



## A nested-epidemic model for the spread of hepatitis C among injecting drug users

Nicolino Esposito \*, Carla Rossi

*Department of Mathematics, University of Tor Vergata, Rome Via Ricerca Scientifica 1, 00133 Rome, Italy*

Received 17 December 2002; received in revised form 4 November 2003; accepted 4 November 2003

---

### Abstract

Injecting drug users (IDUs) are the largest risk group for HCV infection. Studying injecting by classical epidemiological methods is no easy task, largely due to its hidden nature and low prevalence in general population terms. Thus, mathematical modelling can be of major help in performing a qualitative and quantitative evaluation of the costs and possible impact of the various interventions and to produce forecasts of both injecting drug use and HCV spread among IDUs. In the present paper an epidemic Mover–Stayer model for the spread of drug use, which has been recently proposed, is extended to mirror the spread of an infectious disease, in particular hepatitis C, among the injecting drug user population.

In order to model the spread of a disease (HCV) among a population evolving following a different epidemic (injecting drug use) all the compartments of the ‘external epidemic’ (injecting drug use) are subdivided into two sub-compartments: the first one comprising individuals who are not affected by HCV and the second one comprising individuals affected. The resulting model may be defined the ‘two epidemics’ or, better, the ‘nested epidemics’ model. The model is a Mover–Stayer model for what concerns the ‘external epidemic’ (injecting drug use) but is a homogeneous epidemic model for HCV (all individuals are at risk of HCV the same). In the following, the dynamic equations are derived. Some qualitative analysis is performed in order to evaluate the asymptotic behaviour and the impact of possible prevention or harm reduction interventions. The results of a scenario analysis are also presented. The model, though simple, seems to be a very valuable tool for policy makers.

© 2004 Elsevier Inc. All rights reserved.

*Keywords:* HCV epidemic; Injecting drug users; Compartmental models; Population dynamics

---

---

\* Corresponding author.

*E-mail addresses:* [nesposit@mat.uniroma2.it](mailto:nesposit@mat.uniroma2.it) (N. Esposito), [rossi@mat.uniroma2.it](mailto:rossi@mat.uniroma2.it) (C. Rossi).

## 1. Introduction

Problem drug use represents an important social, criminal and public health issue. It is defined as ‘injecting drug use or long duration/regular use of opiates, cocaine and/or amphetamines’ [3]. This definition excludes ecstasy and cannabis users, and those who never, or irregularly, use opiates, cocaine or amphetamines.

Illegal drug use is concentrated in some groups of the population, in particular young adults, males and urban inhabitants, although this varies across countries and differences tend to decrease over time.

Drug injecting refers to the non-medical self-injection of drugs and excludes persons injecting steroids for sporting and non-sporting purposes. In Europe, the main drugs involved are heroin and, to a lesser extent cocaine or amphetamines. Cocaine is not usually injected, except in combination with heroin. Other drugs, such as benzodiazepines, are also sometimes injected.

There are probably between half and one million drug injectors in the EU today, excluding those who inject occasionally or who have injected in the past. This represents less than 0.4% of the EU population aged 15–64, and no more than 5% of the estimate 18 million who use illegal drugs each year [6]. Young adults (aged 15–34 according to the EMCDDA standard with some national differences) present rates up to double or more than those of the whole adult population for injecting drugs. Drug injecting is the common denominator of most serious drug-related health damage in the EU (e.g. HIV, hepatitis B and C, tuberculosis and endocarditis). Reusing and sharing syringes, needles, and other drug injection equipment exposes injecting drug users (IDUs) to the risk of contracting or transmitting HIV and other blood-borne infections such as hepatitis B (HBV) and hepatitis C (HCV).

The study of infective pathologies related to drug injecting is one of the five key indicators proposed by EMCDDA. In fact the information concerning the infections of HIV, hepatitis B and C among IDUs are necessary to estimate the results obtained from previous strategies of prevention and treatment and to plan further interventions.

IDUs have one of the highest HBV incidence rates among all risk groups, and at least half of all new HCV cases occur among IDUs. Studies have shown that infection with HBV and HCV frequently occurs soon after an individual begins injecting drugs. HCV has emerged as a major epidemic among IDUs, with observed prevalence exceeding 70% in many countries in the EU. In particular, in Italy the trend seems stable in the last 4 years for what concerns national level while, at local level, increases are reported in the Northeast area (from 75.8% in 1998 to 78% in 2001) and decreases are reported in the Centre and South area (respectively from 69.6% to 65.9% and from 56.3% to 53.1%).

Many interventions are designed to prevent or to control the spread of blood-borne disease among IDUs.

Such interventions include primary and secondary prevention to forestall initiation into drug use, substance abuse treatment to reduce intensity and the duration of injection drug use, and harm reduction interventions designed to make drug use less dangerous to active IDUs. Studying drug injecting is no easy task, largely due to its hidden nature and low prevalence in the general population terms.

Thus, mathematical modeling can be of major help in performing a qualitative and quantitative evaluation of the costs and possible impact of the various interventions and to produce forecasts of both injecting drug use and health consequences, such as infectious diseases. On the other hand, epidemiological information on incidence and prevalence of acquired infections can be useful to estimate, on the basis of suitable models, the size of the hidden population of IDUs ([21,25]) and evaluate the impact of interventions aimed at secondary prevention or harm reduction [24].

Several models for the spread of infectious diseases have been proposed in the literature [1,9,10,15,16,19] but they just consider the epidemics into ‘close’ sub-populations at high risk of infection (i.e. homosexuals, sex workers or injecting drug users). In the present paper the population of problem drug users is modeled as an ‘open’ group with its own peculiar dynamics [8,23,24].

There is evidence that drug use itself spreads as an infectious disease, i.e. the rate of new cases depends on the number of existing cases and on the number of susceptible [2,12,17]. Thus, mathematical models developed for epidemiological applications may be of use in this field, although the sociological parameters needed to model drug-related problems may be more transient than the biological parameters used to model infectious disease spread.

## 2. The nested epidemic model

Compartmental models represent a powerful mathematical tool well established in modelling the spread of ‘diseases’ in a population [13]. Thus, they provide a framework in which numbers of people in different compartments (each one homogeneous with respect to some specified characteristics) and the relationships between such compartments, modelling the dynamics of the population, can be described in mathematical terms.

The results from the model are the number of people in some compartment of interest at some specific time (prevalence), or the number of people moving to and/or from some compartment during a specified time interval (incidence). Once the population has been split into relevant compartments, it is an easy task to describe mathematically how the size of these compartments will change over time by means of suitable difference or differential equations, according to the basic hypotheses of the model describing the dynamics of the population of interest.

The graph presented in Fig. 1 describes the main features of the model proposed in the present paper to describe the HCV epidemic among IDUs. This model is an extension of a Mover–Stayer type model ([24,25]) and could be seen as a ‘two floors’ model [8].

The first one (down), that is named ‘external epidemic’, mirrors the spread of IDUs from a susceptible population subdivided into two groups: stayers consisting of individuals who, due to their ‘prudent’ behaviour, are considered not to be at risk of ‘infection’ and the group of movers consisting of individuals at risk of ‘infection’.

The other floor (up), that obviously is an ‘internal epidemic’, is intended to model the diffusion of HCV among IDUs.

It should be noted that this model is a Mover–Stayer model in relation to the ‘external epidemic’ but is a homogeneous epidemic model in relation to HCV given that, to provide a tractable analytic model, it is assumed that all IDUs are at an equal risk of HCV.

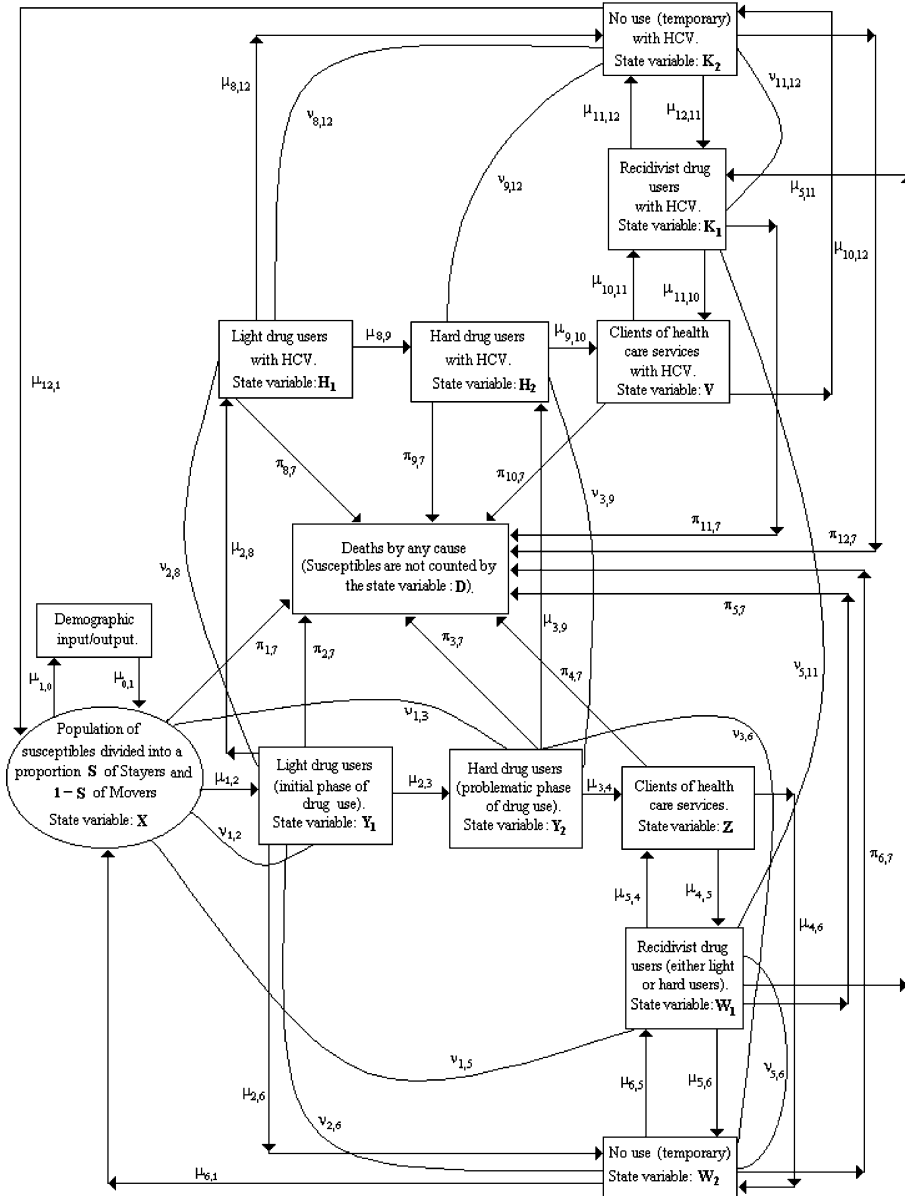


Fig. 1. Graphical representation of the ‘nested epidemics’ model.

It must be observed that a Mover–Stayer model is characterised by the partition of the susceptible population into two groups:

- The Stayers, that is, those individuals who, due to their ‘prudent’ behaviour, cannot be infected and, thus, are not at risk. They always remain in the compartment of susceptibles.
- The Movers, who are at risk of infection, represent the so called ‘core group’. They can move to the drug user compartments and begin a ‘drug user career’.

The movers can be infected either by a contact with an infectious individual (drug user) or by a contact with a pusher operating in the black market of drugs.

A drug user passes through a period of ‘hidden’ use at the beginning of his/her career. This period, called ‘latency period’ [3,5], can be split into several different phases. During this period the drug users can:

1. stop using drugs;
2. continue using drugs;
3. die.

Afterwards, those who continue using drugs, due to health and criminal problems connected with drug use, are normally recorded by some Agency and becomes ‘visible’. Usually, at this stage, he/she starts to be assisted by health care services and can be cured. However, addictive use of drug is a recidivant syndrome, thus, ‘recidivist use’ is a possible further phase of a drug user career. For sake of simplicity, as in Rossi [24] and Esposito and Rossi [8], the model is set up under the hypothesis that the new susceptibles, entering in the population of interest, are divided into Stayers and Movers according to constant proportions  $S_0$  and  $M_0 = 1 - S_0$  (stationarity), with  $0 < S_0 < 1$ . Due to the structure of the ‘two floors’ model described above, this model is called ‘nested epidemic’ model (Table 1).

Table 1  
Parameters and variables of the ‘nested epidemics’ model

Type		Description
$\mu_{i,j}$	Transition rates	Constant
$\pi_{i,j}$	Mortality rates	Constant
$v_{i,j}$	Interaction rates	Constant
$X(t)$	Population of susceptibles (Compartment 1)	Prevalence
$S(t)$	Proportion of stayers	Proportion
$Y_1(t)$	Light drug users (Compartment 2)	Prevalence
$Y_2(t)$	Hard drug users (Compartment 3)	Prevalence
$PXY_1(t)$	Incidence from susceptibles to light drug users	Incidence
$PAY_1Y_2(t)$	Incidence from light drug users to hard drug users	Incidence
$Z(t)$	Clients of health care services (Compartment 4)	Prevalence
$PAY_2Z(t)$	Incidence from hard drug users to clients	Incidence
$W_1(t)$	Recidivist drug users (Compartment 5)	Prevalence
$W_2(t)$	No use (Compartment 6)	Prevalence
$D(t)$	Deaths by any cause (Compartment 7)	Cumulative prevalence
$H_1(t)$	Light drug users with HCV (Compartment 8)	Prevalence
$H_2(t)$	Hard drug users with HCV (Compartment 9)	Prevalence
$V(t)$	Clients of health care services with HCV (Compartment 10)	Prevalence
$K_1(t)$	Recidivist drug users with HCV (Compartment 11)	Prevalence
$K_2(t)$	No use with HCV (Compartment 12)	Prevalence
$PAY_1H_1(t)$	Incidence from light drug users to light drug users with HCV	Incidence
$PAY_2H_2(t)$	Incidence from hard drug users to hard drug users with HCV	Incidence
$PAW_1K_1(t)$	Incidence from recidivist drug users to recidivist drug users with HCV	Incidence

The nested epidemic model is the simplest model (even if by representation it seems complex) because the set of individuals who can develop hepatitis C only comprises IDUs and not the whole susceptible population, which should be divided into various groups with different risk behaviour. Such a model would thus require the estimation of a huge number of interaction parameters, resulting in a quite unstable, over parameterised structure. On the other hand, the present model comprises all the compartments of interest, but no more, according to the suggestion by Einstein: “A model must be as simple as possible, but not simpler” [11].

It must also be observed that ‘natural history’ only refers to drug injecting and not to HCV, since data on the HCV stage in IDUs is not available.

The capital letter inside each compartments represents the ‘level’ of the compartment, i.e. a state variable counting the number of individuals or the prevalence in the compartment, normalised if needed.

In Fig. 1 there are two kinds of connection between the various compartments: arrows and lines. The lines show that the connections are interactions (non-linear epidemic terms in the equations) whereas the arrows are transitions (linear terms) that occur in their directions. In the first floor, the lines connecting the drug use (infectives) compartments and the susceptible (or temporary no-use) compartments denote the possible interactions which may produce transitions from susceptibles (or temporary no-use) to infectives. The other possible transitions from susceptibles (or temporary no-use) to infectives are induced by the pressure of the black market.

As to the parameters and the distributions of the lengths of stay, some of them are already available from the study of the latency period [3]. Others can be derived from therapy data already available in some sites. The demographic parameters regulating the dynamics of the susceptible population, namely  $\mu_{0,1}$ ,  $\mu_{1,0}$ ,  $\pi_{1,7}$  are supposed to be known and are country-specific. The other parameters  $\pi$  can be externally estimated using the information from mortality studies among drug users, which are available for most countries in the EU [4]. The parameters  $\mu_{2,3}$ ,  $\mu_{3,4}$ ,  $\mu_{8,9}$  and  $\mu_{9,10}$  (natural history parameters) can be estimated on the basis of data available on the natural history of drug use. The parameters  $\mu_{4,5}$ ,  $\mu_{4,6}$ ,  $\mu_{5,4}$ ,  $\mu_{5,6}$ ,  $\mu_{6,5}$ ,  $\mu_{6,1}$ ,  $\mu_{10,11}$ ,  $\mu_{10,12}$ ,  $\mu_{11,10}$ ,  $\mu_{11,12}$ ,  $\mu_{12,1}$  and  $\mu_{12,11}$  (therapy parameters) can be obtained at least for order of magnitude from therapy data available in most countries. The parameters  $\mu_{2,8}$ ,  $\mu_{3,9}$ ,  $\mu_{5,11}$ ,  $\nu_{2,8}$ ,  $\nu_{3,9}$  and  $\nu_{5,11}$  are HCV infection rates among IDUs. All the other parameters and the parameter ‘initial proportion of Stayers’,  $S_0$ , can be used as scenario parameters.

All the parameters  $\mu_{i,j}$  and  $\pi_{i,j}$  represent transmission rates per person of the origin compartment per week and appear in the linear terms of the equations, instead the parameters  $\nu_{i,j}$  are interactions rates per week per pair and appear in the bilinear terms of the equations.

The values of all these parameters for Italy (or their order of magnitude) are reported in Table 2 [3–5,8,24].

The parameters in bold character are ‘scenario’ parameters that can be modified to obtain different simulated behaviours of the epidemics.

From the graph reported in Fig. 1, it is straightforward writing the difference equations of the model that are reported in the Appendix A.

The state variables used in the model (with the exception of  $S(t)$ , which is the proportion of Stayers at time  $t$ ) are normalised per million inhabitants.

Table 2  
Values or order of magnitude of parameters

Connections between compartments	$\mu$	$\pi$	$\nu$ (order of magnitude)
0 → 1	0.00025		
1 → 0	0.00002		
1 → 2	$10^{-5}/10^{-6}$		$10^{-5}/10^{-6}$
1 → 3			$10^{-6}/10^{-5}$
1 → 5			$10^{-5}/10^{-6}$
1 → 7		0.00023	
2 → 3	0.009		
2 → 6	0.004/0.0004		$10^{-5}/10^{-6}$
2 → 7		[0.0002–0.0008]	
2 → 8	$10^{-7}$		$8.6677 \times 10^{-6}$
3 → 4	0.004		
3 → 6			$10^{-6}/10^{-5}$
3 → 7		[0.0002–0.0008]	
3 → 9	$10^{-7}$		$8.6677 \times 10^{-6}$
4 → 5	[0.014–0.018]		
4 → 6	[0.007–0.009]		
4 → 7		[0.0002–0.0008]	
5 → 4	0.001		
5 → 6	[0.05–0.1]		$10^{-5}/10^{-6}$
5 → 7		[0.0002–0.0008]	
5 → 11	$10^{-7}$		$8.6677 \times 10^{-6}$
6 → 1	0.0096		
6 → 5	0.001		
6 → 7		[0.0002–0.0008]	
8 → 7		0.0014	
8 → 9	0.009		
8 → 12	0.004/0.0004		$10^{-5}/10^{-6}$
9 → 7		0.0014	
9 → 10	0.004		
9 → 12			$10^{-5}/10^{-6}$
10 → 7		0.0014	
10 → 11	[0.014–0.018]		
10 → 12	[0.007–0.009]		
11 → 7		0.0014	
11 → 10	0.001		
11 → 12	[0.05–0.1]		$10^{-5}/10^{-6}$
12 → 1	0.0096		
12 → 7		0.0014	
12 → 11	0.001		

It must be observed that some hypotheses can be made in order to simplify the model, namely:  
*External epidemic*

- Infectivity parameters are different for the interaction between light drug users and susceptibles and hard drug users and susceptibles.

### Internal epidemic

- HCV infected drug users can contract HCV either by the interaction with infected drug users (bilinear term in the equations) or by the interaction with blood product or infected individuals who are not drug users (linear term in the equations).
- Due to homogeneity and biological reasons, the infectivity parameters for all interactions assume the same value.
- HCV positive drug users can become susceptible again with respect to the external epidemic. For the sake of simplicity, due to the low number of such cases, HCV+ status of such individuals is neglected.

### 3. Epidemic/endemic behaviour for the external epidemic and prior evaluation of the impact of primary and secondary prevention interventions

From the equation for the susceptible population and the equation for the proportion of Stayers it is possible to carry out a qualitative analysis of the epidemic. The approach is similar to that used in Rossi [24]. The analysis focus on the onset incidence indicator, that is, the number of transitions from susceptibles to light drug users per unit time, which is a crucial indicator for monitoring and evaluating drug policy [20].

Let us consider the equations for  $X(t)$  and for the ratio  $S(t + Dt)/S(t)$ :

Dividing the first equation by  $X(t + Dt)$  we can write:

$$1 = \frac{X(t)(1 - \mu_{1,0} - \pi_{1,7})}{X(t + Dt)} - \frac{X(t)}{X(t + Dt)} [1 - S(t)][\mu_{1,2} + v_{1,2}Y_1(t) + v_{1,3}Y_2(t) + v_{1,5}W_1(t)] \\ + \frac{X(t)}{X(t + Dt)} \left[ \mu_{0,1} + \mu_{6,1} \frac{W_2(t)}{X(t)} \right],$$

if the equation for  $S(t + Dt)/S(t)$  is subtracted from the above, we obtain

$$\rho(t) = 1 - \frac{S(t + Dt)}{S(t)} \\ = \left[ 1 - \frac{S_0}{S(t)} \right] \frac{\mu_{0,1}X(t) + \mu_{6,1}W_2(t)}{X(t + Dt)} - \frac{X(t)}{X(t + Dt)} [1 - S(t)][\mu_{1,2} + v_{1,2}Y_1(t) + v_{1,3}Y_2(t) + v_{1,5}W_1(t)].$$

The qualitative analysis of the epidemic is based on the study of the function  $\rho(t)$ .

In particular, if  $\rho(t) < 0$ , then the epidemic is decreasing and going towards the endemic phase, whereas if  $\rho(t) > 0$  the epidemic is spreading [22]. These two situations are characterised by the following relationships:

$$\rho(t) > 0 \iff \left[ 1 - \frac{S_0}{S(t)} \right] \frac{\mu_{0,1}X(t) + \mu_{6,1}W_2(t)}{X(t + Dt)} \\ > \frac{X(t)}{X(t + Dt)} [1 - S(t)][\mu_{1,2} + v_{1,2}Y_1(t) + v_{1,3}Y_2(t) + v_{1,5}W_1(t)], \quad (1)$$



$$\begin{aligned} \rho(t) < 0 &\iff \left[1 - \frac{S_0}{S(t)}\right] \frac{\mu_{0,1}X(t) + \mu_{6,1}W_2(t)}{X(t + Dt)} \\ &< \frac{X(t)}{X(t + Dt)} [1 - S(t)][\mu_{1,2} + v_{1,2}Y_1(t) + v_{1,3}Y_2(t) + v_{1,5}W_1(t)], \end{aligned} \tag{2}$$

where

$$\left[1 - \frac{S_0}{S(t)}\right] \frac{\mu_{0,1}X(t) + \mu_{6,1}W_2(t)}{X(t + Dt)}$$

represents the ‘demographic’ contribution to the dynamics and

$$[1 - S(t)][\mu_{1,2} + v_{1,2}Y_1(t) + v_{1,3}Y_2(t) + v_{1,5}W_1(t)]$$

represents the epidemic contribution to the dynamics.

Relation (1) implies that if  $S(t) = 1$  (all the susceptibles are Stayers) then the epidemic contribution vanishes,  $S(t)$  is decreasing ( $\rho(t) > 0$ ) and the endemic phase starts, whereas, from relation (2), we have that if  $S(t) \leq S_0$ , then  $S(t)$  is increasing ( $\rho(t) < 0$ ), thus, there exists a time  $t^*$  such that for  $t > t^*$   $S_0 \leq S(t) \leq 1$ . It follows that the values  $S_1 = 1$  and  $S_2 = S_0$  are reflecting barriers for the process for  $t > t^*$ , thus there exists a positive value  $\varepsilon$  ( $0 < \varepsilon < 1 - S_0$ ) such that if  $S(t) > 1 - \varepsilon$ , then the endemic phase of the epidemic starts and  $S(t)$  becomes a decreasing function, but, as soon as  $S(t) < 1 - \varepsilon$  then a new epidemic wave starts and  $S(t)$  becomes an increasing function. In other words we can say that the influence of the epidemic term is increasing for  $S(t)$  decreasing, whereas the influence of the demographic term is decreasing for  $S(t)$  decreasing, thus smoothed oscillations occur. We can define the value  $S^* = 1 - \varepsilon$  the threshold epidemic value. It is possible to express the relation to explicitate  $\varepsilon$  as a function of the interesting state variables and transition parameters but it cannot be calculated analytically, thus simulation runs are required to evaluate its value. In order to set up a simulation procedure hypotheses on the parameters of the model should be discussed.

In the following, the analysis of the effect of possible prevention intervention is outlined. Let us consider a primary prevention intervention with efficacy parameter  $\Delta$ , where  $\Delta$  is the probability that a mover becomes a stayer due to the intervention, and let us suppose that both, the intervention and the effect, are observed in the same time unit. In order to evaluate the qualitative impact of the intervention at population level we use, as an over all measure, the onset incidence indicator. Let us consider the following equations:

$$\begin{aligned} \Delta_1 &= X(t + Dt) - X(t) \\ &= X(t)(\mu_{0,1} - \mu_{1,0} - \pi_{1,7}) - X(t)[1 - S(t)][\mu_{1,2} + v_{1,2}Y_1(t) + v_{1,3}Y_2(t) + v_{1,5}W_1(t)] + \mu_{6,1}W_2(t) \\ &\quad + \mu_{12,1}K_2(t) \end{aligned}$$

and

$$\begin{aligned} \Delta_2 &= X(t + Dt) - X(t) \\ &= X(t)(\mu_{0,1} - \mu_{1,0} - \pi_{1,7}) - X(t)[(1 - S(t))(1 - \Delta)][\mu_{1,2} + v_{1,2}Y_1(t) + v_{1,3}Y_2(t) + v_{1,5}W_1(t)] \\ &\quad + \mu_{6,1}W_2(t) + \mu_{12,1}K_2(t), \end{aligned}$$

where the second relationship takes into account the effect of primary prevention intervention with efficacy parameter  $\Delta$ . By calculating the difference of the two expressions, we obtain

$$\Delta_2 - \Delta_1 = X(t)\Delta M(t)[\mu_{1,2} + \xi(t)],$$

where  $M(t) = 1 - S(t)$  is the proportion of movers at time  $t$  and  $\xi(t) = v_{1,2}Y_1(t) + v_{1,3}Y_2(t) + v_{1,5}W_1(t)$ . Thus, it is easily seen that the impact of a primary prevention intervention, with efficacy parameter  $\Delta$ , is bilinear with respect to such parameter and to the proportion of movers among susceptibles. This implies, due to the results of the qualitative analysis of the  $M - S$  model [24] showing that the proportion of movers is monotonically decreasing during the epidemic phase, that the effect of a primary prevention intervention is higher at the beginning of the epidemic. It also implies that the effect of the observation of the adverse consequences of drug abuse cannot be by itself highly effective as primary prevention, due to the long latency time [5]. This fact, unfortunately, prevents from observing such consequences for several years since the beginning of the epidemic. When starting observing them, most movers will already be drug users.

Similarly, the effect of law enforcement interventions can be evaluated by reducing  $\mu_{1,2}$  and the impact of secondary prevention interventions by reducing the  $v_{i,j}$  parameters or by modifying the characteristic therapy parameters, producing a consequent reduction of the size of compartments  $Y_1$ ,  $Y_2$  and  $W_1$ . It can be immediately derived that the impact of such interventions is more effective during a mature phase of the epidemic when the level of  $S(t)$  is high and the sizes of the three drug use compartments is high as well.

Thus  $M(t)$  can be used to measure the maximum expected instantaneous impact of primary prevention interventions and  $\xi(t)$  can be used to measure the maximum expected instantaneous impact of secondary prevention interventions.

Similarly it is possible to consider a primary prevention intervention on the susceptibles of the internal epidemic (hepatitis C) who, as described in Section 2, are the IDUs; in mathematical terms this corresponds to the sum of the three drug use compartments  $Y_1$ ,  $Y_2$  and  $W_1$ . Let us suppose that, due to this intervention, some users change their behaviour becoming more 'prudent', so they can be considered like stayers and do not take part in the spread of HCV.

If we denote by  $S'$  this proportion of HCV-stayers and by  $\Psi$  the efficacy parameter of the intervention, that is the probability that an IDU become a stayer with respect to the internal epidemic, we can evaluate the efficacy of the intervention. It should be noted that  $S'$  represents the proportion of non-HCV infected IDUs who become 'prudent' due to the intervention. Thus,  $S' = 0$  in the absence of intervention under the hypothesis of homogeneity of the internal epidemic.

As above, let us consider the equations:

$$\begin{aligned} \Delta_1 &= (Y_1(t + Dt) + Y_2(t + Dt) + W_1(t + Dt)) - (Y_1(t) + Y_2(t) + W_1(t)) \\ &= Y_1(t)(-\mu_{2,3} - \mu_{2,6} - \pi_{2,7}) + X(t)[1 - S(t)][\mu_{1,2} + v_{1,2}Y_1(t) + v_{1,3}Y_2(t) + v_{1,5}W_1(t)] \\ &\quad + Y_1(t)[1 - S'(t)](-\mu_{2,8} - v_{2,8}(H_1(t) + H_2(t) + K_1(t))) + Y_2(t)(-\mu_{3,4} - \pi_{3,7}) + \mu_{2,3}Y_1(t) \\ &\quad + Y_2(t)[1 - S'(t)](-\mu_{3,9} - v_{3,9}(H_1(t) + H_2(t) + K_1(t))) + W_1(t)(-\mu_{5,4} - \mu_{5,6} - \pi_{5,7}) \\ &\quad + W_2(t)[\mu_{6,5} + v_{2,6}Y_1(t) + v_{3,6}Y_2(t) + v_{5,6}W_1(t)] + \mu_{4,5}Z(t) \\ &\quad + W_1(t)[1 - S'(t)](-\mu_{5,11} - v_{5,11}(H_1(t) + H_2(t) + K_1(t))) \end{aligned}$$

and the analogous equation taking into account the effect of the intervention characterised by the efficacy parameter  $\Psi$ :

$$\begin{aligned} \Delta_2 &= (Y_1(t + Dt) + Y_2(t + Dt) + W_1(t + Dt)) - (Y_1(t) + Y_2(t) + W_1(t)) \\ &= Y_1(t)(-\mu_{2,3} - \mu_{2,6} - \pi_{2,7}) + X(t)[1 - S(t)][\mu_{1,2} + v_{1,2}Y_1(t) + v_{1,3}Y_2(t) + v_{1,5}W_1(t)] \\ &\quad + Y_1(t)[(1 - S'(t))(1 - \Psi)](-\mu_{2,8} - v_{2,8}(H_1(t) + H_2(t) + K_1(t))) + Y_2(t)(-\mu_{3,4} - \pi_{3,7}) \\ &\quad + \mu_{2,3}Y_1(t) + Y_2(t)[(1 - S'(t))(1 - \Psi)](-\mu_{3,9} - v_{3,9}(H_1(t) + H_2(t) + K_1(t))) \\ &\quad + W_1(t)(-\mu_{5,4} - \mu_{5,6} - \pi_{5,7}) + W_2(t)[\mu_{6,5} + v_{2,6}Y_1(t) + v_{3,6}Y_2(t) + v_{5,6}W_1(t)] + \mu_{4,5}Z(t) \\ &\quad + W_1(t)[(1 - S'(t))(1 - \Psi)](-\mu_{5,11} - v_{5,11}(H_1(t) + H_2(t) + K_1(t))). \end{aligned}$$

Taking the difference of the last two equations, we obtain

$$\Delta_2 - \Delta_1 = \Psi M'(t)(Y_1(t) + Y_2(t) + W_1(t))[\mu_{2,8} + \mu_{3,9} + \mu_{5,11} + \zeta'(t)],$$

where

$$M'(t) = 1 - S'(t)$$

and

$$\zeta'(t) = (v_{2,8} + v_{3,9} + v_{5,11})[H_1(t) + H_2(t) + K_1(t)].$$

For the internal epidemic the impact of a primary prevention intervention is bilinear with respect to  $M'(t)$  and to  $\zeta'(t)$ , as it was for the external one. Thus, the same considerations apply.

#### 4. An example of scenario analysis

The simulation procedure, used to obtain a scenario analysis, is written in *S-plus 2000* for PC. All the parameters can be modified at the beginning of each run by means of a user friendly interface. The standard output comprises tables and graphs of prevalence and incidence curves, related to the various compartments, and the various indicators to estimate the impact of prevention interventions. The time unit for simulation is one week and all the values related to incidence and prevalence curves are normalised and expressed per million inhabitants. The graphs presented below (Fig. 2) show the curves corresponding to the prevalence of the three compartments of drug use comparing them with the same prevalence curves related to the compartments of drug use with HCV to highlights the delays between the peaks and, similarly, for the incidence curves. Table 3 summarises the results obtained by simulation. The present scenario has been obtained using the most reliable parameter estimates for the heroin epidemic in Italy [8,24].

The graph presented in Fig. 3 shows the behaviour of the proportion of HCV infected IDUs among the clients of health care services:  $\frac{V}{V+Z}$  where  $V$  is the prevalence of the clients with HCV and  $Z$  that of the non-infected clients. such indicator represents the only available data for monitoring HCV spread among IDUs at present and can be assumed as a measure of the impact of the epidemic.

A fast increase can be observed for such indicator in agreement with empirical data available in the EU.

It must be observed that, without any intervention, the indicator increases approaching, with a velocity depending on the various parameters, the proportion of 100%, whereas it is expected that,

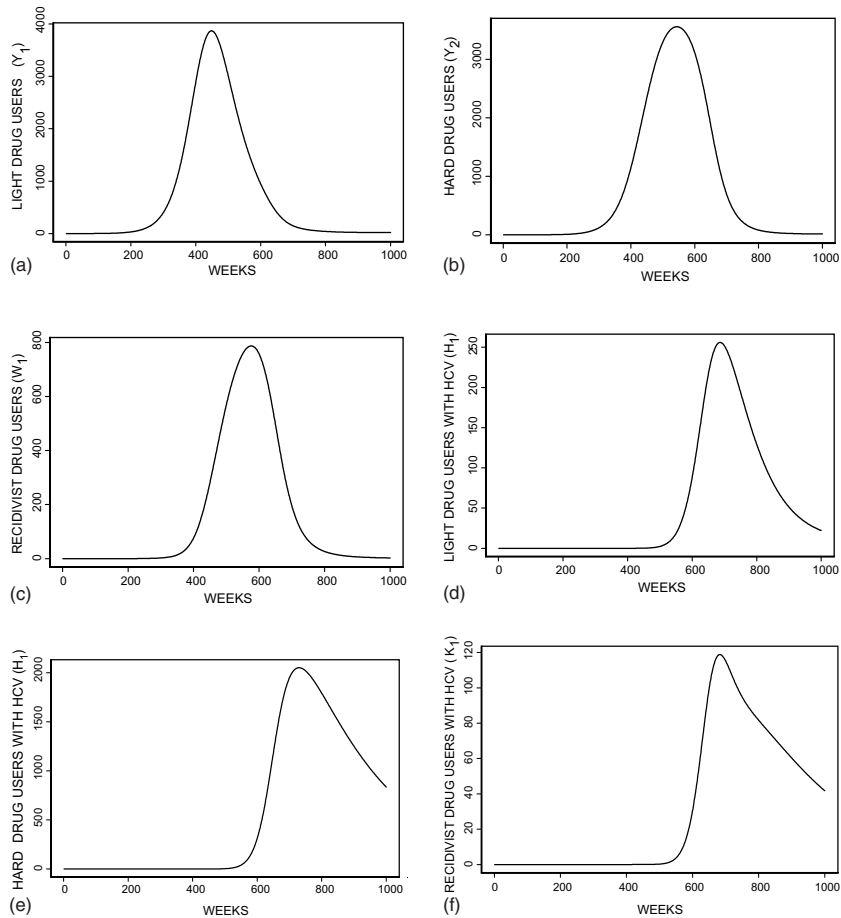


Fig. 2. Prevalence and incidence curves of IDUs compartments. (a) Prevalence curve of light users. (b) Prevalence curve of hard users. (c) Prevalence curve of recidivist users. (d) Prevalence curve of light users with HCV. (e) Prevalence curve of hard users with HCV. (f) Prevalence curve of recidivist users with HCV. (g) Incidence curve from susceptibles to light users. (h) Incidence curve from light users to hard users. (i) Incidence curve from light users to light users with HCV. (j) Incidence curve from hard users to hard users with HCV.

if some intervention would produce an overall proportion of HCV-stayers  $S'_0$ , then the limit of the indicator would be  $1 - S'_0$ .

These considerations allow to estimate the global proportion of HCV-stayers for various countries of the EU simply observing the stationary<sup>1</sup> proportion of the HCV-infected clients. For example, for Italy, we can estimate that [7]:

- in the north-east area, the proportion  $S'$  is less than or equal to 22% (indicator still increasing);
- in the Centre  $S' \cong 30\%$ ;
- in the south  $S' \cong 44\%$ .

<sup>1</sup> This corresponds to the maximum in the time series of such proportions.

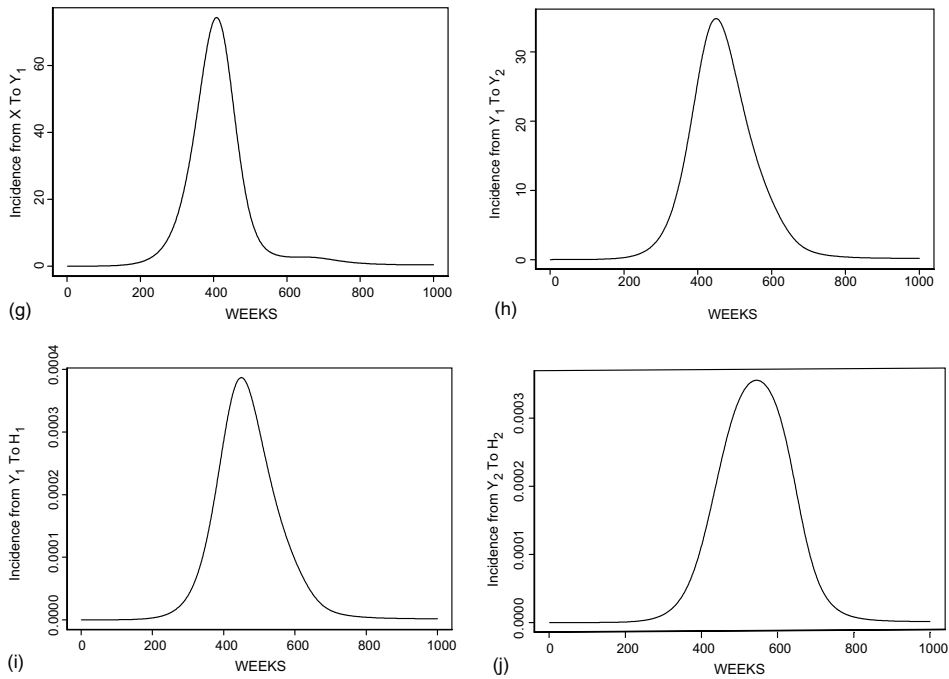


Fig. 2 (continued)

Table 3  
Location of the peaks of the IDUs compartments

State variable	Location of the peak (weeks)	HCV-delay
$Y_1$	450	
$H_1$	680	230
$Y_2$	550	
$H_2$	730	180
$W_1$	580	
$K_1$		200
$PA(XY_1)$	400	
$PA(Y_1H_1)$	450	50
$PA(Y_1Y_2)$	450	
$PA(Y_2H_2)$	550	100

where HCV-delay represents the difference (in time) between the peaks of the correspondent compartment ( $H_1:Y_1$ ;  $H_2:Y_2$ ;  $K_1:W_1$ ;  $PA(Y_1H_1):PA(XY_1)$ ;  $PA(Y_2H_2):PA(Y_1Y_2)$ ). From the summary results reported in Table 3 some policy considerations can be drawn:

- Incidence indicators are more useful to plan prevention interventions (smaller delays).
- Efficient incidence surveillance systems should be organised in order to monitor both drug use trends and infectious diseases spread.

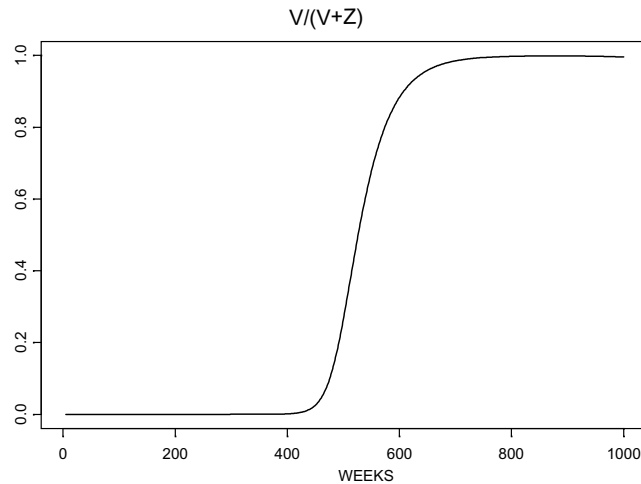


Fig. 3. Behaviour of the proportion of HCV-infected IDUs among clients of health care services.

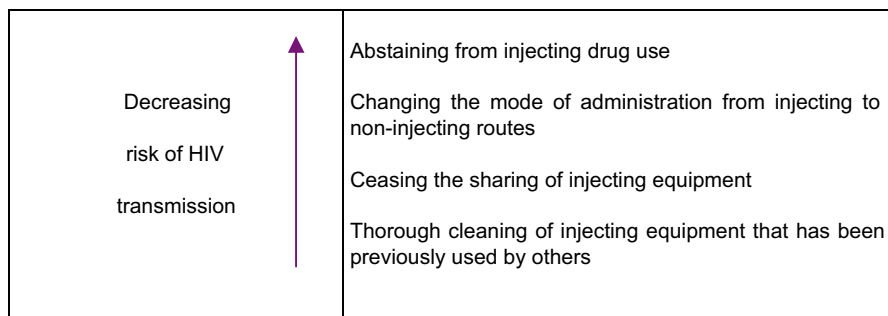


Fig. 4. Hierarchy of intervention goals for reducing transmission of HIV. *Source:* N. Lintzeris, P. Spry-bailey, Harm reduction with problem users. In: M. Hamilton, A. Kellehear, G. Rumbold (Eds.), *Drug use in Australia. A harm minimisation approach*, Oxford, 1998, p. 240.

- Harm reduction interventions [14,18], aimed at preventing infectious disease spread should be implemented soon, as the delay between the peaks of first use incidence curve and HCV incidence curve is just about one year (50 weeks).
- The most valuable prevention interventions should be graduated as represented in Fig. 4.

Thus, in particular, safe injecting rooms such as those implemented in Francoforte, Madrid and other EU cities can be particularly effective in preventing both overdose episodes and infections.

## 5. Final remarks

In the present paper a ‘simple’ operational model has been presented to mirror the spread of infectious diseases in the ‘open’ population of IDUs. The model, though simple, allows:

- to make qualitative analyses and evaluate the possible impact of prevention interventions;
- to make ‘what if’ scenario analyses in order to obtain quantitative information about the spread of infections and the impact of interventions;
- to get useful qualitative and quantitative information for decision makers in order to implement more efficient policies to control both problem drug use and risky behaviours of IDUs.

It would be very useful to implement epidemiological studies in order to obtain more reliable estimates of ‘crucial’ epidemic parameters and to organise surveillance systems to monitor the behaviours of IDUs and the spread the internal epidemics.

### Acknowledgements

The work was partially funded by the European Monitoring Centre on Drugs and Drug Addiction in the framework of the EU funded European Network to develop Policy Relevant 16 Models and socio-Economic Analyses of Drug Use, Consequences and Interventions (TSER/DGXII project ERB 4141 PL980030). We want to thank the two anonymous referees who, with their suggestions and comments, allowed to present a highly improved version of the paper.

### Appendix A. Deterministic difference equations of the model

1. *Susceptible population. State variable: X*

$$X(t + Dt) = X(t)(1 + \mu_{0,1} - \mu_{1,0} - \pi_{1,7}) - X(t)[1 - S(t)][\mu_{1,2} + v_{1,2}Y_1(t) + v_{1,3}Y_2(t) + v_{1,5}W_1(t)] + \mu_{6,1}W_2(t) + \mu_{12,1}K_2(t).$$

2. *Light drug users. State variable: Y<sub>1</sub>*

$$Y_1(t + Dt) = Y_1(t)(1 - \mu_{2,3} - \mu_{2,6} - \mu_{2,8} - \pi_{2,7}) + X(t)[1 - S(t)][\mu_{1,2} + v_{1,2}Y_1(t) + v_{1,3}Y_2(t) + v_{1,5}W_1(t)] - v_{2,8}Y_1(t)[H_1(t) + H_2(t) + K_1(t)].$$

3. *Hard drug users. State variable: Y<sub>2</sub>*

$$Y_2(t + Dt) = Y_2(t)(1 - \mu_{3,4} - \mu_{3,9} - \pi_{3,7}) + \mu_{2,3}Y_1(t) - v_{3,9}Y_2(t)[H_1(t) + H_2(t) + K_1(t)].$$

4. *Clients of health care services. State variable: Z*

$$Z(t + Dt) = Z(t)(1 - \mu_{4,5} - \mu_{4,6} - \pi_{4,7}) + \mu_{3,4}Y_2(t) + \mu_{5,4}W_1(t).$$

5. *Recidivist drug users. State variable: W<sub>1</sub>*

$$W_1(t + Dt) = W_1(t)(1 - \mu_{5,4} - \mu_{5,6} - \mu_{5,11} - \pi_{5,7}) + W_2(t)[\mu_{6,5} + v_{2,6}Y_1(t) + v_{3,6}Y_2(t) + v_{5,6}W_1(t)] + \mu_{4,5}Z(t) - v_{5,11}W_1(t)[H_1(t) + H_2(t) + K_1(t)].$$

6. *No use (temporary). State variable: W<sub>2</sub>*

$$W_2(t + Dt) = W_2(t)(1 - \mu_{6,1} - \pi_{6,7}) - W_2(t)[\mu_{6,5} + v_{2,6}Y_1(t) + v_{3,6}Y_2(t) + v_{5,6}W_1(t)] + \mu_{4,6}Z(t) + \mu_{2,6}Y_1(t) + \mu_{5,6}W_1(t).$$

7. *Deaths for any cause. State variable: D*

$$D(t + Dt) = D(t) + \pi_{2,7}Y_1(t) + \pi_{3,7}Y_2(t) + \pi_{4,7}Z(t) + \pi_{5,7}W_1(t) + \pi_{6,7}W_2(t) + \pi_{8,7}H_1(t) \\ + \pi_{9,7}H_2(t) + \pi_{10,7}V(t) + \pi_{11,7}K_1(t) + \pi_{12,7}K_2(t).$$

8. *Light Drug Users with HCV. State variable: H<sub>1</sub>*

$$H_1(t + Dt) = H_1(t)(1 - \mu_{8,12} - \mu_{8,9} - \pi_{8,7}) + \mu_{2,8}Y_1(t) + \nu_{2,8}Y_1(t)[H_1(t) + H_2(t) + K_1(t)].$$

9. *Hard drug users with HCV. State variable: H<sub>2</sub>*

$$H_2(t + Dt) = H_2(t)(1 - \mu_{9,10} - \pi_{9,7}) + \mu_{8,9}H_1(t) + \mu_{3,9}Y_2(t) + \nu_{3,9}Y_2(t)[H_1(t) + H_2(t) + K_1(t)].$$

10. *Clients of health care services with HCV. State variable: V*

$$V(t + Dt) = V(t)(1 - \mu_{10,11} - \mu_{10,12} - \pi_{10,7}) + \mu_{9,10}H_2(t) + \mu_{11,10}K_1(t).$$

11. *Recidivist drug users with HCV. State variable: K<sub>1</sub>*

$$K_1(t + Dt) = K_1(t)(1 - \mu_{11,12} - \mu_{11,10} - \pi_{11,7}) + K_2(t)[\mu_{12,11} + \nu_{8,12}Y_1(t) + \nu_{9,12}Y_2(t) \\ + \nu_{11,12}W_1(t)] + \mu_{10,11}V(t) + \mu_{5,11}W_1(t) + \nu_{5,11}W_1(t)[H_1(t) + H_2(t) + K_1(t)].$$

12. *No use (temporary) with HCV. State variable: K<sub>2</sub>*

$$K_2(t + Dt) = K_2(t)(1 - \mu_{12,1} - \pi_{12,7}) - K_2(t)[\mu_{12,11} + \nu_{8,12}Y_1(t) + \nu_{9,12}Y_2(t) + \nu_{11,12}W_1(t)] \\ + \mu_{8,12}H_1(t) + \mu_{10,12}V(t) + \mu_{11,12}K_1(t).$$

13. *Proportion of stayer. State variable: S*

$$S(t + Dt) = S(t) \frac{X(t)(1 - \mu_{1,0} - \pi_{1,7})}{X(t + Dt)} + S_0 \frac{\mu_{0,1}X(t) + \mu_{6,1}W_2(t) + \mu_{12,1}K_2(t)}{X(t + Dt)}.$$

## Functions and constants of the ‘nested epidemics’ model

$M(t)$	Proportion of Movers/impact indicator of primary prevention interventions for the external epidemic	Proportion/function
$\rho(t)$	Epidemic/endemic indicator	Function
$\xi(t)$	Measure of expected impact of a secondary prevention intervention for the external epidemic	Function
$\Delta$	Efficacy rate of prevention intervention for the external epidemic	Constant
$\Psi$	Efficacy rate of prevention intervention for the internal epidemic	Constant
$S'(t)$	Proportion of HCV-stayer	Proportion
$M'(t)$	Proportion of HCV-Movers/impact indicator of primary prevention interventions for the internal epidemic	Proportion/function
$\xi'(t)$	Measure of expected impact of a secondary prevention intervention for the internal epidemic	Function



## References

- [1] S.M. Blower, D. Hartel, H. Dowlatabi, R.M. Anderson, R.M. May, Drug, sex and HCV: a mathematical models for New York City, *Philos. Trans. R. Soc. London B* 321 (1991) 171.
- [2] R. De Alarcòn, The spread of a heroin abuse in a community, *Bull. Narcotics* 21 (1969) 17.
- [3] EMCDDA, Pilot project to estimate time trends and incidence of problem drug use in the European Union, Final report. Lisbon, 1999.
- [4] EMCDDA, Co-ordination of implementation, follow-up and analysis of cohort studies on mortality among drug users in European Union Member states, Final report. Lisbon, 1999.
- [5] EMCDDA, Study on incidence of problem drug use and latency time to treatment in the European Union, Final report. Lisbon, 2000.
- [6] EMCDDA, Annual report on the state of drugs problem in the European Union, Office for Official Publications of the European Communities, Luxembourg, 2001.
- [7] EMCDDA, Annual report on the state of drugs problem in the European Union, Office for Official Publications of the European Communities, Luxembourg, 2002.
- [8] N. Esposito, C. Rossi, Modelling injecting drug use and hepatitis C in injecting drug users, EMCDDA monograph series, 2003, in press.
- [9] D. Greenhalgh, G. Hay, Mathematical modelling of the spread of HIV/AIDs amongst injecting drug users, *IMA. J. Math. Appl. Med. Biol.* 14 (1997) 11.
- [10] K.P. Hadeler, Modeling AIDs in structured Populations, in: *Proceedings of I.S.I. 47th session*, Paris, 1989, pp. 83–99.
- [11] F. Harburg, The three essential elements of learning and development, 2002, Available from <<http://www.clomedia.com/content/anmviewer.asp>>.
- [12] L.G. Hunt, C.D. Chambers, *The Heroin Epidemics*, Spectrum, New York, 1976.
- [13] M. Iannelli, The mathematical description of epidemics: some basic models and problems, In: G. Da Prato (Ed.), *Mathematical Aspects of Human Disease*. Pisa, 1992, pp. 11–32.
- [14] A. Judd, M. Hickman, A. Renton, G.V. Stimson, Hepatitis C infection among injecting drug users: has harm reduction worked? *Addict. Res.* 7 (1999) 1.
- [15] E.H. Kaplan, Needles that kill: Modelling human immunodeficiency virus transmission via shared drug injection equipment in shooting galleries, *Rev. Inf. Diseases* 11 (1989) 289.
- [16] E.H. Kaplan, E. O’Keefe, Let the needles do the talking! Evaluating the New Haven needle exchange, *Interfaces* 23 (1993) 7.
- [17] D.R. Mackintosh, G.T. Stewart, A mathematical model of a heroin epidemic: implications for control policies, *J. Epidemiol. Community Health* 33 (1979) 299.
- [18] M. Owel, Harm reduction within six European national drug policies: a necessary option or a deficiency? M.A. Dissertation, Master’s degree in European Criminology and Criminal Justice systems, University of Ghent, Academic year 1999–2000, 2000.
- [19] D. Peterson, K. Willard, M. Altmann, L. Gatewood, G. Davodson, Monte-Carlo simulation of HIV infection in an intravenous drug-user community, *J. AIDS* 3 (1990) 1086.
- [20] L. Ravà, M.G. Calvani, S. Heisterkamp, L. Wiessing, C. Rossi, Incidence indicators for policy making: models, estimation and implications, *UN Bull. Narcotics* LIII (1–2) (2001) 135.
- [21] L. Ravà, C. Rossi, Estimating the size of a hidden population involved in the HIV/AIDs epidemic: a method based on back-calculation and dynamical models, in: J. Anderson, M. Katzper (Eds.), *Simulation in the Medical Sciences*, The Society for Computer Simulation, San Diego, CA, 1999, p. 57.
- [22] C. Rossi, A stochastic Mover–Stayer model for HIV epidemic, *Mathemat. Biosci.* 107 (1991) 521.
- [23] C. Rossi, A Mover–Stayer type model for epidemics of problematic drug use, *Bull. Narcotics* LIII (1–2) (2001) 39.
- [24] C. Rossi, Operational models for epidemic of problematic drug use: the Mover–Stayer approach to heterogeneity. *Socio-Economic Planning Sciences*, 2003, in press.
- [25] C. Rossi, Estimating the prevalence of injecting drug users on the basis of Markov models of the HIV/AIDs epidemic: applications to Italian data, *Health Care Management Science* 2 (1999) 173.