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ABSTRACT

Equipment sharing among injecting drug users (IDUs) is a key risk factor in infection by hepatitis C virus (HCV). Both the effectiveness and cost-effectiveness of interventions aimed at reducing HCV transmission in this population (such as opioid substitution therapy, needle exchange programs or improved treatment) are difficult to evaluate using field surveys. Ethical issues and complicated access to the IDU population make it difficult to gather epidemiological data. In this context, mathematical modelling of HCV transmission is a useful alternative for comparing the cost and effectiveness of various interventions. Several models have been developed in the past few years. They are often based on strong hypotheses concerning the population structure. This review presents compartmental and individual-based models in stochastic and deterministic frameworks in order to underline their strengths and limits in the context of HCV infection among IDUs. The final section discusses the main results of the papers.

KEYWORDS

Antiviral treatment; dynamic modelling; harm reduction policies; hepatitis C; injecting drug users; vaccination

INTRODUCTION

In northern countries, injecting drug users (IDUs) are the main population at risk of infection with hepatitis C virus (HCV), with a prevalence ranging between 15% and 90% (1). The risk of HCV transmission is high for all drug-equipment sharing that can lead to blood contact: injection equipment (syringes, cotton or cups (2)), straws (3) and crack pipes (4).

Risk reduction measures have been taken to reduce HIV and HCV transmission among IDUs. These measures have focused mainly on opioid substitution treatments such as methadone and buprenorphine, and on needle exchange programs (5). However, other measures are possible. Indeed, some European countries have financed and launched supervised injection and needle exchange programs in prisons (6). Moreover, the landscape of therapy for HCV infection, where treatment was suboptimal until recently, is rapidly changing. More efficient and tolerable treatment strategies have become available. Previr-containing regimens – already available – have significantly increased the chances of a sustained virologic response (SVR, i.e. undetectable levels of HCV for an extended period of time) for patients infected with genotype 1 HCV, the most prevalent HCV genotype in western Europe and North America among IDUs (5, 7). Using these combinations, for patients treated for the first time, the SVR rate for genotype 1 reaches 70-75% vs. 50% for treatments with pegylated interferon and ribavirin (8-12). Other, more effective pan-genotypic drugs that are used orally and may be prescribed for a shorter duration are at advanced stages of development (13). Given that non-viremic patients (i.e. those with a SVR) cannot transmit the infection (14), we are now considering the use of treatment as a means of preventing transmission of HCV in this population (« treatment as prevention »).

However, the implementation of harm reduction programs (HRP), like needle exchange programs, and the use of these new treatments to avoid transmission imply additional costs.

For optimal use of available resources, it is important to evaluate the effectiveness and cost-effectiveness of these strategies. For this purpose, clinical studies and traditional epidemiological studies such as historical comparisons, cohorts and/or case-control studies encounter problems of feasibility, cost and time, especially in the IDU population, which is difficult to reach. Mathematical modeling is an alternative; indeed, it may enable an estimation of the efficiency and cost of multiple strategies of harm reduction, screening and treatment effects upon HCV transmission within a short period of time. The main goal of the present article is to review mathematical models used to simulate transmission of HCV among IDUs, and to evaluate their pros and cons.

The first section briefly summarizes reviews of the literature. The second describes compartmental models and their properties. The third section describes individual-based models and their properties. In the fourth section, we examine deterministic and stochastic models. The final section presents results obtained and recommendations for public health policies.

SEARCH STRATEGY AND SELECTION CRITERIA

The aim of the review was to identify dynamic mathematical models used for transmission of HCV among IDUs in the literature and to evaluate their strengths and limits. Eligible studies had to satisfy two conditions: 1) describe a dynamic mathematical model for transmission of HCV; and 2) study a population of IDUs. In accordance with Cochrane collaboration guidelines (15), we conducted our search in the Medline database using the keywords *mathematical*, *mode*l, *hepatitis C* and *drug user* and variations of these words. Our review takes into account the bibliographies of all identified publications and includes all items found until November 2013.

RESULTS

We selected 37 of the retrieved articles that fulfilled the above criteria (16-52). The modeled populations were mainly from the United Kingdom (16-21, 24, 25, 35, 36, 41, 44, 45, 49, 52), Australia (26, 30, 31, 33, 34, 41, 47, 48). Two articles involved analyses in developing countries: that of Durier *et al.* studied a population of IDUs in Vietnam (23), while Vickerman *et al.* examined a population of IDUs in Pakistan (22).

The main objectives of these studies were: (i) to present a model of transmission of HCV and provide analytical results concerning the mathematical properties of the model (28, 35-38, 50); (ii) to evaluate the impact of HRP (on the prevalence, incidence, number of infections and QALY gained) (19, 20, 22, 23, 25, 29, 33, 36-39, 45, 47, 48, 50, 51), (iii) to compare epidemics dynamic of HCV and HIV infections (1, 21, 22, 27, 28, 33, 39, 40, 42, 43, 51); (iv) to evaluate the impact of treatment of HCV infection on transmission (16, 17, 23, 27, 34, 41, 45-47, 49) and cost (18, 41); and (v) to evaluate the impact of potential HCV vaccination strategy (30, 32, 48). Objectives and main results of these articles are detailed in Table 1.

Mathematical models used in the articles were divided into two categories: compartmental models and individual-based (or agent-based) models (IBMs). The assumptions underlying the two models and their strengths and weaknesses are presented in the following sections.

COMPARTMENTAL MODELS

Description

Compartmental models were the most frequently used class of models for HCV epidemic simulation among IDUs; i.e. 32 of the 37 articles in our review (see Table 1). They considered transmission of HCV infection at the macroscopic scale, dividing the population into compartments corresponding to different states of the infection process: susceptible,

infectious, recovered, etc. (53, 54). Subjects moved from one state to another at dynamic transition rates.

A simple example applicable to HCV infection among IDUs, is the susceptible-infectious-susceptible (SIS) model in Figure 1 (55). This is a two-compartment model that corresponds to a disease in which re-infection after recovery is possible (i.e. no immunity). An individual is either susceptible to being infected (compartment S) or infectious, i.e. able to transmit the disease (compartment I).

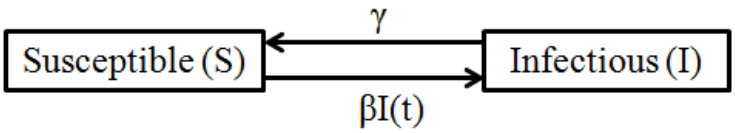

Figure 1 Schematic representation of a SIS compartmental model with individual transition rates. The model divides the population into two compartments: susceptible and infectious. At time t, S(t) is the number of susceptible persons and I(t) the number of infectious persons. Each susceptible becomes infectious at a rate of βI(t), and each infectious reverts to susceptible at rate γ.

For a constant population of size *N*, we denote by *S(t)* and *I(t)* the respective sizes of the susceptible and infectious populations. *β* corresponds to the rate of contact with an infectious person that lead to transmission.

Pollack used a similar model in 2001 (37, 38, 50). However, authors frequently introduce new elements to adapt the model to the necessity of each analysis. As an additionnal compartment to capture acute hepatitis C (19, 21-23, 26, 27, 32, 35, 36, 39-44, 51) for taking into account the possibility of spontaneous recovery during that period, which occurs in 25% to 30% of infections (56). Some authors included in their model the uncertain possibility of immunization (57) of previously infected IDUs against re-infection (16, 17, 21, 22, 34-36,

44). In another approach, Esposito *et al.* added compartments to model the use of intravenous drugs as an epidemic linked to the HCV epidemic (29).

Limits

Compartmental models cannot satisfactorily take into account certain intrinsic characteristics of HCV transmission among IDUs. First, the number of covariates differentiating individuals are limited. The same transition rates are applied to a whole that is presumed to be *homogeneous*. The only characteristic of an individual is the compartment in which he/she is located. Secondly, the infection rate is based upon the hypothesis that the population is *totally mixed*, in the sense that each susceptible individual can potentially be infected by any infectious person: the infection rate for susceptible individuals $\beta I(t)$ increases with the number of infected people in the population.

IDUs have highly variable risks of infection because of differences in injection frequency, numbers of syringe sharing and number of sharing partners (58). In addition, because of different treatment efficiencies based on HCV genotypes, recovery rates from HCV infection are different. The above hypotheses might be inappropriate in the case of HCV infection among IDUs, the lack of flexibility of the compartmental models in terms of population heterogeneity leading to neglect this variability. In 2001, Pollack had already underline that, while a simple model enables obtaining several important results, a heterogeneous totally mixed population implies biases in the estimation of the effectiveness of HRP and does not enable to assess effectiveness of targeting interventions (37, 38, 50). Stratification of the population into different risk groups is a solution for taking into account heterogeneity of IDUs (19-23, 26, 27, 29, 36, 39-43, 51). Vickerman *et al.* considered 3 levels of risk corresponding to no syringe sharing, low- and high-frequency syringe sharing (19-21). Matser *et al.* stratified their model by HIV status (27). Corson *et al.* structured their population by

experience at injection: recent injectors were more likely to be infected than experienced injectors (36). Zeiler *et al.* aimed at estimating the impact of methadone maintenance programs and structured their population by methadone intake (26).

However, this possibility is limited by the number of new compartments introduced. Indeed, stratification of the population is equivalent to introducing different compartments for each group. Taking into account numerous risk factors may be problematic. The following characteristics are known to impact HCV transmission and treatment success: time since first injection; risk of transmission that is higher in recent frequent injectors (59); substitution therapy with reduced risk of transmission from those who receive substitution (60); gender, since the spontaneous recovery rate is higher in women (61); HIV-HCV co-infection, associated with lower treatment success (62).

The hypothesis of a *totally mixed* population (or random mixing) is also poorly suited for describing infectious contacts with a blood-borne pathogen among IDUs. It has been shown that IDUs share their injection material with a restricted group of injection partners. Wylie *et al.* found that IDUs in Canada have few other IDUs in their individual network: a median of 3·5 was found for a period of 30 days (58). Brewer *et al.* found a mean number of 18 injecting partners (not necessarily involving syringe/needle sharing) during a 12-month period of presumed HCV infection among HCV-positive IDUs in Seattle (63). Sacks-Davis *et al.* reported, in Melbourne, a median number of 3 injection partners/IDU, with a median duration of 3 years for a partnership, and they found that HCV phylogeny was associated with the injection network (64). These results imply that the number of potential infectious contacts is restricted to a small group for each infected IDU, which slows transmission of the virus in the population. Authors who used compartmental models and who stratified their population sometimes included *assortative mixing*: they varied the mixing of the different risk groups

(40-42). However, this solution does not enable taking into account small subgroups at the individual or community scale, but only groups at a population scale.

IBMs can help modelers to incorporate these two assumptions via more realistic (though more complex) modeling techniques.

INDIVIDUAL-BASED MODELS

Description

Individual-based models simulate the patient's trajectory at an individual level, so that we can attach to each of them a specific set of characteristics (age, gender, alcohol consumption, frequency of risk-taking, etc.), on which the different transition rates may (65-67).

For HCV epidemic modeling among IDUs, only a few authors have used IBMs. Mather *et al.* consider a model taking into account isolated groups of individuals with possible immunization of individuals (48). De Vos *et al.* developed a model taking into account HCV and HIV infections in which mortality and transmission of viruses were based on individual characteristics: age, time since the first injection and time since infection (39). Hahn *et al.* developed an IBM to take into account different behaviors and levels of risk exposure in the population (30). The authors distinguished two at-risk practices: risky needle sharing (RNS) and ancillary equipment sharing (AES); the probability of infection varied based on the level of risk exposure (corresponding to frequencies of RNS and AES) and HCV stage of the partner (higher infectivity during acute infection). For each sharing event, a sharing partner was randomly assigned within the population: authors assumed that there was a high turnover of sharing partners in the population, so each sharing event could occur with any other IDU in the population. This method is equivalent to considering a totally mixed population.

IBMs may generalize the random mixing assumption but by assigning to each individual a group of specific partners. Only individuals directly in contact with one or more infectious

individuals may be infected, and the risk varies with the number of infectious contacts. To implement this type of analysis, we need to model the network of infectious contacts of IDUs, that is, the network of material sharing. Hutchinson *et al.* and Rolls *et al*. presented IBMs that took into account the social network of the population (25, 31, 47).

Modeling contact network

The network of contacts can be represented by a graph, *i.e.* a set of vertices representing individuals and interconnected by a set of edges representing potentially infectious contacts between them (Figure 2).

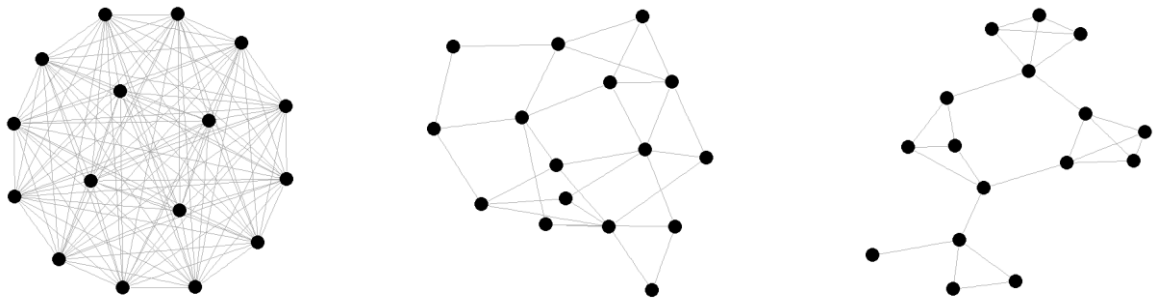

Figure 2 Examples of a graph. The left graph represents a totally connected population of size 16. The middle graph represents a population with selective relationships between individuals. The right graph represents a population with community structure.

Various social network models have been described in the literature ((68) and therein). The choice of these models depends on the expected characteristics of the simulated population. Some simple graphs which are easily implemented have unrealistic characteristics and neglect major aspects of the social structure because they are based only on individual information like the *degree*, which is, for each person, the degree is the number of individuals in contact with that person in the network. For example, the *configuration model* is constructed from a

chosen degree distribution (69, 70). Following this distribution, a degree is attributed to each member of the population, giving a semi-edge to each individual. Each semi-edge is then connected to another at random. Hutchinson *et al.* use this kind of model (25). The number of partners for the IDU *i* is X_i+1, with X_i generated by a geometric probability distribution, i.e. $P(X_i = k) = (1-p)^{k-1}p$. This distribution was suggested by data on the distribution of degree in a population of IDUs in Glasgow at the beginning of the 90's.

Hutchinson *et al.* use a dynamic network model: there is a turnover of sharing partners for each individual each year. Indeed, in a real population of IDUs, the contact pattern may change: the identities of the different sharing partners change over time as relationships between IDUs evolve (25). A static network model, with identities of sharing partners fixed over time, may miss a crucial aspect of the social network. A static network may be a good approximation if contacts change at a slow rate relative to epidemic dynamics. Inversely, if contacts change quickly relatively to the spread of the disease, then the dynamic effects cannot be neglected (71).

Such graphs models only use local information, e.g. the degree, which can be obtained relatively easily using traditional epidemiological studies, by requesting the number of sharing partners or injection partners for each participant. To take more realistic structures into account, more complex models such as *intersection graph models* (72, 73), *household graph models* (74, 75) and *stochastic block models* (76) have been proposed. The latter are difficult to calibrate due to the need for information on the global topography of the network. We may have to determine the size of the communities and the probability of connection between individuals of the same group and between individuals of different groups, etc. We cannot obtain such information through traditional studies: independent sampling of the individuals provides only information about the personal networks of the participants. To catch the global topography of the network, we must use specific methodologies such as

chain-referral sampling used by Friedman *et al.* to study the network of a population of IDUs in New York City (77). In such surveys, new participants are recruited by previous participants among partners. The final result is a subgraph of the populations' network. Rolls *et al.* applied an IBM to a real network of 258 IDUs in Melbourne, obtained by using *chain-referral sampling* (31). In a more recent paper, they calibrated an exponential random graph model on these data (47). This approach enabled the authors to obtain a very realistic network structure. However, it was limited to a small sample due to the difficulty in tracing the contact network of different IDUs. They compared results of their model with the empiric network and with a fully connected network (equivalent of the totally mixed hypothesis of compartmental models) (31). They found that time to infection was shorter in a fully connected network, indicating that the structure of the network highly impacts output in HCV transmission.

STOCHASTIC AND DETERMINISTIC APPROACHES

The various models in the previous sections can describe a stochastic or deterministic evolution of the HCV.

The stochastic approach can be modeled by considering the process as a chain of events (infections, recovery, etc.) occurring at random times among individuals. At each event, the transition that occurs is determined by probabilities ensuring the respect of the global transition rates. This approach takes into account the randomness of durations of the different health stages in the population.

When dealing with a large populations, averaging of randomness leads to determinist evolutions that can be described by ordinary differential equations (54). For example, the evolution of the number of infected people for a compartmental SIS model without demographic effects (birth or death) is given by the following differential equations (55):

$$\frac{dI(t)}{dt} = \beta I(t)S(t) - \gamma I(t) \quad (1)$$

$$\frac{dS(t)}{dt} = -\beta I(t)S(t) + \gamma I(t) \quad (2)$$

dS(t)/dt and *dI(t)/dt* correspond, respectively, to the instantaneous variation in the number of susceptible and infectious individuals at time t.

Conversely, stochasticity can be modeled by adding noise to the deterministic equations shown above.

In 1991, Ball provided an overview of the advantages and disadvantages of these two approaches for modeling epidemics (78). The differential equations often admit unique solutions for fixed sets of parameters and initial conditions, and these solutions can be approximated by numerical methods. Exact simulations are usually available for stochastic models, in the sense that no numerical approximation is needed and what is simulated has the exact distribution. Moreover, the spread of an epidemic intrinsically depends on random events at an individual level, and the simulations from IBMs give individual trajectories and thus allow statistical exploitation of individual results.

For small groups, variability in the trajectory for the epidemic may be observed, and some of these groups will behave differently from the solution of differential equations. Figure 3 shows the result obtained for a group of 100 persons with only 1 infected individual at time t=0. Stochastic simulations reflect the difficulty that the epidemic sometimes has in taking off with a few initial infected subjects: the trajectory shapes are similar, but there is sometimes a random lag at the beginning (see **Figure 3**).

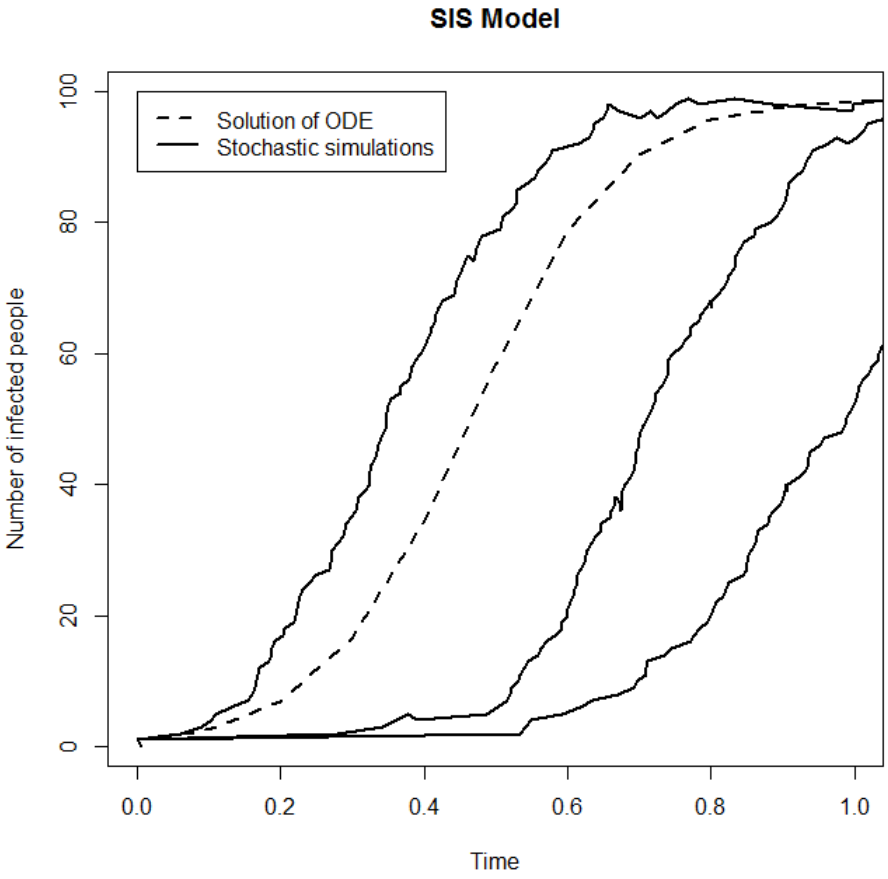

Figure 3 Evolution of the number of infected people in a population of 100 individuals, with 1 infected individual at time t=0. The model is a SIS-model with β=0.1 and γ=0.1. The dotted line represents the solution obtained in a deterministic framework, while the plain lines represent simulations of the stochastic framework.

Modeling of HCV transmission among IDUs in northern countries seems to be in adequacy with the assumptions necessary for a deterministic approach, i.e. a relatively large population with a high risk of transmission. Indeed, 27 of the 37 articles took into account deterministic differential equations to study their model. The populations considered in the articles reported in Table 1 were usually large, i.e. more than 1,000. However, real populations of IDUs are subdivided into small groups of injecting partners for which a deterministic approximation must be subject to caution. The infection could spread rapidly within a group, but might not necessarily pass from one group to another.

MAIN RESULTS OF THE REVIEWED PAPERS

The objectives of articles on HCV transmission among IDUs are numerous. However, important results consistently emerge.

Vaccination

The potential effect of a vaccination against HCV was evaluated in three articles. Mather *et al.* showed that even immunizing half the population with a vaccine which has an 80% efficacy has a significant impact on the spread of infection (48). For Dontwi *et al.,* potential vaccination must be carried out early and should cover a large portion of the population so as to significantly reduce the force of infection (32). Hahn *et al.* tested scenarios that specifically target certain individuals in the population (30). They found that vaccination is most effective when it targets high-risk individuals (with more frequent risk-taking) without taking into account serological status, or when targeting HCV-seronegative persons.

Harm reduction policies

The first author to take an interest in estimating the impact of harm reduction by a model was Pollack, who examined a needle exchange program (37, 38, 50). His results suggested that, while such a program may have an impact and could potentially eradicate the infection, the cost quickly becomes prohibitive for highly transmissible infections like HCV. However, he suggested that the association of this program with a methadone maintenance therapy strategy would reduce transmission of the virus in the population and, as a consequence, decrease the cost of needle exchange programs. He stated that, for HCV, a combination of different strategies is necessary to significantly impact HCV transmission (38). However, he underlined that the absence of heterogeneous behavior and the totally-mixed hypothesis could impact the

results. Vickerman *et al.* also found that widespread sustained coverage of syringe sharing in the population (reduction > 40%) is necessary in order to obtain a significant reduction in prevalence after 10 years (22).

Hutchinson *et al.* estimated the impact of HRP on HCV transmission, by varying the size of sharing partner groups (25). For the period 1988-2000, they estimated that 4,500 infections would have been prevented in Glasgow with HRP. They also found that reducing the mean number of partners to one (*versus* between 2 and 3 partners in the baseline scenario) might prevent 5,300 infections during the same period (with this measure alone). Moreover, wide and sustained decrease of needle/syringe sharing would be necessary to have a similar impact on transmission (5,200 infections prevented): only 11% to 20% of IDUs should be authorized to share a needle/syringe during that period.

Some authors suggested that the target of these interventions could be optimized. Vickerman *et al.* suggested targeting recent injectors not reached by HRP and not already infected (19). They found that a significant reduction in prevalence could occur among recent IDUs (<4 years) with a reduction in sharing frequency <25%, although among experienced IDUs (>8 years), similar results would only occur with a reduction >50%. Similarly, Corson *et al.* suggested that interventions are most efficient during the first 5 years of the injecting career (36). Esposito *et al.* showed a delay of one year between the peak of drug use and the peak of prevalence for HCV, suggesting also that early interventions during the injecting drug career could significantly impact HCV transmission (29), suggesting also that early intervention during the intravenous drug career could significantly impact HCV transmission.

In the context of limited resources, De Vos *et al.* suggested that IDUs at low risk (i.e. less frequent syringe sharing) should be targets for HRP so as to maximize their impact (39). They questioned also whether the decrease in HCV incidence in Amsterdam since 1990 was related to HRP. They found that realistic results with their model could only be obtained in the

presence of HRP, but demographic changes in the IDU population primarily explained the decrease.

Impact of harm reduction strategies on HIV and HCV infection among IDUs

The impact of HRP upon HIV transmission is much stronger than upon HCV transmission (33). Coutin *et al.* and Pollack showed that the higher infectivity of HCV compared to HIV implied that greater effort is needed to significantly impact HCV transmission in their model (28, 38). Vickerman *et al.* estimated that reducing the injection risk by 30% would result in a reduction in the incidence/prevalence of 50%/28% for HIV and 37%/10% for HCV after 5 years (21). De Vos *et al.* found similar results (40). Murray *et al.* estimated the number of annual injection partners below which infections by material sharing were less likely to occur than infections by other sources to be 17 partners/year for HIV and 3 partners/year for HCV (33). They estimated the actual number of partner to be intermediate (≈6), which explains the success obtained against HIV and more questionable results for HCV.

Matser *et al.* estimated the importance of HIV as competing with mortality from HCV complications (i.e. how many IDUs do not die of HCV infection because they have already died from HIV infection). They found that this competing mortality explained in part the recent decrease in HCV-related mortality among drug users in Amsterdam (27).

HCV treatment

The impact of HCV treatment on transmission is considered to be effective despite the risk of reinfection (16, 17, 23, 27, 34). Some authors recommended specific targets and application modalities.

Zeiler *et al.* studied the impact of HCV treatment in Australia, taking into account methadone maintenance therapy (26). The main concern of that paper was to determine the optimal

distribution of treatment in the population. The results suggested treating active IDUs rather than IDUs under methadone maintenance therapy, with the hypothesis of equal adherence to treatment in the two groups. The conclusion would be reversed only if adherence by active IDUs was <44% of that of IDUs under methadone maintenance therapy. Also in Australia, Hellard *et al.* found that even a modest annual rate of treatment (25/1,000 IDUs) could have an impact on long-term HCV prevalence (50% decrease after 30 years)(34). Martin *et al.* found similar results for the United Kingdom (17): for a baseline prevalence of 20%, 40% and 60%, an annual treatment rate of 10/1,000 IDUs would achieve a reduction in prevalence of 31%, 13% and 7%, respectively after 10 years (17). Durier *et al.*, in Vietnam (with few HRP) found similar results (23). They estimated a strategy of treatment as prevention, and suggested treating early (during the first year) to avoid a maximum of infections.

In two articles, Martin *et al.* estimated the cost-effectiveness of HCV treatment in the United Kingdom (16, 18, 49). Their results showed that treating active IDUs and ex- or non-IDUs was cost-effective, but for a prevalence below 60%; treating active IDUs was more cost-effective because of avoided re-infection (18). This result remained valid even with a SVR rate in active IDUs that was 50% lower than that of ex- or non-IDUs (which may reflect lower adherence to treatment).

Martin *et al.* estimated the impact of a coming direct-acting antiviral, with treatment of shorter duration and easier to follow (41). They compared efficiency and cost in three different geographic settings: Edinburgh, Melbourne and Vancouver. The study showed that halving the prevalence would be extremely expensive, particularly in Melbourne and Vancouver where the prevalence is high. In these two settings, a sharp increase in treatment coverage would be necessary to significantly impact prevalence.

Finally, Rolls et al. targeted individual according to their neighbors on the social network (47).They found that treat primary and secondary contacts of infected IDUs is the most effective strategy.

CONCLUSION

To date, several different models have been used to study transmission of HCV among IDUs. Most of them were built to answer a specific question taking into account only the characteristics of IDUs that pertained to that question, and thus averaging the non-relevant characteristics. Specific points seem to recurrently emerge in these articles: the long-term effects of HRP and HCV treatment on HCV prevalence, the advantage of specifically targeting more risky IDUs (recent injectors, active IDUs or IDUs not on methadone maintenance therapy), and the importance of implementing these measures early (at the beginning of the injecting career for HRP, and at the beginning of chronic infection for treatment). However, more general models are needed to compare a combination of different strategies of risk reduction (needle exchange programs, substitution therapy), screening and treatment (efficacy of new treatments) (45). Mathematical modeling can enable evaluating the cost associated with those different strategies and guiding optimal resource allocation.
Thus far, most models are compartmental and rely on strong assumptions. The development of more realistic models that include heterogeneous drug user populations (individual-based models on a social network) seems necessary but such models are still in preliminary stages (25, 30, 31, 39). One of the main difficulties lies in the lack of data for calibrating the model. Indeed, data are required concerning the risk of HCV transmission during an exchange, the frequency of material sharing, and--more difficult--social networks and their dynamics over time. As pointed out by Kretzschmar *et al.,* the construction of such models therefore requires multidisciplinary collaboration that includes clinical (transmission risk, treatment efficacy),

epidemiological (current state of infection, screening, treatment), mathematical (modeling) and sociological (social network characteristics among IDUs) components (79).

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STATEMENT OF INTERESTS

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ABBREVIATIONS

HCV: Hepatitis C virus

HRP: Harm reduction policies

IBM: Individual Based Model

IDU: injecting drug user

SVR: Sustained virological response

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Table 1: Summary of the review

Reference	Objectives	Model/approach	Main results
Mather *et al.* European Journal of Epidemiology 1998 (48)	To obtain predicted outcomes of different strategies and to identify sensitive parameters of the model	Individual-based model / stochastic approach	The rate of spread of HCV trough an IDU population is not really sensitive to the initial prevalence, but it is sensitive to the proportion of groups members with whom the individual has contact and the probability of infection per contact with an infective (encouraging HRP) A hypothetical vaccine with 80% efficacy would have a measurable impact on the spread of the infection, even with moderate coverage rate (around 50%)
Pollack Journal of Policy Analysis and Management 2001 (38)	To assess the impact of a syringe exchange program on HCV so as to understand why it is effective for HIV but not for HCV in an IDU population	Compartmental model/ deterministic differential equations - Analytic results (steady state analysis)	Modest interventions are only effective for hard-to-transmit infections (like HIV), while for HCV, with a high prevalence, only a massive program will have an impact. Moreover, for a high-prevalence setting, the impact will occur over the long term
Pollack Medical Decision Making 2001 (37)	To assess the effectiveness and cost-effectiveness of a syringe exchange program	Compartmental model/ deterministic differential equations - Analytic results (steady-state analysis)	The syringe exchange program is effective and cost-effective when R0 is low, but becomes less effective when R0 is high and cost become prohibitive, which is more realistic (in short-term analysis). This is necessary to combine syringe exchange program with intervention aimed at decreasing the R0, such as the methadone maintenance program This kind of program is effective for HIV but less so for HCV because of differences in the force of infection.

Pollack European Journal of Epidemiology 2001 (50)	To assess biases that represent short-term analysis compared to a long-term analysis (i.e. taking into account changes in prevalence in steady-state analysis) in the evaluation of harm reduction intervention among IDUs	Compartmental model/ deterministic differential equations - Analytic results (steady-state analysis)	The short-term incidence underestimates the effectiveness of a program of long-term syringe exchange if the steady-state prevalence, in the absence of intervention, is below 50%. Conversely, if it is over 50%, the short-term incidence overestimates effectiveness.
Murray *et al.* International Journal of Epidemiology 2003 (33)	To assess the impact of behavioral changes on the prevalence of HIV and HCV among IDUs	Compartmental model/ deterministic differential equations	The needle exchange program has less impact on HCV than on HIV A sizeable decrease in syringe sharing is necessary to obtain a significant impact
Esposito *et al.* Mathematical Biosciences 2004 (29)	To present a mathematical model taking into account the "epidemic" of drug use	Compartmental model/ deterministic differential equations	HRP must be initiated early to be efficient Incidence is the best indicator of impact (delays are shorter than for prevalence)
Hutchinson *et al.* Hepatology 2005 (24)	To assess current and future consequences of hepatitis C among IDUs in Scotland	Compartmental model/ stochastic approach	Cases of decompensated cirrhosis in Scotland will double between 2000 and 2020
Hutchinson *et al.* International Journal of Drug Policy 2006 (25)	To model the hepatitis epidemic among IDUs in Glasgow and implications for prevention	Individual-based model on a simulated contact network of IDUs/ stochastic approach	The estimated prevalence in the 90s was lower than currently observed. This result can be corrected by increasing viremia during the acute phase, which could confirm the higher rate of viremia during that period. Current public health messages (not sharing needles) are inadequate for HCV (but effective for HIV). The authors propose encouraging IDUs to share with only a small group of trusted persons (tested negative) and predict that 5,300 infections could have been avoided between 1988 and 2000

Vickerman *et al.* International Journal of Epidemiology 2007 (19)	To assess the impact of decreased needle sharing on HCV transmission	Compartmental model/ deterministic differential equations	Need to work on new injectors - currently not the case Need to target all IDUs, not just those with a high frequency of syringe sharing Frequency sharing must be significantly reduced to achieve a prevalence ≤ 10%
Hahn *et al.* Epidemics 2009 (30)	To assess the impact of vaccinations (at different levels of effectiveness) on the HCV epidemic among IDUs	Individual-based model / stochastic approach	Several scenarios of vaccination were tested: - randomly vaccinate the population - vaccinate individuals with more risky behavior - vaccinate individuals seronegative for HCV (sero-targeting) The third scenario is the most effective, followed by the second. The first scenario gives similar results with coverage of a larger population
Vickerman *et al.* Sexually Transmitted Infection 2009 (22)	To explore different hypotheses to explain the low prevalence of HCV among IDUs in Rawalpindi, Pakistan and to estimate the impact of interventions	Compartmental model/ deterministic differential equations	Most syringe sharing involves low risk, because it concern only a small group of the users' acquaintances - Existence of a small group that carries out high-risk sharing with strangers, in which the prevalence is high Predicted increase in HIV prevalence in 5-10 years For HCV, this depends on the impact of co-infections with HIV / HCV on the infectivity of HCV Interventions: reduction of syringe sharing > 40% is required for a significant decrease in the prevalence of HIV and HCV in 10 years

Zeiler *et al.* Drug and Alcohol Dependence 2010 (26)	To study the importance of methadone maintenance treatment	Compartmental model/ deterministic differential equations	Advantage of treating active users rather than users on methadone because of re-infection and high turnover of IDUs on methadone.
Dontwi *et al.* American Journal of Scientific and Industrial Research 2010 (32)	To assess the impact of a possible vaccine against HCV among IDUs	Compartmental model/ deterministic differential equations	Potential vaccination carried out early and covering a large part of the population would significantly reduce the force of infection and, ultimately, the extent of the epidemic
Coutin *et al.* Journal of Applied Probability 2010 (28)	To present a mathematical model for the spread of a virus in an open population such as HCV and HIV, and evaluate sensitivity to parameters	Compartmental model/ deterministic differential equations and stochastic approach (with analytical study of the convergence of the stochastic model to the deterministic model)	A sort of quarantine ensures a long-term decline in prevalence (but is impractical) Increasing the number of IDUs leads to a decrease in prevalence (also impractical) The differing force of infection explain the different results between HIV and HCV
Martin *et al.* Journal of Hepatology 2011 (16)	To study the impact of treatment on prevalence of hepatitis C among IDUs	Compartmental model/ deterministic differential equations	Treatment has a significant impact on transmission of HCV in the population despite the risk of reinfection
Martin *et al.* Journal of Theoretical Biology 2011 (17)	To assess the level of treatment required to eradicate or control the epidemic of hepatitis C among IDUs	Compartmental model/ deterministic differential equations	Treatment has a significant impact on transmission of HCV in the population despite risk of re-infection, even for low treatment rates (<6% of chronically infected annually)

Martin *et al.* PLoS One 2011 (49)	To optimize the number of treatments taking into account economic constraints	Compartmental model/ deterministic differential equations	An increase in the annual budget allocated to treatment would be cost-effective and would more rapidly reduce prevalence
Vickerman *et al.* Drug and Alcohol Dependence 2011 (21)	To understand the trends in HIV and hepatitis C prevalence among IDUs in different settings	Compartmental model/ deterministic differential equations	Existence of a threshold for the prevalence of HCV, below which HIV prevalence is negligible This threshold depends on the environment (practices, etc.) Heterogeneity of risk: defining the scope of possible values for the prevalence of HIV / HCV Strategies for long-term intervention needed to reduce the prevalence of HCV
Matser *et al.* Addiction 2011 (27)	To estimate the effect of hepatitis C treatment and HIV co-infection on the disease burden of hepatitis C among IDUs in Amsterdam	Compartmental model/ stochastic approach	The decrease in the number of health problems related to HCV (cirrhosis) can be explained by the introduction of competing causes of high mortality (especially HIV) and, to a lesser extent, by the treatment. Increasing HCV treatment would further reduce future disease burden
Rolls *et al.* Journal of Theoretical Biology 2011 (31)	To propose a model of transmission of HCV among IDUs	Individual-based model on an empirical contact network of IDUs/ stochastic approach	Re-infection rates are higher than rates of primary infection Comparison with a fully connected graph (equivalent to the assumption of compartmental models) does not achieve this Event transmission rate estimated: 1%

Castro Sanchez *et al.* Epidemics 2012 (42)	To choose a model, identifying parameters to which the model is sensitive, fitting the model	Compartmental model/ deterministic differential equations	Identification of a model for the force of infection and risk groups The most sensitive parameters are those linked to syringe sharing and transmission rates in chronic stages of HIV and HCV infection
Corson *et al.* Mathematical Medicine and Biology 2012 (35)	To present a mathematical model for the spread of HCV in IDUs To determine the level of needle or syringe sharing, needle cleaning or needle exchange necessary for an eventual elimination of HCV	Compartmental model/ deterministic differential equations	The model predicts $R_0 < 1$ and thus an eventual elimination of HCV infection for one of the following situations: - syringe sharing rate $\leq 54{\cdot}67$/year - needle cleaning $\geq 0{\cdot}74$ - needle turnover $\geq 562{\cdot}37$/year
Corson *et al.* Journal of Mathematical Biology 2012 (36)	To present a mathematical model for the spread of HCV in IDUs To study the basic reproductive number (R_0) To study the impact of needle exchange	Compartmental model/ deterministic differential equations	For $R_0 \leq 1$: tends toward elimination of HCV infection For $R_0 > 1$: unique endemic equilibrium distribution The interventions are more efficient if they target recent IDUs (<5 years of injection)
Martin *et al.* Hepatology 2012 (18)	To estimate the cost-effectiveness of HCV therapy among IDUs	Compartmental model/ stochastic approach	Treating active injectors and non-injectors is cost-effective, but if HCV prevalence is below 60%, it is more cost-effective to treat active injectors
Durier *et al.* PLoS One 2012 (23)	To estimate the preventive effect of HCV therapy and HRP in a developing country context	Compartmental model/ deterministic differential equations	Even a low level of treatment and harm reduction polices / low substitution treatment has a significant impact on prevalence Adding harm reduction polices and substitution treatment in greater numbers provides an additional gain

			Advantage of implementing measures to diagnose patients at earlier stages of the disease ("Treatment as Prevention")
Vickerman *et al.* Addiction 2012 (20)	To investigate the impact of scaling-up opiate substitution therapy (OST) and high coverage needle and syringe programs on HCV prevalence	Compartmental model/ deterministic differential equations	Scaling-up opiate substitution therapy and needle sharing programs can reduce hepatitis C prevalence among IDUs, but reductions may be modest and require long-term sustained intervention coverage.
Hellard *et al.* Medical Journal of Australia 2012 (34)	To estimate the effect of HCV treatment on HCV prevalence among IDUs	Compartmental model/ deterministic differential equations	Modest rates of current HCV treatment among IDUs in Victoria, Australia could halve HCV infection prevalence in 30 years
De Vos *et al.* Epidemics 2012 (40)	To understand the dynamics of HCV and HIV infection among IDUs	Compartmental model/ deterministic differential equations	The link between HIV and HCV prevalence is linked to distribution of risk, and assortativity of groups of risk There is a threshold for HCV prevalence below which HIV does not spread
De Vos *et al.* Addiction 2013 (39)	To understand the effect of HRP on the decline in the incidence of HCV and HIV among IDUs since 1990	Individual-based model/ stochastic approach	It is difficult to reproduce realistic behavior of epidemics without HRP; however, most of the decline can be explained by demographic changes
De Vos *et al.* Journal of Theoretical Biology 2013 (51)	To estimate the effectiveness of targeted intervention on HIV and HCV among IDUs	Compartmental model/ deterministic differential equations	Harm-reduction policies are most effective toward HIV if used in a high-risk group, but they must be used in a low-risk group to impact HCV. High-risk individuals are already infected by HCV (the prevalence is high) so it is too late to prevent their infection, while this is not the case for HIV (low prevalence due to lower force of infection)

Vickerman *et al.* Drug and Alcohol Dependence 2013 (43)	To understand the link between HIV/HCV co-infections and the HIV sexual transmission rate in a population of IDUs	Compartmental model/ deterministic differential equations	To reproduce the realistic prevalence of HCV among HIV-infected IDUs, it is necessary to include sexual transmission Moreover, the level of co-infection seems to be a marker of HIV sexual transmission among IDUs
Martin *et al.* Hepatology 2013 (41)	To estimate the effectiveness of future direct-acting antivirals on HCV prevalence among IDUs in 3 different settings (Edinburgh, Melbourne and Vancouver)	Compartmental model/ deterministic differential equations	The impact will be limited by current treatment coverage To halve the prevalence of HCV, the cost would be high, especially in Melbourne and Vancouver, where the prevalence is highest
Corson *et al.* Drug and Alcohol Dependence 2013 (44)	To understand the role of injecting paraphernalia (filters, cookers and water)	Compartmental model/ deterministic differential equations	The transmission probability is estimated to be at least 8 times lower through paraphernalia- than through needle- or syringe-sharing Paraphernalia sharing is estimated to significantly contribute to HCV infections (62% of HCV infections in Scotland with current estimated needle/syringe sharing rates and paraphernalia sharing rates)
Martin *et al.* BMJ open 2013 (52)	To estimate the cost-effectiveness of HCV case-findings for IDUs via dried blood spot (DBS) testing in addiction services and prisons	Compartmental model/ deterministic differential equations	For a £20,000 per QALY gained willingness-to-pay threshold, DBS testing is cost-effective in addiction services, but not in prison. If we increase continuity of care (proportion of initiated treatments/referrals that are continued when entering/exiting prison) to 40%, DBS testing become effective in prison.
Martin *et al.* CID 2013 (45)	To estimate the impact of combining opiate substitution therapy, high-coverage needle and syringe exchange programs and HCV treatment on prevalence and	Compartmental model/ deterministic differential equations	HCV treatment is necessary to achieve a large reduction (>45%) in HCV prevalence over 10 years. Opiate substitution therapy, high-coverage needle

	incidence		and syringe exchange programs and new direct-acting antivirals should reduce the number of necessary treatments.
Elbasha Mathematical Biosciences and Engineering 2013 (46)	To assess the impact of treatment on transmission of HCV in an IDU population	Compartmental model/ deterministic differential equations	The incidence can increase or decrease with treatment according to the re-infection rate, but the prevalence is always lower with treatment than without
Rolls *et al.* PLoS One 2013 (47)	To investigate the effect of the number of contacts on time to primary infection and the role of spontaneously clearing nodes on incidence rates; and the effect of treatment strategies based on networks properties on incidence rates of primary infections and reinfections	Individual-based model on a simulated contact network of IDUs/ stochastic approach	The number of contacts and injecting frequency play a key role in reducing the time before primary infection The spontaneous clearance has a local effect (i.e. around the concerning individual) on infection risk and the total number of spontaneous recovery has a global effect on the incidence of both primary and re-infection rates Network-based treatment strategies that chose IDUs and treat their contact are most effective and allow to reduce the number of treatment needed to achieve a desired effect