as "infectious particles") [10, 15–17]. Let us suppose that the infective inoculum for the needle is of i units infective for tissue culture (UITC). So, the probability $P(i)$ of finding i UITC in a needle with a residual volume of ν ml of blood, after biting an infected individual is

$$P(i) = \sum_{n=0}^{\infty} \frac{e^{-n\nu}(n\nu)^i}{i!} P(n|\varphi), \tag{18}$$

where n corresponds to the plasmatic concentration of HIV (in UITCs) in a randomly selected individual from an infective population with an average φ UITCs per milliliter of blood.

Assuming that one UITC is *sufficient* to infect a needle, then the probability of having *at least* one infective inoculum δ is

$$\delta = P(i \geq 1) = [1 - P(0)]. \tag{19}$$

In order to illustrate the above analysis let us consider two possible situations:

(1) The infective inoculae are homogeneously distributed among the infected population. Then

$$P(n|\varphi) = \begin{cases} 1 & \text{if } n = \varphi \\ 0 & \text{if } n \neq \varphi \end{cases} \tag{20}$$

and so $P(i)$ reduces to the Poisson distribution

$$P(i) = \frac{e^{-\varphi\nu}(\varphi\nu)^i}{i!}. \tag{21}$$

Therefore

$$\delta = 1 - e^{-\varphi\nu}. \tag{22}$$

(2) The infective inoculae are heterogeneously distributed among the infected population. Then

$$\delta = P(i \geq 1) = 1 - \sum_{n=0}^{\infty} e^{-n\nu} P(n|\varphi). \tag{23}$$

Now, assuming that the distribution of infective inoculae among the infected population $P(n|\varphi)$ is a negative binomial distribution with parameter κ [4], as described previously for several epidemiological studies [1], with form

$$P(n|\varphi) \equiv P(n|\varphi, \kappa) = (1-\epsilon)^{\kappa} \frac{\Gamma(\kappa+n)}{\Gamma(\kappa)} \frac{\epsilon^n}{n}, \tag{24}$$

where

$$\epsilon = \frac{\varphi}{\varphi + \kappa}. \tag{25}$$

Considering that the probability generating function G for the negative binomial distribution is given by [4]

$$G(z) = (1-\epsilon)^{\kappa}(1-\epsilon z)^{-\kappa}, \tag{26}$$

we finally obtain

$$\delta = P(i \geq 1) = 1 - (1-\epsilon)^{\kappa}(1-\epsilon e^{-\nu})^{-\kappa}, \tag{27}$$

where ν, as mentioned above, is the residual volume of blood in the needle and κ can be obtained from the distribution of inoculae in the population, being defined as

$$\kappa = \frac{\varphi^2/\sigma^2}{1-(\varphi/\sigma^2)}, \tag{28}$$

where φ is the mean and σ^2 is the variance of the inoculum distribution among the population.

3.2. *HETEROGENEITY IN THE EXPOSURE RATES*

We now consider a very important difference between the behavior of the biological vector and an inanimate carrier, the needle. It is reasonable to assume that the biting rate is a constant for the mosquitoes, since we have no reason to assume that one mosquito bites more than another. Furthermore, since the biting is a randomly distributed and a relatively rare event, for the mosquito population, it is clear that the average value of the biting rate a should be sufficient.

On the other hand, a needle is necessarily driven by an IVDU. This implies a gross variation in the biting rate. In addition, individuals vary greatly in the habits of sharing needles among themselves. Also, it is reasonable to suppose that different communities of IVDUs have different habits. So we consider, for the purpose of this section, only isolated communities, defined as a group of IVDUs where everybody relates to everybody else and to nobody else outside the community. We relax this assumption in the next section.

In order to illustrate the above considerations, let us consider, for simplicity, the situation in which there are only two classes of IVDUs in the community, defined according to their rate of IVD use and sharing habits.

Let $x_1(t)$ be the fraction of noninfected IVDU at time t of class 1, which uses IVD ma_1 times per unit of time and shares needles with probability p_1. Similarly, let $x_2(t)$ be the fraction of noninfected IVDU at time t of class 2, which uses IVD ma_2 times per unit of time and shares needles with probability p_2. Let $y_1(t)$ and $y_2(t)$ be the corresponding fractions of infected IVDUs. We assume that $x_1(0)$ and $x_2(0)$ are constants, that is, the proportion of individuals with different habits is such that their fractions remain constants. Equations (15), (13), and

(14) are now replaced by

$$\begin{aligned} dx_1/dt &= ry_1 - p^i a_1 p_1 x_1 \\ dx_2/dt &= ry_2 - p^i a_2 p_2 x_2 \\ dy_1/dt &= -ry_1 + p^i a_1 p_1 x_1 \\ dy_2/dt &= -ry_2 + p^i a_2 p_2 x_2 \\ dp^i/dt &= \delta(m - p^i)(a_1 y_1 + a_2 y_2) - (\mu + \alpha) p^i. \end{aligned} \tag{29}$$

Using the same method as before we find that the trivial solution is stable (unstable) according to whether

$$R_0 = \frac{\delta m\left[a_1^2 p_1 x_1(0) + a_2^2 p_2 x_2(0)\right]}{r(\mu + \alpha)} \tag{30}$$

is smaller (greater) than 1.

Comparing the expression for R_0 given by (17) and the above, we see that the average daily biting rate a^2 is replaced by an appropriately averaged quantity $[a_1^2 p_1 x_1(0) + a_2^2 p_2 x_2(0)]$.

In general with $n \times l$ classes, R_0 becomes

$$R_0 = \frac{\delta m \sum_{j=1}^{n} \sum_{i=1}^{l} \left[a_i^2 p_j x_{ij}(0)\right]}{r(\mu + \alpha)}, \tag{31}$$

where $x_{ij}(0)$ is the fraction of uninfected IVDU at time $t = 0$, which uses IVD a_1 times per unit of time and shares needles with probability p_j.

The proportion y_{ij} of infected individuals in each class, the proportion x_{ij} of uninfected individuals in each class, and the proportion p^i of *infective* needles at equilibrium can be easily calculated by putting equations from system (29) as equal to zero. As the resulting expressions are too long we will not include them in this paper. The proportion of *infected* needles can be obtained by putting $\mu = 0$ in the equation that gives the proportion of *infective* needles. This last proportion is equivalent to Macdonald's sporozoite rate.

3.3. *INTERACTIONS BETWEEN DISTINCT COMMUNITIES*

In the previous subsections we have considered isolated communities of IVDUs. In this section we address the problem of interaction between distinct communities of IVDUs.

For simplicity, we assume only two communities, each containing two groups of IVDUs. We denote the members of the two communities by superscripts I and II, and the individual members of each inner group by subscripts 1 and 2.

Denoting β_i^{I} and β_i^{II} the proportion of shared needles used by individuals inside their own communities, we have the following system of equations for the proportion of infected individuals y and infected needles p^{i}:

$$\frac{d}{dt}y_j^{\mathrm{I}} = \left[\beta_j^{\mathrm{I}}p^{\mathrm{iI}} + \left(1-\beta_j^{\mathrm{I}}\right)p^{\mathrm{iII}}\right]p_j^{\mathrm{I}}a_j^{\mathrm{I}}x_j^{\mathrm{I}} - ry_j^{\mathrm{I}} \qquad j=1,2$$

$$\frac{d}{dt}y_j^{\mathrm{II}} = \left[\beta_j^{\mathrm{II}}p^{\mathrm{iII}} + \left(1-\beta_j^{\mathrm{II}}\right)p^{\mathrm{iI}}\right]p_j^{\mathrm{II}}a_j^{\mathrm{II}}x_j^{\mathrm{II}} - ry_j^{\mathrm{II}} \qquad j=1,2$$

$$\begin{aligned}\frac{d}{dt}p^{\mathrm{iI}} &= \delta\left(m^{\mathrm{II}}R - p^{\mathrm{iI}}\right)\left(\beta_1^{\mathrm{I}}a_1^{\mathrm{I}}y_1^{\mathrm{I}} + \beta_2^{\mathrm{I}}a_2^{\mathrm{I}}y_2^{\mathrm{I}}\right)\\ &\quad + \delta\left(m^{\mathrm{I}} - p^{\mathrm{iI}}\right)\left[\left(1-\beta_1^{\mathrm{II}}\right)a_1^{\mathrm{II}}q_1^{\mathrm{II}}y_1^{\mathrm{II}} + \left(1-\beta_2^{\mathrm{II}}\right)a_2^{\mathrm{II}}q_2^{\mathrm{II}}y_2^{\mathrm{II}}\right.\\ &\quad \left. -(\mu+\alpha)p^{\mathrm{iI}}\right]\end{aligned}$$

$$\begin{aligned}\frac{d}{dt}p^{\mathrm{iII}} &= \delta\left(m^{\mathrm{II}} - p^{\mathrm{iI}}\right)\left(\beta_1^{\mathrm{II}}a_1^{\mathrm{II}}y_1^{\mathrm{II}} + \beta_2^{\mathrm{II}}a_2^{\mathrm{II}}y_2^{\mathrm{II}}\right)\\ &\quad + \delta\left(m^{\mathrm{II}} - p^{\mathrm{iI}}\right)\left[\left(1-\beta_1^{\mathrm{I}}\right)a_1^{\mathrm{I}}q_1^{\mathrm{I}}y_1^{\mathrm{I}} + \left(1-\beta_2^{\mathrm{I}}\right)a_2^{\mathrm{I}}q_2^{\mathrm{I}}y_2^{\mathrm{I}}\right.\\ &\quad \left. -(\mu+\alpha)p^{\mathrm{iII}}\right], \qquad (32)\end{aligned}$$

where q_i^{I} and q_i^{II} $(i=1,2)$ are the proportional of individuals that share needles with individuals from the other community.

Now if the communities are isolated, that is, $\beta_j^{\mathrm{I}} = 1 = \beta_j^{\mathrm{II}}$ $(j=1,2)$ and $q_i^{\mathrm{I}} = 0 = q_i^{\mathrm{II}}$ $(i=1,2)$, the system (32) decouples and we get the same result as above, viz., two distinct R_0 given by

$$R_0^{\nu} = \frac{\delta m^{\nu}\left[\left(a_1^{\nu}\right)^2 p_1^{\nu}x_1^{\nu}(0) + \left(a_2^{\nu}\right)^2 p_2^{\nu}x_2^{\nu}(0)\right]}{r(\mu+\alpha)} \quad \text{for } \nu=1,2. \qquad (33)$$

In general, we do not expect isolated communities for IVDUs. We, therefore, have to study under which circumstances it makes sense to consider the whole community as composed by distinct "patches," each describing different social behavior from their components.

The presence of community I affects the threshold for infection to prevail of community II, and vice-versa, as following. If the two communities interact "weakly," that is, a number of individuals from one community share needles rarely with individuals from the other community, the thresholds for the infection to prevail are approximately

$$R_0^{\mathrm{I}} \simeq \frac{\Phi_1}{r(\mu+\alpha)} \tag{34}$$

and

$$R_0^{\mathrm{II}} \simeq \frac{\Phi_2}{r(\mu+\alpha)}, \tag{35}$$

where Φ_i are auxiliary functions described in the Appendix. Analyzing these auxiliary functions, the reader can easily note that (34) and (35) are natural generalizations of (33).

If $R_0^{\mathrm{I}} > 1$, then the infection prevails in community I regardless community II and the other way round; if $R_0^{\mathrm{II}} > 1$, the infection prevails in community II regardless community I. When both R_0 are greater than 1, the infection prevails in both communities at the same time.

When the interaction between the two communities is "strong," that is, individuals of one community share needles frequently with individuals from the other, then the Hurwitz criterion [13] guarantees that the trivial solution is stable if $R_0^{\mathrm{I}} < 1$ and $R_0^{\mathrm{II}} < 1$, as above, but a further condition must be satisfied, namely,

$$\Phi_1 + \Phi_2 > 2(\Phi_3 + \Phi_4)^{1/2}. \tag{36}$$

However, when the interaction between the two communities is strong, the patches ought to be redefined whenever possible.

4. A PRELIMINARY ESTIMATION OF R_0 FOR A REAL COMMUNITY OF IVDUS

In order to illustrate the application of the above described concepts to a real transmission situation, some of the parameters necessary to

calculate R_0, y, and p^i from a community of IVDUs of the city of Santos, Brazil were determined. This was done by the application of a questionnaire to 65 individuals sampled by snowballing, relating the IVD use practices to HIV transmission. The city of Santos was chosen due to the fact that it presents the highest incidence of HIV infection in Brazil [26]. Some of the parameters were determined from literature data. Others were calculated from answers given to a questionnaire. The questions related to the estimation of R_0 are the following:

1. number of drug injections in a typical day (average);
2. number of days of IVD use in a typical month;
3. proportion of events in which a needle was shared when using IVD;
4. number of days a needle is kept for reuse; and
5. average period of time a IVDU remains in the same community.

It should be mentioned that the results presented here are intended to exemplify the theory above and are part of a more extensive study comprising more than 200 individuals, the results of which will be presented in a future publication. The sample of 65 individuals represents an isolated community in the sense that they all relate to each other, as assumed by the model.

The daily rate of IVD use in this population has shown a fairly high degree of variation (ranging from 0.033 to 1) with the number of drug injections on each of these days varying from 1 to 30. The number of needles per individual m is assumed to be dependent only on the needles' availability and not on the IVDU habits. Therefore, we calculated its value from the average values of a and ma found in this population, which resulted in the value of 0.7 needles per human. The daily "survival" rate of the needles population, i.e., the average period of time needles spend among the IVDUs population was found to be $1/\alpha = 2.1$ days.

The proportion of needles which get the infection after biting an infective individual δ was estimated from the data described by Ho et al. [10]. From these data we get the average concentration of infective inoculum per unit of blood volume ($\varphi = 30$ UITC/ml) and its respective variance ($\sigma^2 = 1.0 \times 10^3$). Therefore by taking the residual volume of blood in the lumen of the needles as equal to 6.6 μl (a typical 30×7 needle), we obtain the value of $\delta = 0.18$ assuming a homogeneous, and $\delta = 0.24$ assuming a heterogeneous distribution of infective inoculae, respectively.

In this section the parameter r was defined as the inverse of the period an HIV positive individual remains in the IVDU community. For this specific community this value corresponds to roughly 1 year.

TABLE 1

Value of the Parameters for the Calculation of R_0, Estimated from the Community of IVDU in the City of Santos

Parameter	Value	Way of estimation
δ	0.18	Section 3.1 and 14
a	11.55* days^{-1}	Questionnaire
m	0.7	Questionnaire
r	365 days^{-1}	Questionnaire
α	2.1 days^{-1}	Questionnaire
μ	960 days^{-1}	Coagulation time

*Average value.

The parameter μ defined as the inverse of the average period of needles' invectiveness was determined by assuming that this period depends mainly on the coagulation time of the residual blood inside the needle. This value was estimated as 960 days^{-1}.

The values of the parameters are summarized in Table 1.

The basic reproduction ratio R_0 was calculated with parameters from Table 1, according to (17), resulting in the value of 35.3. This value should be compared with that described in [11].

For this particular community the prevalence of HIV infection at equilibrium y was found to be 67%, which should be compared with the actual value found, 61.5%. Our results point not only to a good agreement between theory and practice but also to the fact that this specific community is near its theoretical equilibrium level of endemicity. The proportion of infected and infective needles estimated by the model is 33 and 0.1%, respectively, although these parameters were not subjected to experimental verification.

5. FINAL COMMENTS

This work consists of theoretical developments that follow the steps of previous authors, particularly of Macdonald [19–21], and Kaplan [1, 2]. Some of the models presented in this paper are mathematically similar to previously published works. For example, (4) of the present paper is after suitably adjusting the notation and accounting for minor differences in assumptions very similar to (23) in the paper by Kaplan

[11]. Also, (15) and (14) of this paper are very close to (2) and (4) of the paper [11].

The parameters estimated through the proposed theory may be of great value for the comprehension of the studied phenomena and for the development of tools with predictive capacity. So, for instance, the estimation of the basic reproduction ration R_0 for HIV gives a fairly good idea of the intensity of transmission among the studied community. The derived parameters, like the inoculation rate h can be applied to dynamic models of HIV transmission that could be helpful on the prediction of future behavior of the system and on the design of control strategies. Therefore, a particular intervention program, like syringe and needle exchange, can have an impact on specific parameters related to the estimation of R_0. So, a needle distribution program would increase the needles mortality rate α and would lower the average daily biting rate a (and the probability of sharing p_j) of the needles, provided that the resulting α is sufficiently great. On the other hand, the needles' density as related to the human population m could increase. However, as the average number of bites per needle a has its value squared in (17) its effect would be more determinant on reducing the value of R_0. In addition, a cleaning needles/syringes program could increase the value of μ significantly, and so on. Furthermore, the critical density of needles, below which the infection would disappear from the population, could, at least theoretically, be estimated from the method proposed. This parameter, however, could have very little epidemiological meaning in the case of IVDUs.

The analogy with Macdonald's developments as described in Section 2 is clearly unrealistic because it does not consider the several heterogeneities known to contribute to HIV transmission among IVDUs. For instance, it assumes that all IVD users have exactly the same IVD use habits, which implies that every needle has the same daily biting rate. In addition, the probability of a needle of getting the infection δ is considered to be independent on the HIV concentration in the blood. Those assumptions are good approximations for biological vectors but are clearly inappropriate for needle related transmission of HIV.

Those heterogeneities are treated in Section 3, in which a properly averaged needles biting rate is defined and a calculation for δ as a function of the host viraemia is proposed.

An important characteristic of HIV transmission is the fact that distinct communities have different transmission intensity patterns. Therefore, any model dealing with HIV transmission should consider the possibility of individual mobility, sharing habits with more than one specific community. This implies a spatial transmission structure with

distinct community being patches in a large population. The model proposed in Section 3 deals with this situation and gives conditions to the estimation of distinct R_0 for each patch, depending on sharing needles habits within and between all the patches. In this case we must assign a matrix, or a set, of R_0 to characterize the transmission of infection within and between various groups [3]. It should be noted that this approach is also suitable for other transmission routes of HIV, like the sexual behavior, and could be easily adaptable to true vector-borne infections, like malaria, in which geographical distribution of mosquitoes is important.

The example presented in Section 4 is intended to illustrate the theory proposed. It includes all the heterogeneities described above and considers a weakly interacting patch. The value of R_0 found for this community is compatible with a transmission intensity resulting in 61% HIV seroprevalence, as is the case. In addition, the calculated seroprevalence in equilibrium was found to be 67% and the proportion of infected needles was found to be equal to 33%, although only 0.1% of all circulating needles were infective. As mentioned above, these latter parameters were not subjected to experimental verification. The proper way to verify the values of these parameters would be through HIV cultures techniques in order to detect at least one UITC in the residual blood. To the best of our knowledge, this technique is not sensitive enough to be applied to such a small volume of blood. On the other hand, sensitive techniques, like viral antigens detection by ELISA and viral RNA detection by PCR, can result positive even with only viral fragments that are not necessarily infective. Indeed, recent estimates suggest that up to 100,000 more noninfectious virions (which are detectable by those techniques) than free infectious viruses are present in the plasma of seropositive individuals [14]. Therefore, although ELISA and PCR are the methods of choice to detect *infected* needles, some work still must be done in order to standardize them to detect *infective* needles.

The proposed method is not devoid of limitations. So the deduction of the models described assume certain conditions not always fulfilled in real situations. For instance, the total population of IVDUs is assumed to be constant with time. In addition, it is assumed that HIV transmission is exclusively dependent on contaminated blood, without taking account of other transmission routes, in particular the sexual one.

Finally, we believe that the greatest contribution of this work is in proposing an alternative way to estimate transmission quantifiers of a pathogenic agent indirectly transmitted. It also calls the attention to

certain behavioral characteristics of the community of IVDUs already known but not quantitatively related, insofar the development of this paper to HIV transmission. Furthermore, these transmission quantifiers can be useful in the assessment of intervention strategies, as mentioned above.

The refinement of the proposed theory will obviously depend on detailed field work, which would make possible the estimation of the necessary parameters for the calculations described above. We already have a field project and we hope that in the near future we will be able to present estimations of HIV transmission among IVDUs with higher epidemiological reliability.

6. APPENDIX

In this appendix we present the auxiliary functions of (34)–(36). For simplicity we give the results for two communities (superscript I and II), each with two subgroups (subscripts 1 and 2).

$$\Phi_1 = \left(m^{\mathrm{I}}\left(\beta_1^{\mathrm{I}}\right)^2 + m^{\mathrm{II}}\left(1-\beta_1^{\mathrm{I}}\right)^2 q_1^{\mathrm{I}}\right)\delta\left(a_1^{\mathrm{I}}\right)^2 p_1^{\mathrm{I}} x_1^{\mathrm{I}}(0)$$

$$+\left(m^{\mathrm{I}}\left(\beta_2^{\mathrm{I}}\right)^2 + m^{\mathrm{II}}\left(1-\beta_2^{\mathrm{I}}\right)^2 q_1^{\mathrm{II}}\right)\delta\left(a_2^{\mathrm{I}}\right)^2 p_2^{\mathrm{I}} x_2^{\mathrm{I}}(0)$$

$$\Phi_2 = \left(m^{\mathrm{II}}\left(\beta_1^{\mathrm{II}}\right)^2 + m^{\mathrm{I}}\left(1-\beta_1^{\mathrm{II}}\right)^2 q_1^{\mathrm{II}}\right)\delta\left(a_1^{\mathrm{II}}\right)^2 p_1^{\mathrm{II}} x_1^{\mathrm{II}}(0)$$

$$+\left(m^{\mathrm{II}}\left(\beta_2^{\mathrm{I}}\right)^2 + m^{\mathrm{I}}\left(1-\beta_2^{\mathrm{II}}\right)^2 q_2^{\mathrm{II}}\right)\delta\left(a_2^{\mathrm{II}}\right)^2 p_2^{\mathrm{II}} x_2^{\mathrm{II}}(0)$$

$$\Phi_3 = m^{\mathrm{I}} m^{\mathrm{II}}\Big[\left(\left(\beta_1^{\mathrm{I}} - \beta_1^{\mathrm{II}}\right)\left(\beta_1^{\mathrm{I}} q_2^{\mathrm{I}} - \beta_2^{\mathrm{I}} q_1^{\mathrm{I}}\right) + \beta_1^{\mathrm{I}}\beta_2^{\mathrm{I}}\left(q_1^{\mathrm{I}} - q_2^{\mathrm{II}}\right)\right)$$

$$\times \delta^2\left(a_1^{\mathrm{I}}\right)^2 p_1^{\mathrm{I}} x_1^{\mathrm{I}}(0)\left(a_2^{\mathrm{I}}\right)^2 p_2^{\mathrm{I}} x_2^{\mathrm{I}}(0)\Big]$$

$$+ m^{\mathrm{I}} m^{\mathrm{II}}\Big[\left(\beta_1^{\mathrm{II}} - \beta_2^{\mathrm{II}}\right)\left(\left(\beta_1^{\mathrm{II}} q_2^{\mathrm{II}} - \beta_2^{\mathrm{II}} q_1^{\mathrm{II}}\right) + \beta_1^{\mathrm{II}}\beta_2^{\mathrm{II}}\left(q_1^{\mathrm{II}} - q_2^{\mathrm{II}}\right)\right)$$

$$\times \delta^2\left(a_1^{\mathrm{II}}\right)^2 p_1^{\mathrm{II}} x_1^{\mathrm{II}}(0)\left(a_2^{\mathrm{II}}\right)^2 p_2^{\mathrm{II}} x_2^{\mathrm{II}}(0)\Big]$$

and

$$\begin{aligned}\Phi_4 = m^{\mathrm{I}}m^{\mathrm{II}}\Big[&\big(1-(\beta_1^{\mathrm{I}}+\beta_1^{\mathrm{II}})\big)\Big[\big(1-(\beta_1^{\mathrm{I}}+\beta_1^{\mathrm{II}})\big)q_1^{\mathrm{I}}q_1^{\mathrm{II}}\\ &\quad-\beta_1^{\mathrm{I}}\beta_1^{\mathrm{II}}(1-q_1^{\mathrm{I}}q_1^{\mathrm{II}})\Big]\\ &\times\delta^2\big(a_1^{\mathrm{I}}\big)^2p_1^{\mathrm{I}}x_1^{\mathrm{I}}(0)\big(a_1^{\mathrm{II}}\big)^2p_1^{\mathrm{II}}x_1^{\mathrm{II}}(0)\Big]\\ +m^{\mathrm{I}}m^{\mathrm{II}}\Big[&\big(1-(\beta_1^{\mathrm{I}}+\beta_1^{\mathrm{II}})\big)\Big[\big(1-(\beta_1^{\mathrm{I}}+\beta_2^{\mathrm{II}})\big)q_1^{\mathrm{I}}q_2^{\mathrm{II}}\\ &\quad-\beta_1^{\mathrm{I}}\beta_2^{\mathrm{II}}(1-q_1^{\mathrm{I}}q_2^{\mathrm{II}})\Big]\\ &\times\delta^2\big(a_1^{\mathrm{I}}\big)^2p_1^{\mathrm{I}}x_1^{\mathrm{I}}(0)\big(a_1^{\mathrm{II}}\big)^2p_1^{\mathrm{II}}x_2^{\mathrm{II}}(0)\Big]\\ +m^{\mathrm{I}}m^{\mathrm{II}}\Big[&\big(1-(\beta_2^{\mathrm{I}}+\beta_1^{\mathrm{II}})\big)\Big[\big(1-(\beta_2^{\mathrm{I}}+\beta_1^{\mathrm{II}})\big)q_2^{\mathrm{I}}q_1^{\mathrm{II}}\\ &\quad-\beta_2^{\mathrm{I}}\beta_1^{\mathrm{II}}(1-q_2^{\mathrm{I}}q_1^{\mathrm{II}})\Big]\\ &\times\delta^2\big(a_2^{\mathrm{I}}\big)^2p_2^{\mathrm{I}}x_2^{\mathrm{I}}(0)\big(a_1^{\mathrm{II}}\big)^2p_1^{\mathrm{II}}x_1^{\mathrm{II}}(0)\Big]\\ +m^{\mathrm{I}}m^{\mathrm{II}}\Big[&\big(1-(\beta_2^{\mathrm{I}}+\beta_2^{\mathrm{II}})\big)\Big[\big(1-(\beta_2^{\mathrm{I}}+\beta_2^{\mathrm{II}})\big)q_2^{\mathrm{I}}q_2^{\mathrm{II}}\\ &\quad-\beta_2^{\mathrm{I}}\beta_2^{\mathrm{II}}(1-q_2^{\mathrm{I}}q_2^{\mathrm{II}})\Big]\\ &\times\delta^2\big(a_2^{\mathrm{I}}\big)^2p_2^{\mathrm{I}}x_2^{\mathrm{I}}(0)\big(a_2^{\mathrm{II}}\big)^2p_2^{\mathrm{II}}x_2^{\mathrm{II}}(0)\Big]\end{aligned}$$

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