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Sujet :

Modélisation dynamique de la transmission du virus de l'hépatite C chez les utilisateurs de drogues injectables : efficacité et coût-efficacité des interventions de réduction des risques et des traitements antiviraux

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Production scientifique

Articles originaux publiés ou acceptés

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Abréviations

AAD : Antiviraux à action directe

ANRS : Agence nationale de recherche sur le sida et les hépatites virales

CAARUD : Centres d'accueil et d'accompagnement à la réduction des risques pour usagers de drogues

CSAPA : Centre de soins, d'accompagnement et de pévention en addictologie

HAS : Haute autorité de santé

IBPS : Interacting branching particle system

ICER : Ratio coût-efficacité incrémental

OFDT : Observatoire français des drogues et toxicomanies

OMS : Organisation mondiale de la santé

PIB : Produit intérieur brut

TasP : Treatment as Prevention

UDI : Utilisateur de drogues injectables

VHC : Virus de l'hépatite C

VIH : Virus de l'immunodéficience humaine

QALY : année de vie ajustée sur la qualité

TROD : Test rapide d'orientation diagnostique

Résumé en français

L'infection par le virus de l'hépatite C (VHC) est largement répandue chez utilisateurs de drogues injectables (UDI) en France. Malgré la mise en place d'interventions visant à réduire le risque infectieux dans cette population, comme l'accès au matériel d'injections stérile et les traitements de substitution aux opiacés, la séroprévalence reste à environs 70%.

Depuis 2011, de nouveaux traitements antiviraux plus courts, plus efficaces et mieux tolérés que la précédente bithérapie combinant la prise orale de ribavirine avec des injections d'interférons deviennent disponibles pour traiter l'hépatite C chronique. Ces nouveaux traitements pourraient également être utilisés pour empêcher la transmission du VHC en traitant les individus infectieux rapidement après l'infection (« Treatment as Prevention »). Pour traiter les UDI infectés rapidement, une cascade de soins performante est toutefois nécessaire.

L'objectif de cette thèse est d'évaluer l'efficacité et le coût-efficacité d'améliorations des dispositifs de réduction des risques et de la cascade de soins de l'hépatite C chronique (dépistage, lien aux soins, initiation du traitement antiviral et efficacité de ce traitement) dans une population d'UDI en région parisienne. Pour cela, nous avons utilisé un modèle de transmission dynamique du VHC, individu-centré et prenant en compte la cascade de soins et l'histoire naturelle de l'hépatite C chronique ainsi que le réseau social de la population.

Nos résultats montrent qu'une amélioration des dispositifs de réduction des risques actuels n'aurait qu'un impact limité sur la santé des UDI. Une stratégie de type « Treatment as Prevention » nécessiterait des améliorations importantes de l'ensemble de la cascade de soins de l'hépatite C pour être efficace. Plus particulièrement, il serait nécessaire de traiter indépendamment de la sévérité de la maladie. Une telle stratégie permettrait un contrôle de l'épidémie en diminuant la transmission du VHC et la morbi-mortalité associée. Cette stratégie serait de plus coût-efficace. Toutefois, une élimination du VHC à moyen terme par l'utilisation du traitement uniquement resterait improbable.

Mot-clés : modèle dynamique ; hépatite C ; utilisateurs de drogues injectables ; traitements antiviraux ; réduction des risques ; coût-efficacité

Résumé en anglais

Hepatitis C virus (HCV) infection is widespread among people who inject drugs (PWID) in France. Despite the implementation of risk reduction measures like access to sterile injecting equipment and opioid substitution theapies to decrease the infectious risk in this population, the seroprevalence remains around 70%.

Since 2011, new antiviral regimens prescribed for a shorter duration, more effective and with a higher tolerability than the previous dual-therapy combining ribavirin oral intake with injections of interferons are becoming available to treat chronic hepatitis C. These new treatments could be used to prevent HCV transmission by treating infectious individuals rapidly after infection (« Treatment as Prevention »). For an early initiation of the treatment, an effective cascade of care is required.

The objective of this thesis was to estimate the effectiveness and cost-effectiveness of improvements in risk reduction interventions and in the cascade of care of chronique hepatitis C (testing, linkage to care, antiviral treatment initiation and effectiveness of the latter) in a PWID population in Paris Area. We used a dynamic model for HCV transmission including the cascade of care and natural history of chronic hepatitis C, and the social network of the population.

Our results show that an improvement in current risk reduction intervention would have a limited impact on the health of PWID. Initiating antiviral treatment independently of the severity of the liver disease would have an important impact on the HCV disease incidence and prevalence. However, for a "Treatment as Prevention" strategy to be highly effective and cost-effective high improvements in the entire cascade of care of chronic hepatitis C are needed. Particularly, This strategy would allow to control the epidemic by decreasing HCV transmission and the related morbidity-mortality and it would be cost-effective. However, a middle-term elimination of HCV by the use of the treatment would remain unlikely.

Keywords: dynamic model ; hepatitis C ; injecting drug user ; antiviral treatment ; risque reduction interventions ; cost-effectiveness

1 Introduction

1.1 Hépatite C

1.1.1 Histoire naturelle de la maladie

L'hépatite C est une infection virale responsable d'environ 500 000 morts annuellement dans le monde (WHO 2014). La maladie commence par une phase d'infection aiguë, définie comme la période de six mois suivant l'infection, à l'issue de laquelle un quart des malades éliminent spontanément le virus (Micallef et al. 2006). Dans le cas contraire, l'infection devient chronique.

Durant les premiers stades de la maladie, l'hépatite C chronique est généralement asymptomatique, mais l'inflammation chronique du foie est responsable d'une fibrose hépatique (perte d'élasticité des tissus). Cette fibrose, quantifiée par un score allant de F0 à F4 (score Métavir (The French METAVIR Cooperative Study Group 1994)) évolue jusqu'à aboutir à l'apparition d'une cirrhose (F4) chez 15 à 30% des infectés après 20 ans d'infection (WHO 2014). Deux principales complications sont alors susceptibles de se produire : la décompensation (avec une probabilité de 4% par an) et le carcinome hépatocellulaire (CHC) (avec une probabilité de 2% par an) dont la mortalité est élevée en l'absence de transplantation hépatique (D'Amico et al. 2006). On estime que l'hépatique C chronique est responsable de 350 000 à 500 000 morts chaque année dans le monde, pour 130 à 150 millions d'infectés (WHO 2014). En France, on estimait en 2004 le nombre de personnes séropositives pour le VHC, c'est-à-dire sont actuellement infectées par le VHC ou l'ont été par le passé, à 370 000, ce qui correspondrait à 230 000 infectés chroniques (Meffre et al. 2010).

1.1.2 Traitement

Durant les années 2000, le traitement standard de l'hépatite C était une bithérapie associant la prise orale d'un antivirale, la ribavirine, à des injections hebdomadaires d'interféron pégylé. Ces traitements, d'une durée de 24 à 48 semaines, présentaient des effets indésirables sévères affectant durablement la qualité de vie des malades, comme une anémie, une dépression ou des éruptions cutanées (Sulkowski et al. 2011). De plus, le taux de réponse virologique soutenue (RVS), défini comme la proportion de patients présentant une charge virale indétectable à l'issue du traitement, variait fortement en fonction du génotype (ou souche) du virus. Il existe 6 principaux génotypes de l'hépatite C, numérotés de 1 à 6, et le taux de RVS variait de 45% pour le génotype 1 à presque 80% pour les génotypes 2 et 3 (Shepherd et al. 2004). Sachant que le génotype 1 est le plus répandu en France, représentant plus de la moitié des infections (Payan et al. 2005), le taux de RVS moyen obtenu était relativement modéré.

Depuis 2011, l'arrivée de nouveaux traitements a permis d'élever l'efficacité des traitements pour l'ensemble des génotypes du virus de l'hépatite C (VHC). Les nouveaux antiviraux à action directe (AAD), disponibles depuis 2014 pour l'ensemble des malades, permettent d'atteindre des taux de RVS supérieurs à 90% dans les essais cliniques de phase III, tous génotypes confondus (Bourliere et al. 2011; Lawitz et al. 2013; Afdhal et al. 2014; Afdhal et al. 2014; Kowdley et al. 2014; Pawlotsky 2014; Poordad

et al. 2014; Sulkowski et al. 2014; Zeuzem et al. 2014). De plus, les traitements sont plus courts (12 semaines), mieux tolérés (peu d'effets indésirables) et moins contraignants pour les patients, grâce à l'arrivée de régimes de traitements sans injection d'interféron. Ces traitements sont toutefois associés à des coûts élevés (plus de 41 000 euros pour 12 semaines de traitements par Sofosbuvir, le premier de cette nouvelle génération de traitements (Ministère des affaires sociales 2014)), ce qui a conduit à s'interroger sur la possibilité de traiter l'ensemble des malades. Les recommandations actuelles sont de traiter prioritairement les malades à partir du stade de fibrose F2 (Ministère des affaires sociales 2014). L'agence européenne pour l'étude du foie (EASL) et l'agence française pour l'étude du foie (AFEF) préconisent toutefois un traitement élargi dans les populations où le risque de transmission du virus est élevé, comme chez les usagers de drogues injectables (UDI) (Association Française pour l'Etude du Foie 2015; European Association for the Study of the Liver 2015).

1.2 Hépatite C chez les utilisateurs de drogues injectables

L'utilisation de drogues injectables représente la principale voie de transmission du VHC dans les pays à hauts revenus (Cornberg et al. 2011; Nelson et al. 2011). Le virus est majoritairement transmis par le partage de matériel d'injection entre les usagers : seringues, cuillères et coton (Mathei et al. 2006).

En France, la séroprévalence du VHC - c'est-à-dire la proportion d'individus chez qui des anticorps anti-VHC sont détectables et qui donc ont déjà été infectés par le virus - est de 55 à 60% chez les UDI, contre moins de 1% dans la population générale (Jauffret-Roustide et al. 2009; Meffre et al. 2010). Les stratégies de réduction des risques reposent principalement sur deux mesures. La première est l'accès à du matériel d'injection stérile principalement dans les Centres d'Accueil et d'Accompagnement à la Réduction des risques pour Usagers de Drogues (CAARUD) ou les Centres de Soins, d'Accompagnement et de Prévention en Addictologie (CSAPA), et par la disponibilité de kits d'injections en pharmacie (Stéribox®) ou dans des distributeurs automatiques. La seconde mesure est l'accès aux traitements de substitution aux opiacés (TSO) comme la buprénorphine ou la méthadone. En France, plus de 2 millions de Stéribox® ont été vendues ou distribuées en 2011 (OFDT 2014), et on estime que 85% des injecteurs actifs (i.e. s'étant injectés dans le dernier mois) ont eu accès à un traitement de substitution au cours des 6 derniers mois (enquête ANRS-Coquelicot, communication privée). Si ces mesures ont permis une amélioration générale de la santé des populations UDI, et ont notamment eu un impact important sur l'incidence de l'infection par le virus de l'immunodéficience humaine (VIH) dans ces populations, l'impact sur la transmission du VHC a été plus modeste (Jauffret-Roustide et al. 2006). Ceci s'explique principalement par l'infectiosité plus élevée du VHC par rapport au VIH, le VHC infectant généralement les UDI très rapidement après leur initiation à l'injection (Sutton et al. 2006).

Dans d'autres pays, d'autres mesures de réduction des risques ont été prises, comme l'ouverture de salles de consommation à moindres risques permettant aux UDI d'effectuer leurs injections dans de bonnes conditions d'hygiène et en présence de personnel médical. Les enquêtes menées au sein d'un centre

d'injection supervisé à Vancouver ont permis de démontrer une diminution de la fréquence de partage de seringues chez les usagers fréquentant le centre (Milloy et al. 2009). En France, l'ouverture de salles de consommation à moindre risque est envisagée depuis plusieurs années et une telle salle pourrait voir le jour à titre expérimental à Paris avant la fin de l'année 2015, pour une durée de 6 ans (Assemblée Nationale 2014).

L'arrivée récente des nouveaux AAD, plus efficaces et mieux tolérés, a permis d'envisager une autre stratégie pour empêcher la transmission du VHC chez les UDI, à l'origine développée dans le cadre du VIH : le « Treatment as Prevention » (TasP). Dans le cadre du VHC, le TasP repose sur l'idée que, puisque les infectés ne transmettent plus le virus après une RVS, le traitement n'apporte pas seulement un bénéfice individuel (la guérison), mais peut aussi prévenir la transmission du virus à d'autres individus de la population. Cependant, pour être efficace, une telle stratégie nécessite une initiation précoce du traitement, et donc une cascade de soins efficace : le dépistage doit avoir lieu rapidement après l'infection et les individus diagnostiqués comme infectés doivent être orientés rapidement vers des structures de soins adaptées pour y débuter un traitement le plus rapidement possible, ce qui est en contradiction avec l'idée précédemment évoquée de ne traiter les malades qu'aux stades avancés de la maladie. De plus, l'adhérence au traitement, réputée mauvaise chez les UDI, doit être optimisée afin de rendre cette stratégie la plus efficace possible.

1.3 Modélisation des maladies infectieuses

L'évaluation de l'impact de mesures de réduction des risques, de nouveaux traitements et d'améliorations dans la cascade de soins de la maladie (amélioration du dépistage, des liens avec le système de santé, de l'accès et de l'adhérence au traitement) se heurte à des problèmes de faisabilité et de coûts. Premièrement, l'utilisation de drogues étant pénalisée en France, les populations concernées sont difficiles d'accès. Deuxièmement, l'hépatite C chronique est une maladie dont les effets sur la santé se manifestent sur le long terme (généralement plus de 20 ans après l'infection), et donc, mesurer l'impact d'interventions sur la santé des individus ne peut pas se faire en un temps raisonnable. Enfin, l'évaluation de l'impact d'une intervention sur la transmission de la maladie dans la population (comme dans une stratégie de TasP) nécessiterait un suivi à la fois des individus touchés par l'intervention et des individus auxquels ils sont susceptibles de transmettre la maladie. La modélisation mathématique de la transmission du VHC dans une population d'UDI est une alternative permettant d'évaluer rapidement et pour un coût modeste l'impact d'interventions de santé publique sur la santé des UDI et la transmission du VHC dans cette population.

Les premiers modèles décrits dans la littérature sont souvent désignés sous l'appellation de « modèles compartimentaux ». La construction d'un tel modèle repose sur deux points : premièrement, la définition des différents états possibles pour les individus composants la population (compartiments), et deuxièmement, la définition des règles de transitions entre ces différents états. C'est le cas dans le modèle SIR (Susceptible-Infectieux-Remis) de Kermack et McKendrick (Kermack et al. 1927), qui

propose de modéliser par un système d'équations différentielles ordinaires une épidémie en population close, et constitue historiquement le premier modèle de ce type (une représentation de ce modèle est donnée Figure 1).

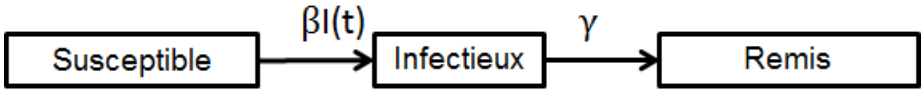

Figure 1 - Modèle SIR de Kermack et McKendrick. Les individus sains (susceptibles) sont infectés au taux βI(t), avec β le taux de contact avec un individu infectieux transmettant l'infection et I(t) le nombre d'individus infectés dans la population au temps courant t; et les individus infectieux guérissent à un taux **γ.**

La modélisation de Kermack et McKendrick est déterministe : l'épidémie étant décrite par un système d'équations différentielles ordinaires, les solutions obtenues seront toujours les mêmes pour un ensemble de conditions initiales donné. De plus, les modèles compartimentaux reposent sur deux hypothèses. Premièrement, la population est supposée hétérogène, c'est-à-dire qu'un individu est uniquement caractérisé par le compartiment auquel il appartient. Deuxièmement, la population est supposée totalement mélangée : un individu susceptible peut-être infecté par n'importe quel individu infectieux de la population. Dans le modèle de Kermack et McKendrick, on retrouve cette hypothèse au niveau du taux d'infection βI(t) : pour les individus susceptibles, le taux d'infection augmente de la valeur β pour chaque individu infectieux à l'instant t.

Ces deux hypothèses semblent en désaccord avec ce qui est connu de l'épidémiologie du VHC chez les UDI. En effet, l'hétérogénéité est forte dans cette population. Par exemple, le risque d'infection est plus élevé chez les injecteurs inexpérimentés (Sutton et al. 2006; Hagan et al. 2008; Sutton et al. 2008) ; le taux de mortalité varie selon l'âge et le genre de l'usager (Lopez et al. 2004) ; et les coinfections VIH/VHC ainsi que la consommation d'alcool favorisent la progression de la maladie vers la cirrhose (Thein et al. 2008). L'hypothèse d'une population totalement mélangée est aussi problématique : le VHC se transmettant par le sang uniquement, un individu infecté n'est en réalité susceptible de transmettre la maladie qu'à un groupe restreint d'individus de son réseau social, avec qui ce type de contact est possible.

Des solutions sont envisageables afin de relâcher ces hypothèses. En effet, l'introduction de nouveaux compartiments permet de séparer la population suivant certaines caractéristiques, et donc, de faire varier les taux de transition en fonction de celles-ci. De plus, au lieu d'une population totalement mélangée, un mélange assortatif est possible : en introduisant de nouveaux compartiments, correspondant à différents niveaux de risque par exemple, on peut faire varier le taux de contact β entre les individus de ces compartiments. Toutefois, ces solutions sont limitées : stratifier la population en fonction de plusieurs caractéristiques peut alourdir considérablement le modèle. De plus, l'assortativité ne permet pas de prendre en compte une structure sociale à proprement parler, mais uniquement les taux de contact d'individus en fonction d'une caractéristique donnée.

Depuis l'introduction des modèles compartimentaux, d'autres développements méthodologiques ont été apportés : la formulation individu-centrée des équations de Kermack et McKendrick permettant la prise en compte de l'aléa des durées de séjours dans un compartiment par l'utilisation de distributions de probabilité comme règles de transition (modèles stochastiques) ; de l'hétérogénéité des individus par l'individualisation des règles de transition ; ou encore la modélisation du réseau social par un graphe aléatoire, permettant de limiter les possibilités de transmission de l'agent infectieux dans la population aux individus ayant des contacts potentiellement infectieux. Une présentation plus détaillée des modèles dynamiques, ainsi que les avantages et les inconvénients de ces différentes approches dans le cadre de la modélisation de la transmission du VHC chez les UDI sont présentés au chapitre 2.

1.4 Analyse coût-efficacité

Le coût élevé des nouveaux AAD a suscité de nombreuses interrogations sur l'impact qu'aurait la prise en charge des infectés chroniques sur le budget de l'assurance maladie en France, où le traitement de l'hépatite C bénéficie d'un régime dérogatoire permettant sa prise en charge à 100% par le système de sécurité sociale (Ministère des affaires sociales 2014). Cette crainte a conduit à l'inclusion dans le projet de loi de financement de la sécurité sociale 2015 d'un mécanisme spécifique à l'hépatite C visant à mettre à contribution les laboratoire pharmaceutiques en cas de dépassement d'un seuil de dépense fixé à 450 millions d'euros (Assemblée Nationale 2014).

Les mesures de réduction des risques font également peser un coût sur les dépenses publiques mais dans des proportions bien moins importantes. Le budget annuel moyen d'un CAARUD est de 278 000 euros (Cadet-Taïrou et al. 2014) et celui d'un CSAPA de 746 000 euros (Palle et al. 2013), pour des files actives de l'ordre de 500 UDI. Le budget annuel de fonctionnement de la salle d'injection à moindres risques prévue à Paris est évalué à 800 000 euros.

Dans un contexte de ressources limitées, il est nécessaire de dépenser les ressources disponibles de la manière la plus optimale possible, c'est-à-dire de maximiser l'impact des ressources investies sur la santé des populations visées. C'est le but des analyses coût-efficacité.

Les analyses coût-efficacité ont pour objectif de comparer l'efficience de plusieurs interventions sur un objectif donné, l'efficience étant définie comme le rapport entre les coûts engendrés par une stratégie et les résultats qu'elle permet d'obtenir (l'efficacité) (Folland et al. 2007). Dans le cadre d'une problématique de santé publique, plusieurs indicateurs d'efficacité peuvent être définis, comme le nombre de décès ou d'infections évités, ou plus classiquement le nombre d'années de vies gagnées dans la population d'étude. La comparaison de stratégies se fait ici sur la base du coût marginal (ou coût supplémentaire) par année de vie gagnée d'une stratégie par rapport à l'autre, qu'on appelle le ratio coût-efficacité incrémental (ou ICER pour I*ncremental Cost-Effectiveness Ratio*) :

$$ICER = \frac{\Delta C}{\Delta E}$$

avec ΔC la différence de coût entre les deux stratégies et ΔE la différence d'efficacité associée.

Ces mesures présentent toutefois l'inconvénient de ne pas prendre en compte le bien-être des individus, c'est-à-dire leur qualité de vie dans l'état de santé dans lequel ils se trouvent. Dans le cadre des traitements antiviraux du VHC par exemple, les effets secondaires des traitements incluant des injections d'interféron tels que l'anémie ou la dépression ont un impact important sur la qualité de vie des malades (Siebert et al. 2005). Pour prendre en compte cette dimension, il est possible de pondérer le temps passé dans certains états de santé par une mesure de la qualité de vie associée à cet état, un poids de 1 correspondant à une année de vie en bonne santé. On parle alors d'années de vie ajustées sur la qualité, ou QALYs (pour *Quality-Adjusted Life-Years*) (Weinstein et al. 2009). Dans ce cas, l'ICER correspond à un coût par année de vie ajustée sur la qualité de vie (par QALY).

L'interprétation de cet ICER est variable selon les pays. En effet, ce coût par QALY doit être ramené aux ressources disponibles, qui sont par nature limitées. Pour cela, il est commun d'utiliser une valeur seuil, en dessous de laquelle l'intervention est considérée comme coût-efficace, et au-dessus de laquelle elle ne l'est plus. Cette valeur correspond à la propension du pays à payer pour améliorer l'état de santé de la population, compte tenu des ressources disponibles. En France, aucune valeur seuil n'est établie (Haute Autorité de Santé 2011). Toutefois, l'Organisation Mondiale de la Santé préconise d'utiliser un seuil lié au Produit Intérieur Brut (PIB) par habitant du pays (World Health Organization 2003) : une intervention est considéré comme très coût-efficace si l'ICER est inférieur au PIB par habitant du pays, comme coût-efficace si l'ICER est compris entre une et trois fois le PIB par habitant du pays, et comme non coût-efficace au-delà. En France, le PIB par habitant est d'environ 30 000€ (World Bank 2014).

1.5 Objectifs et plan de la thèse

L'objectif principal de ce travail de thèse est d'estimer, au sein d'une population d'UDI en France, l'impact de mesures de réduction des risques et d'amélioration dans la cascade de soins de l'hépatite C sur la transmission du virus et la morbi-mortalité associé, et en terme de coût-efficacité. L'objectif intermédiaire est la modélisation mathématique de la transmission du virus de l'hépatite C (VHC) au sein d'une population d'UDI.

Les stratégies évaluées sont :

Stratégie 1 : La diminution de la prise de risques par l'amélioration des mesures existantes (accès au matériel stérile et TSO) ou l'introduction de salles de consommation à moindre risque.

Stratégie 2 : L'augmentation du nombre de traitements antiviraux dans la population UDI (TasP). Cette stratégie consiste à améliorer la cascade de soins de l'hépatite C chronique en dépistant les malades plus rapidement, en améliorant les liens des malades avec le système de santé et en changeant les recommandations afin d'initier le traitement le plus précocement possible.

Stratégie 3 : L'amélioration du taux de RVS des traitements par une meilleure adhérence des patients.

Stratégie 4 : La combinaison des trois premières stratégies. En effet, une diminution efficace de la transmission du VHC chez les UDI ne sera probablement pas le résultat d'une unique mesure isolée, mais plutôt d'un ensemble de mesures.

De nombreux modèles dynamiques de transmission du VHC chez les UDI ont été proposés dans la littérature, particulièrement depuis le début des années 2010. Les méthodologies employées par leurs auteurs sont variables, et les structures de ces modèles, habituellement construits pour évaluer uniquement l'une des quatre stratégies évoquées ci-dessous, ne permettent pas d'évaluer l'impact d'interventions combinées sur la cascade de soins et donc une comparaison de leur efficience. Nous avons effectué une revue de littérature de ces modèles qui est l'objet du chapitre 2. Cette revue détaille également les différentes familles de modèles employés en modélisation dynamique des maladies infectieuses, ainsi que leurs forces et leurs limites dans le contexte particulier du VHC chez les UDI.

Le chapitre 3 présente d'abord notre modèle dynamique, stochastique et individu-centré. Le modèle peut être divisé en trois parties.

La première partie du modèle était le réseau social de la population UDI. Il s'agissait de modéliser les possibilités de transmission de la maladie d'un individu à l'autre dans la population. De manière similaire à une précédente étude de modélisation de Rolls *et al.* conduite à Melbourne (Rolls et al. 2011), nous avons considéré le réseau des partenaires d'injection : deux individus sont liés s'ils s'injectent ensemble. Cette définition du réseau social, au lieu du simple réseau de partage de matériel, permet de prendre en compte le risque global entre individus s'injectant ensemble. Les réseaux utilisés lors des simulations ont été générés informatiquement par le biais de modèle de graphe aléatoire, en prenant en compte diverses contraintes : degré moyen (i.e. nombre moyen de contacts dans la population), occurrence de certains motifs (par exemple les triangles) dans les réseaux réels, etc. Dans ce chapitre, le modèle utilisé était relativement simple : il s'agissait d'un graphe d'Erdős–Rényi, modèle dans lequel chaque couple d'individu est relié avec une probabilité *p* fixée.

La deuxième partie consistait à modéliser la transmission du VHC, ainsi que la cascade de soins : le dépistage, le lien avec le système de soins, la perte de vue et le traitement sont intégrés au modèle. Un schéma présentant différents états et les transitions possibles est présenté Figure 2.

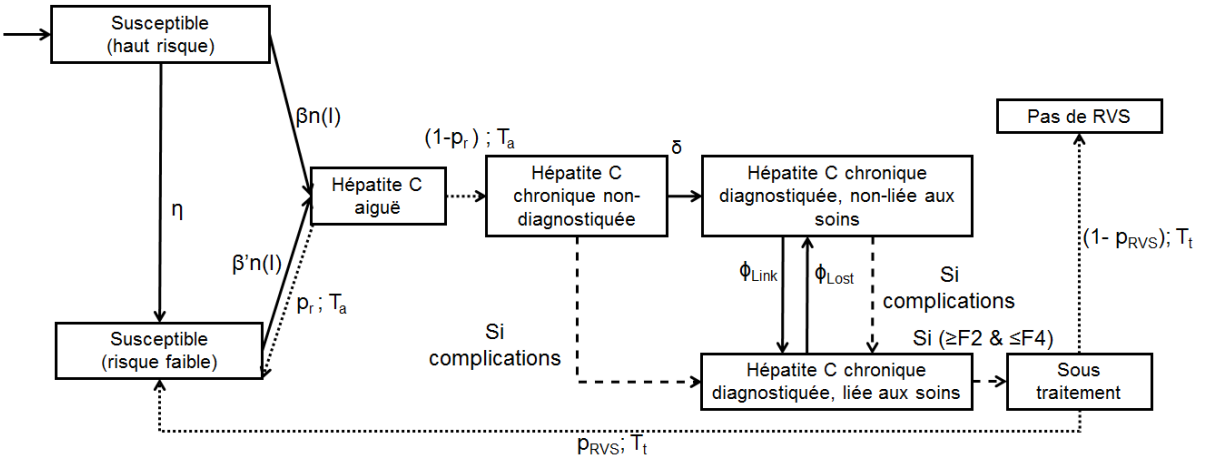

Figure 2 – Modèle individu-centré pour l'infection par le VHC et la cascade de soins de l'hépatite C. RVS : réponse virologique soutenue. Les lettres grecques correspondent à des taux annuels de transition.

n(I) est le nombre de partenaires d'injection infectés de l'individu. La durée de l'hépatite C aiguë (T_a) et du traitement (T_t) sont déterministes. L'issue de ces états est déterminée par un tirage de loi de Bernoulli de probabilité p_r (probabilité de rémission spontanée) et p_{RVS} (probabilité de RVS après le traitement), respectivement.

Enfin, la troisième partie est une modélisation de l'histoire naturelle de l'hépatite C chronique, basée sur un modèle précédemment publié (Deuffic-Burban et al. 2012). La progression de la maladie hépatique y est quantifiée par le score Métavir allant de F0 à F4 (la cirrhose). En F4, deux complications de la cirrhose peuvent survenir : la décompensation et le CHC. Ces complications peuvent elles-mêmes conduire au décès.

L'implémentation informatique du modèle reposait sur l'algorithme de Gillespie, qui permet de simuler les processus stochastiques de ce type à partir de taux de transition entre les différents états (Gillespie 1976). Le modèle a été intégralement programmé dans le langage C++. Le C++ est un langage de programmation compilé, orienté objet, qui permettait d'obtenir des temps de calcul plus modeste et une plus grande souplesse que les alternatives disponibles (comme l'utilisation de logiciels commerciaux ou de langages de programmation non-compilés). Malgré cela, la nature individu-centrée du modèle, la taille de la population simulée et le nombre de simulations effectués dans les différentes études qui composent cette thèse imposaient des temps de calcul très longs. Pour remédier à ce problème, l'exécution des programmes a été effectuée en utilisant les ressources du centre de calcul intensif de la région Nord-Pas-de-Calais (Université Lille 1, CPER Nord-Pas-de-Calais/FEDER, France Grille, CNRS).

Dans le chapitre 3, nous avons ensuite évalué l'impact des stratégies évalués et en particulier les stratégies 2, 3 et 4, décrites ci-dessus en modifiant les taux de transition et en améliorant le taux de dépistage, les taux de lien aux soins et de perte de vue, les conditions d'initiation du traitement et l'adhérence au traitement (i.e. en faisant varier le taux de RVS) dans le modèle décrit Figure 2. Dans un premier temps, l'impact de ces stratégies a été évalué dans la population des UDI en Île-de-France (i.e. l'incidence et la prévalence après 10 années de simulation) et sur le nombre de complications de la cirrhose (décompensation et CHC) évités lors des 40 premières années de simulation. Une étude similaire a également été conduite, en utilisant ce même modèle, et en l'appliquant à la population d'UDI de Montréal au Québec, et est l'objet du chapitre 4 de cette thèse. Le contexte de Montréal est différent du contexte français au niveau du traitement notamment : le traitement est pris en charge sans condition de sévérité de la maladie (à la différence de la France, où le traitement n'est normalement pris en charge qu'à partir du stade F2 (Ministère des affaires sociales 2014)), mais le taux de traitement, défini comme la proportion d'individus diagnostiqués et liés aux soins qui initient un traitement dans l'année, est extrêmement faible : environ 5% des individus susceptible d'être traités le sont chaque années.

Ce modèle a ensuite été amélioré. Une modélisation de la participation des UDI aux mesures de réduction des risques a été introduite, incluant l'accès au matériel stérile et les traitements de substitution

aux opiacés. L'état de l'individu par rapport à la réduction des risques avait pour effet de modifier le risque d'infection dans le modèle. Un modèle de réseau plus sophistiqué appelé « modèle de ménage » a été utilisé. Il s'agit de modèles probabilistes, prenant en compte l'existence de sous-groupes au sein desquels les individus sont fortement connectés, mais avec une probabilité de lien très faible entre individus appartenant à des groupes différents. Ces modèles ont été largement étudiés dans la littérature mathématique. Les paramètres de ce modèle, en l'absence de données sur la population d'UDI en France, ont été estimés à partir des données sur la population d'UDI Melbourne (Rolls et al. 2011). Nous avons d'abord utilisé cette version modifiée du modèle, incluant un modèle plus sophistiqué pour le réseau social et la réduction des risques chez les UDI, afin d'évaluer une probabilité d'élimination du VHC chez les UDI par une stratégie de TasP. En effet, avec l'arrivée des nouveaux AAD, la possibilité de l'élimination du VHC, définie comme l'atteinte d'une incidence nulle dans un contexte géographique donné (Dowdle 1998), est régulièrement mise en avant. Nous avons donc cherché à évaluer la probabilité d'élimination du VHC à 10 ans par une stratégie de TasP « optimale », incluant une cascade de soins améliorée (dépistage, lien aux soins et adhérence optimale), un traitement non-conditionné à la sévérité de la fibrose (donc dès F0) et les nouveaux AAD. Les paramètres utilisés correspondaient au scénario le plus efficace de l'étude sur la population UDI d'Île-de-France du chapitre 3. L'évaluation la probabilité de survenue d'un évènement dans un modèle se fait classiquement par des méthodes de Monte-Carlo : on effectue un grand nombre de simulations du modèle afin d'estimer la fréquence de survenue de l'évènement en question dans le jeu de simulations. Toutefois, lorsque l'évènement en question se produit rarement, cette méthode pose problème : un nombre très important de simulations est nécessaire afin d'observer la survenue de l'évènement. Le chapitre 5 passe en revue deux méthodes alternatives utilisées dans ce genre de situation : l'échantillonnage préférentielle (ou « importance sampling ») (Asmussen et al. 2007; Bucklew 2013) et la méthode IBPS (pour « interacting branching particle system ») (Villén-Altamirano et al. 1991; Dean et al. 2011). Ces méthodes sont comparées sur quelques cas-tests, et finalement appliquées à l'estimation de la probabilité d'élimination du VHC à 10 ans chez les UDI d' Île-de-France par une stratégie de TasP.

Cette version du modèle a ensuite été utilisée afin d'évaluer le coût-efficacité de mesures de réductions des risques et des scénarios les plus efficaces des analyses présentées au chapitre 4. Les résultats de cette analyse coût-efficacité sont présentés au chapitre 6.

Pour ces études, les valeurs des paramètres du modèle ont été recherchées dans la littérature ou estimées à partir de données non-publiées d'enquêtes épidémiologiques. Les évaluations des paramètres utilisées lors des analyses présentées dans les chapitres 3, 5 et 6 provenaient principalement de l'enquête ANRS-Coquelicot, une enquête de prévalence du VHC chez els utilisateurs de drogues en deux volets (un premier volet en 2004, l'autre en 2011) (Jauffret-Roustide et al. 2006; Jauffret-Roustide et al. 2009). Cette enquête est une étude transversale conduite dans cinq grandes villes françaises (Lille, Strasbourg, Paris, Bordeaux and Marseille) sélectionnées pour représenter la diversité de l'addiction aux drogues en France. Les individus étaient recrutés dans des structures de soins et de services pour usagers de

drogues : centres de réduction des risques, centres de traitement, et centres d'hébergement. Les critères d'inclusion étaient : être âgé de 18 ans ou plus, et avoir injecté ou sniffé de la drogue au moins une fois dans sa vie. Vu notre population d'étude, nous avons estimé nos paramètres chez les individus qui reportaient s'être déjà injectés. Les autres paramètres ont été recherchés dans la littérature scientifique, ou estimés par calcul bayésien approché (Marin et al. 2012). Le calcul bayésien approché (ou ABC, pour « Approximate Bayesian Computation ») est une méthode d'estimation dérivée de l'inférence bayésienne permettant, à partir d'un ensemble de statistiques attendues (dites statistiques cibles) dans les résultats du modèle (par exemple, une prévalence finale), permet de rechercher les valeurs de paramètres rendant ces valeurs de statistiques les plus vraisemblables. Une présentation plus détaillée de l'ABC est donnée au chapitre 3.

Ces valeurs de paramètres, qu'elles proviennent d'études épidémiologiques ou qu'elles soient inférées par des méthodes statistiques, sont sujettes à des incertitudes, qui peuvent avoir un impact sur les résultats obtenus, voir sur les conclusions des analyses. L'analyse de sensibilité permet, en estimant l'impact de modifications de la valeur des paramètres sur les résultats obtenus, de quantifier l'impact de ces incertitudes. L'estimation des indices de Sobol par des méthodes de Monte-Carlo, classiquement utilisés pour évaluer la sensibilité des résultats d'un modèle à la valeur des variables d'entrée, pose problème dans le cadre d'un modèle stochastique tel que celui utilisé pour les analyses présentées dans cette thèse, notamment à cause du nombre élevé de simulations à effectuer, qui nécessite un temps de calcul important. Le chapitre 7 présente une introduction à l'analyse de sensibilité par le calcul des indices de Sobol, les problèmes liés à leur estimation dans un cadre stochastique, et propose deux nouveaux estimateurs non-paramétriques utilisables dans ce contexte. La convergence de ces estimateurs a été étudiée, et démontre une convergence plus rapide que les estimateurs classiquement utilisés. De premiers résultats numériques, encore préliminaires, sont présentés dans ce chapitre.

2 Revue de littérature des modèles dynamiques de transmission du VHC chez les UDI précédemment publiés

2.1 Résumé

Avant le milieu des années 2000, peu de modèles dynamiques de transmission du VHC chez les UDI avaient été proposés. Les publications dans ce domaine se sont multipliées au cours de ces dernières années, motivées principalement par l'étude de l'impact de stratégies de réduction des risques (principalement l'accès au matériel d'injection et les traitements de substitution aux opiacés), la comparaison des dynamiques épidémiques du VHC et du VIH chez les UDI, et l'impact des traitements antiviraux sur la transmission du VHC au sein des populations d'UDI. D'autres sujets ont aussi été abordés, comme les centres d'injection supervisés, le dépistage en milieu carcéral ou l'impact d'une potentielle vaccination contre le VHC. La diversité de ces objectifs et les choix méthodologiques des auteurs de ces études ont abouti à des modèles parfois très différents, que ce soit au niveau de la structure des modèles (prise en compte de la cascade de soins de l'hépatite C chronique, de l'histoire naturelle de la maladie, etc.) ou des hypothèses de modélisation (modèles compartimentaux ou individus-centrés, déterministes ou stochastiques).

L'objectif de cet article était d'effectuer une revue de littérature des modèles dynamiques de transmission du VHC chez les UDI, de présenter les différentes approches utilisées afin d'établir leurs forces et leurs limites pour cette problématique, et d'établir une synthèse des principaux résultats obtenus grâce à ces modèles.

Pour cela, une recherche a été effectuée sur la base de données Medline en utilisant les mots-clés *mathematical*, *model*, *hepatitis C*, *drug users* et leurs variantes. La recherche initiale incluait toutes les publications jusqu'en juin 2014.

La recherche bibliographique initiale a permis d'identifier 37 articles publiés. Une mise à jour effectuée en août 2015 a permis d'inclure 8 articles supplémentaires, décrits dans le Tableau 1 ci-dessous. D'un point de vue méthodologique, la majorité des modèles publiés (38/45) sont de nature compartimentale : la population est repartie entre différents états (par rapport à l'infection, la cascade de soins, l'histoire naturelle, les caractéristiques sociales et épidémiologiques, etc.), les flux de populations entre ces différents états étant déterminés par des règles de transitions (le plus souvent, des taux de transitions). Cette approche compartimentale présente plusieurs avantages. Les méthodes sont bien documentées et implémentées dans différents logiciels. Les temps de calculs sont modestes et, si l'on considère une approche stochastique, en grande population les trajectoires peuvent être approchées par un système d'équations différentielles ordinaires (on parle alors d'approche déterministe). De plus, les paramètres nécessaires sont populationnels, et donc estimables par l'utilisation de données épidémiologiques classiques. Ces modèles sont toutefois basés sur deux hypothèses importantes. La première est que la population d'un compartiment est supposée homogène : la seule caractéristique d'un individu est son état dans le modèle. Or, de nombreuses caractéristiques individuelles peuvent avoir un impact sur la

vitesse de transition d'un individu d'un état à l'autre. Par exemple, le temps écoulé depuis l'initiation à l'injection a un impact sur le risque d'infection, celui-ci étant plus élevé au cours des premières années d'injection (Sutton et al. 2006; Hagan et al. 2008; Sutton et al. 2008). Le taux de mortalité varie selon l'âge et le genre de l'usager (Lopez et al. 2004). Les coinfections VIH/VHC ainsi que la consommation d'alcool favorisent la progression de la maladie vers la cirrhose (Thein et al. 2008). Le génotype du virus modifie les chances de succès du traitement, particulièrement avec la bithérapie peginterferon/ribavirine, pour laquelle le taux de RVS n'est que de 45-50% pour les génotypes 1-4 contre 75-80% pour les génotypes 2 et 3 (NICE 2006). Si l'ajout de nouveaux compartiments permet de prendre en compte les caractéristiques qualitatives ou quantitatives discrètes des individus, en pratique le nombre de compartiments du modèle et de paramètres nécessaires pour décrire les transitions entre ceux-ci augmentent rapidement, ce qui complexifie grandement le modèle et augmente le nombre de paramètres à estimer. La deuxième hypothèse est que la population est également supposée totalement mélangée : la force d'infection est distribuée uniformément sur l'ensemble des individus susceptibles. Encore une fois, cette hypothèse peut être relâchée par l'ajout de nouveaux compartiments correspondant à différentes catégories de population et permettant de faire varier le risque de transmission de l'infection entre celles-ci, on parle alors de mélange assortatif.

Pour s'affranchir de ces hypothèses, une autre approche, pour l'instant peu utilisée dans le cadre de l'infection par le VHC chez les UDI (7 articles), consiste à utiliser un modèle individu-centré. Dans ce type de modèle, ce ne sont plus des flux de populations entre compartiments qui sont modélisés, mais la transition d'individus d'un état à l'autre du modèle (Gillespie 1976; Epstein et al. 1996; Bonabeau 2002). Les taux de transition sont donc individuels, et il est possible d'attribuer à chaque individu un ensemble de caractéristiques qui vont influer sur les taux de transition. De plus, on peut prendre en compte explicitement dans le modèle les contacts potentiellement infectieux entre individus, et donc de restreindre les possibilités de transmission du virus dans la population. Dans le cas de l'hépatite C, qui est une maladie transmise principalement par le sang, ces contacts infectieux chez les UDI sont principalement dus au partage de matériel d'injection (seringues, mais aussi coton et cuillères (Mathei et al. 2006)) entre partenaires d'injection. Une équipe de recherche basée à Melbourne, en utilisant des données locales recueillies sur le réseau social de la population d'UDI locale, a proposé un modèle prenant en compte le réseau des partenaires d'injection (Rolls et al. 2011; Rolls et al. 2013). Ils ont ainsi démontré l'effet protecteur de ce réseau (comparé à une hypothèse de mélange total des individus) et donc l'intérêt de ce type de modèles lors de l'étude de la transmission du VHC. Cependant, simuler un modèle individu-centré nécessite des temps de calcul plus importants, puisque la trajectoire de chaque individu doit-être simulée. Ce type de modèle est également plus difficile à calibrer, puisqu'il nécessite des données individuelles, plus difficiles à obtenir par des enquêtes épidémiologiques. C'est particulièrement le cas des données relatives au réseau de partenaires d'injection : afin de capturer la structure du réseau, il est nécessaire de faire appel à des méthodes d'échantillonnage spécifiques, comme le « snowball sampling » (Goodman 1961) ou le « respondent-driven sampling » (Heckathorn 1997).

Ces techniques sont basées sur le recrutement de participants dans une étude par vagues successives, les participants de la vague *N+1* étant recrutés parmi les connaissances des participants de la vague *N*. Suite au constat de l'absence de données sur les réseaux sociaux des UDI en France, nous avons initié une étude du même type afin d'obtenir des données similaires aux données australiennes, dont l'investigatrice principale est Marie Jauffret-Roustide, et qui actuellement en phase de recrutement.

En ce qui concerne les résultats de ces études, plusieurs éléments ressortent. Premièrement, les mesures visant à réduire la transmission du VHC chez les UDI doivent être mises en place le plus tôt possible pour être efficaces. Les stratégies de réduction des risques sont plus efficaces lorsqu'elles ciblent les injecteurs récemment initiés : durant les 4 premières années d'injection pour Vickerman et *al.* (Vickerman et al. 2007) et les 5 premières années d'injection pour Corson *et al.* (Corson et al. 2012). Concernant l'utilisation du traitement comme prévention de la transmission du VHC (« TasP »), les résultats montrent que même un accès limité au traitement permettrait d'obtenir une diminution importante de la prévalence (Martin et al. 2011; Hellard et al. 2012) : à Victoria (Australie) par exemple, 25/1000 UDI traités annuellement aboutiraient à une diminution de 50% de la prévalence après 30 ans (Hellard et al. 2012). L'attribution de ces traitements devraient également être faite selon le risque de transmission de l'individu : il est suggéré de traiter en priorité les injecteurs récemment initiés au lieu des plus expérimentés (Durier et al. 2012) et les injecteurs actifs au lieu des substitués (Zeiler et al. 2010; Martin et al. 2012). Ce dernier point permettrait également d'améliorer le coût-efficacité du traitement (Martin et al. 2012). Enfin, une étude plus récente en Australie montre que des stratégies basées sur le réseau social consistant à traiter également les partenaires d'injection infectieux des individus traités permettrait de maximiser l'impact du traitement sur la transmission de la maladie (à taux de traitement constant), en prévenant le risque de réinfection (Hellard et al. 2014).

En conclusion, plusieurs modèles de transmission du VHC chez les UDI ont été publiés, le plus souvent pour répondre à une question précise de santé publique. Les structures de ces modèles ont le plus souvent été construites pour répondre à la question initiale et négligent donc les autres aspects de cette problématique, rendant difficile l'utilisation d'un même modèle pour l'évaluation de différentes interventions. De plus, la majorité des modèles publiées sont compartimentaux, et reposent sur des hypothèses fortes. L'utilisation de modèles individu-centrés incluant le réseau social de la population reste marginale, principalement à cause du manque de données. La construction de tels modèles nécessite des compétences en modélisation mathématique, en médecine clinique, en épidémiologie et en sociologie, et donc la mise en place de collaborations multidisciplinaires.

Cette revue de littérature a été publiée dans *Journal of Viral Hepatitis* (Cousien et al. 2015).

Tableau 1 : Mise à jour de la revue de littérature – articles publiés entre juin 2014 et août 2015

Référence	Pays (population d'étude)	Objectifs	Modèle/Approche	Principaux résultats
Hart-Malloy *et al.* (Hart-Malloy et al. 2013)	Etats-Unis	Estimer la prévalence du VHC chez les UDI de l'état de New-York, et évaluer l'impact sur celle-ci d'une reduction du partage de materiel d'injection et de la mise à disposition de materiel sterile.	Modèle compartimental/Approche stochastique	La prévalence à l'équilibre est estimée à 63.6%. L'élimination du VHC (définie comme l'obtention d'une prévalence <1%) nécessite une intervention combinant la désinfection des seringues, une meilleure disponibilité du matériel d'injection et une diminution du partage de matériel.
De Vos *et al.* (de Vos et al. 2014)	Pays-Bas	Etudier l'impact du traitement sur la transmission du VHC en fonction de la population préférentiellement traitée (UDI à risque faible ou élevé d'infection)	Modèle compartimental/Equations différentielles déterministes (analyses à l'équilibre)	Il existe un seuil de prévalence en dessous duquel traiter les UDI ayant des comportements à haut risque est plus efficace, et au-dessus duquel traiter les UDI ayant des comportements à risques faible est plus efficace. Ce résultat s'explique par le poids des réinfections dans un contexte de prévalence élevée.
De Vos *et al.* (de Vos et al. 2015)	Pays-Bas	Evaluer l'impact du traitement sur la transmission du VHC en fonction de la population préférentiellement traitée (UDI à risque faible ou élevé d'infection)	Modèle compartimental/Equations différentielles déterministes (analyses à l'équilibre)	Application des résultats de l'article précédent : le seuil de prévalence à partir duquel traiter les individus les plus à risque a moins d'impact que traiter les individus les plus à risque correspond à 50% de seringues échangées contaminées. Une

Référence	Pays (population d'étude)	Objectifs	Modèle/Approche	Principaux résultats
				réduction du risque d'infection de 50% dans la population permet de faire monter ce seuile à 59% de seringues contaminées.
Martin *et al.* (Martin et al. 2015)	Royaume-Uni	Evaluer l'impact à 10 ans d'un passage aux nouveaux AAD et de meilleurs taux de traitement sur la prévalence de l'hépatite C chronique dans 7 villes du Royaume-Uni	Modèle compartimental/Equations différentielles déterministes	Avec les nouveaux AAD, une diminution de la prévalence de plus de 15% peut être obtenue sur chacun des sites après 10 ans à des taux de traitements atteignables (26/1000 UDI/an)
Bennett *et al.* (Bennett et al. 2015)	Royaume-Uni	Estimer l'impact de traitements antiviraux plus efficaces et d'une augmentation du taux de traitements sur la prévalence du VHC et le nombre d'années de vies dans la population, ainsi que les coûts associés.	Modèle compartimental/Equations différentielles déterministes	Bien qu'une amélioration du taux de SVR seul (par les nouveaux traitements) permet d'obtenir une prévalence <5% à long terme (60 ans), une amélioration du taux d'accès au traitement est centrale pour diminuer le fardeau de la maladie.
Echevarria *et al.* (Echevarria et al. 2015)	Etats-Unis	Evaluer l'impact d'un meilleur accès au traitement chez les UDI de Chicago	Modèle compartimental/Equations différentielles déterministes	Le modèle montre que pour réduire la prévalence de 50% en 10 ans (dans les populations concernées), le taux de traitement doit être de 35/1000 UDI dans l'ensemble de la population ; de 19/1000 UDI chez les UDI participant à un programme de réduction des risques et de 5/1000 UDI chez les jeunes UDI. Une réduction importante de la

Référence	Pays (population d'étude)	Objectifs	Modèle/Approche	Principaux résultats
				prévalence à des taux de traitement modérés est donc atteignable, particulièrement dans les deux dernières sous-populations mentionnées.
Scott *et al.* (Scott et al. 2015)	Indeterminé	Evaluer l'impact d'une vaccination contre le VHC chez les UDI en fonction de la population ciblée (vaccination indépendante du traitement ou après un traitement réussi uniquement, vaccination en fonction du niveau de risque)	Modèle compartimental/Equations différentielles déterministes	Une vaccination VHC, même faiblement efficace et avec un taux de couverture faible, permettrait d'obtenir une réduction de prévalence. L'impact de la vaccination sur la prévalence est similaire que l'on traite indépendamment du traitement ou non, et que l'on cible en fonction du niveau de risque. Cependant, une vaccination après le traitement serait plus simple à mettre en place.
Hellard *et al.* (Hellard et al. 2014)	Australia	Etudier l'impact de stratégies de traitement basées sur le réseau social des UDI sur la transmission du VHC	Modèle individu-centré avec représentation du réseau social	Les résultats montrent que traiter les partenaires d'injection des individus infectés permet, à taux de traitement égal, une plus grande diminution de l'incidence (en évitant les réinfections) que de traiter aléatoirement.

2.2 Article 1 (publié, Journal of Viral Hepatitis)

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JVH

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REVIEW

Dynamic modelling of hepatitis C virus transmission among people who inject drugs: a methodological review

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SUMMARY. Equipment sharing among people who inject drugs (PWID) 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 programmes or improved treatment) are difficult to evaluate using field surveys. Ethical issues and complicated access to the PWID 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 to underline their strengths and limits in the context of HCV infection among PWID. The final section discusses the main results of the papers.

Keywords: antiviral treatment, dynamic modelling, harm reduction policies, hepatitis C, injecting drug users.

INTRODUCTION

In high-income countries, people who inject drugs (PWID) are the main population at risk of infection with hepatitis C virus (HCV), with a seroprevalence 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 PWID. These measures have focused mainly on opioid substitution treatments such as methadone and buprenorphine, and on needle exchange programmes [5]. However, other measures are possible. Indeed, some European countries have financed and launched supervised injection and needle exchange programmes 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, that is 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 PWID [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 [13,14]. Given that nonviremic patients (i.e. those with a SVR) cannot transmit the infection [15], 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 programmes (HRP), such as needle exchange programmes, and the use of these new treatments to avoid transmission

Abbreviations: AES, ancillary equipment sharing; ERGM, exponential random graph model; HCV, hepatitis C virus; HRP, harm reduction policies; IBM, individual-based model; IDU, injecting drug user; QALY, quality-adjusted life year; RNS, risky needle sharing; SVR, sustained virological response.

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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 PWID population, which is difficult to reach. Mathematical modelling is an alternative; indeed, it enables 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 this article was to review mathematical models used to simulate transmission of HCV among PWID, and to evaluate their pros and cons.

The first section briefly summarizes the corpus of papers found. The second describes compartmental models and their properties. The third section describes individual-based models (IBMs) and their properties. 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 PWID in the literature and to evaluate their strengths and limits. Eligible studies had to satisfy two conditions: (i) describe a dynamic mathematical model for transmission of HCV; and (ii) study a population of PWID. In accordance with Cochrane Collaboration guidelines [16], we conducted our search in the Medline database using the keywords *mathematical*, *model*, *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 June 2014.

RESULTS

Of 214 articles identified, we examined 57 of them in detail and kept 32 articles that fulfilled the above criteria (see Fig. 1 for details about the reasons for exclusion). We added five articles from other sources, giving a total of 37 original articles [17–53]. The modelled populations were mainly from the UK [17–22,26,35,36,43,45–48], Australia [27,31,33,43,50,51] and USA [30,37–39,49,52]. Two articles involved analyses in developing countries: that of Durier *et al.* [25] studied a population of PWID in Vietnam, while Vickerman *et al.* [24] examined a population of PWID in Pakistan.

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 [28,35–39]; (ii) to evaluate the impact of HRP [on the chronic/antibody prevalence, incidence, number of infections and quality-adjusted life years (QALYs) gained] [21,22,24–26,29,33,36–41,50,51], (iii) to compare epidemics dynamic of HCV and HIV infections [1,23,24,28, 33,40–42,44,45]; (iv) to evaluate the impact of treatment of HCV infection on transmission [17–19,25,34,43,49,50] and cost [20,43]; and (v) to evaluate the impact of potential HCV vaccination strategy [30,32,51]. Objectives and main results of these articles are detailed in Table 1.

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

In addition, we distinguished two approaches in these articles: stochastic or deterministic. In the stochastic approach, the epidemic is considered as a chain of events (infections, recovery, etc.) occurring at random times

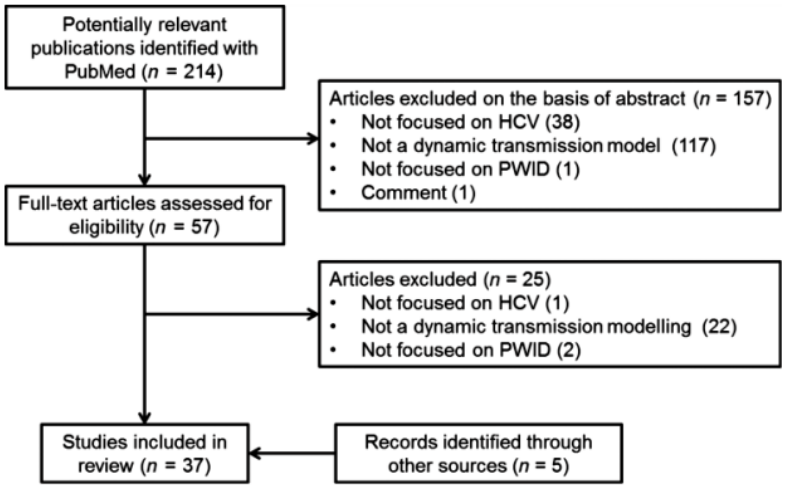

Fig. 1 Identification of the relevant articles.

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Table 1 Summary of the review

Reference	Country (setting)	Objectives	Model/Approach	Main results
Mather *et al.* [51]	Australia	To obtain predicted outcomes of different scenarios of immunization by a hypothetical vaccine and to identify sensitive parameters of the model	Individual-based model/ stochastic approach	The rate of spread of HCV through an PWID population is not really sensitive to the initial prevalence, but it is sensitive to the proportion of group members with whom the individual has contact and the probability of infection per contact (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 [39]	USA	To assess the impact of a syringe exchange programme on HCV so as to understand why it is effective for HIV but not for HCV in a PWID population	Compartmental model/ deterministic differential equations – Analytic results (steady-state analysis)	Modest interventions (reduce incidence by a third) are only effective for hard-to-transmit infections (such as HIV), while for HCV, with a high prevalence, only a massive programme will have an impact. Moreover, for a high-prevalence setting, the impact will occur over the long term
Pollack [38]	USA	To assess the effectiveness and cost–effectiveness of a syringe exchange programme	Compartmental model/ deterministic differential equations – Analytic results (steady-state analysis)	The syringe exchange programme is effective and cost–effective when R_0 is low (2.9 for HIV), but becomes less effective when R_0 is high (6.9 for HCV) and cost becomes prohibitive (>250.000$ per averted infection), which is more realistic (in short-term analysis). This is necessary to combine syringe exchange programmes with intervention aimed at decreasing the R_0, such as the methadone maintenance programme
Pollack [37]	USA	To assess biases that represent short-term analyses compared to a long-term analyses (i.e. taking into account changes in prevalence in steady-state analyses) in the evaluation of harm reduction intervention among PWID	Compartmental model/ deterministic differential equations – Analytic results (steady-state analysis)	The short-term incidence underestimates the effectiveness of a programme 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.* [33]	Australia	To assess the impact of different levels of needle sharing on the prevalence of HIV and HCV among PWID	Compartmental model/ deterministic differential equations	The needle exchange programme has less impact on HCV than on HIV: 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
Esposito *et al.* [29]	Italy	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)

(continued)

Table 1 *(continued)*

Reference	Country (setting)	Objectives	Model/Approach	Main results
Hutchinson *et al.* [26]	United Kingdom	To model the hepatitis epidemic among PWID in Glasgow and implications for prevention	Individual-based model on a simulated contact network of PWID/ stochastic approach	The estimated seroprevalence in the 1990s 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 PWID to share with only a small group of trusted persons (tested negative) and predict that by reducing the mean number of partners to one (*vs* 2–3), 5300 infections could have been avoided between 1988 and 2000
Vickerman *et al.* [21]	United Kingdom	To assess the impact of decreased needle sharing on HCV transmission	Compartmental model/ deterministic differential equations	Current public health interventions aiming at reducing needle/ syringe sharing (like needle/syringe exchange) should target new or recently initiated injectors to have an optimal impact. There is therefore a need to work on new injectors, which is currently not the case. Moreover, we have to target all PWID, not just those with a high frequency of syringe sharing Frequency sharing must be significantly reduced (to 1–2 times a month) to achieve a seroprevalence ≤10%
Bayoumi *et al.* [53]	Canada	To estimate the cost–effectiveness of Vancouver's supervised injection facility	Compartmental model/ deterministic differential equations	If a reduction of needle sharing is the only effect of the supervised injection facility: incremental net savings of almost $14 million and 920 life years saved after 10 years When adding an increase use of safe injection practices and increased referral to methadone maintenance treatment: incremental net savings of almost $18 million and 1175 life years saved after 10 years The cost saving is mainly due to HIV infections averted
Hahn *et al.* [30]	USA	To assess the impact of vaccinations (at different levels of effectiveness) on the HCV epidemic among PWID	Individual-based model/ stochastic approach	Several scenarios of vaccination were tested: Randomly vaccinate the population Vaccinate individuals with more risky behaviour Vaccinate individuals seronegative for HCV (serotargeting) The third scenario is the most effective, followed by the second, suggesting that random vaccination is not a good strategy

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Table 1 *(continued)*

Reference	Country (setting)	Objectives	Model/Approach	Main results
Vickerman *et al.* [24]	Pakistan	To explore different hypotheses to explain the low prevalence of HCV among PWID in Rawalpindi, Pakistan, and to estimate the impact of interventions	Compartmental model/ deterministic differential equations	Most syringe sharing involves low risk, because it concerns 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 A reduction of syringe sharing >40% could reduce the number of HCV/HIV infections of around 45% after 10 years if all PWID are reached
Zeiler *et al.* [27]	Australia	To study the impact of HCV treatment allocation according to methadone taking	Compartmental model/ deterministic differential equations	Advantage of treating active users rather than users on methadone because of re-infection and high turnover of PWID on methadone
Dontwi *et al.* [32]	Unspecified	To assess the impact of a possible vaccine against HCV among PWID	Compartmental model/ deterministic differential equations	Potential vaccination carried out early and covering a large part of the population (>80%) would significantly reduce the force of infection (nearly 90%) and, ultimately, the extent of the epidemic
Coutin *et al.* [28]	Unspecified	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 quarantine (i.e. isolate the population to prevent transmission) ensures a long-term decline in HCV prevalence but is impractical Increasing the number of PWID leads to a decrease in HCV prevalence (also impractical) The differing force of infection explains the different results between HIV and HCV
Martin *et al.* [18]	United Kingdom	To study the impact of treatment on chronic prevalence of hepatitis C among PWID	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.* [19]	United Kingdom	To assess the level of treatment required to eradicate or control the epidemic of hepatitis C among PWID	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 for chronic prevalence <40%; 10–20% for a chronic prevalence of 60%)
Martin *et al.* [17]	United Kingdom	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 chronic prevalence

(continued)

Table 1 *(continued)*

Reference	Country (setting)	Objectives	Model/Approach	Main results
Vickerman *et al.* [23]	Unspecified	To understand the trends in HIV and hepatitis C seroprevalence among PWID in different settings	Compartmental model/ deterministic differential equations	Existence of a threshold for the seroprevalence of HCV, below which HIV prevalence is negligible. This threshold depends on the environment (practices, etc.) The existence of different levels of risk groups and the size of these groups could explain the range of observed values for the prevalence of HIV/HCV in different settings Strategies for long-term intervention needed to reduce the seroprevalence of HCV
Rolls *et al.* [31]	Australia	To propose a model of transmission of HCV among PWID	Individual-based model on an empirical contact network of PWID/stochastic approach	Re-infection rates (20.6/100 PY) are higher than rates of primary infection (14.4/100 PY) Comparison with a fully connected graph (equivalent to the assumption of compartmental models) does not achieve this Event transmission rate estimated: 1%
Cipriano *et al.* [52]	USA	To estimate the cost, effectiveness and cost–effectiveness of HCV and HIV screening (antibody and/or viral RNA testing) for PWID in OST	Compartmental model/ deterministic differential equations	Depending on screening frequency, adding HIV/HCV RNA testing to antibody testing averts between 14.8 and 30.3 HIV infections and between 3.1 and 7.7 HCV infections in a population of 26 100 screened PWID entering OST Strategies including HCV testing have incremental cost–effectiveness ratio >$100 000/QALY gained, unless awareness of HCV infection status results in a decrease >5% of needle sharing
Castro Sanchez *et al.* [44]	Italy	To choose a model, identifying parameters to which the model is sensitive, fitting the model	Compartmental model/ deterministic differential equations	Selection of a model (from two evaluated models) for the force of infection, and identification of the number of risk groups in the population (two: low and high risk) The most sensitive parameters are those linked to syringe sharing and transmission rates in chronic stages of HIV and HCV infection
Corson *et al.* [35]	United Kingdom	To present a mathematical model for the spread of HCV in PWID 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 ≤54·67/year Needle cleaning ≥0·74 Needle turnover ≥562·37/year
Corson *et al.* [36]	United Kingdom	To present a mathematical model for the spread of HCV in PWID		Demonstration that with the authors model for $R_0 \leq 1$ tends towards elimination of HCV infection; meanwhile, for $R_0 > 1$,

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Table 1 *(continued)*

Reference	Country (setting)	Objectives	Model/Approach	Main results
		To study the basic reproductive number (R_0) To study the impact of needle exchange	Compartmental model/ deterministic differential equations	unique endemic equilibrium distribution. In Glasgow, R_0 is estimated to be 3.613 The interventions are more efficient if they target recent PWID (<5 years of injection)
Martin *et al.* [20]	United Kingdom	To estimate the cost–effectiveness of HCV therapy among PWID	Compartmental model/ deterministic differential equations	Treating active injectors and noninjectors is cost–effective, but if HCV chronic prevalence is below 60%, it is more cost–effective to treat active injectors
Durier *et al.* [25]	Vietnam	To estimate the preventive effect of HCV therapy, methadone maintenance therapy and needle/ syringe exchange programmes in a developing country context	Compartmental model/ deterministic differential equations	Even a low level of treatment (25%; 4 years into infection) has a significant impact on chronic prevalence (reduction >21% after 11 years) Adding needle/syringe exchange programmes 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.* [22]	United Kingdom	To investigate the impact of scaling-up opiate substitution therapy (OST) and high-coverage needle and syringe programmes on HCV chronic prevalence	Compartmental model/ deterministic differential equations	Scaling-up opiate substitution therapy and needle sharing programmes can reduce hepatitis C chronic prevalence among PWID, but reductions may be modest and require long-term sustained intervention coverage: in the United Kingdom, to reduce the chronic prevalence from 40% to <30% over 10 years needs a coverage ≥80%)
Hellard *et al.* [34]	Australia	To estimate the effect of HCV treatment on HCV chronic prevalence among PWID	Compartmental model/ deterministic differential equations	Modest rates of current HCV treatment among PWID in Victoria, Australia (25 per 1000 PWID), could halve HCV chronic prevalence in 30 years
De Vos *et al.* [42]	the Netherlands	To understand the dynamics of HCV and HIV infection among PWID	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.* [41]	the Netherlands	To understand the effect of HRP on the decline in the incidence of HCV and HIV among PWID since 1990	Individual-based model/ stochastic approach	It is difficult to reproduce realistic behaviour of epidemics without HRP; however, most of the decline can be explained by demographic changes
De Vos *et al.* [40]	the Netherlands	To estimate the effectiveness of targeted intervention on HIV and HCV among PWID	Compartmental model/ deterministic differential equations	HRP are most effective towards 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,

(continued)

Table 1 *(continued)*

Reference	Country (setting)	Objectives	Model/Approach	Main results
				while this is not the case for HIV (low prevalence due to lower force of infection)
Vickerman *et al.* [45]	United Kingdom	To understand the link between HIV/HCV co-infections and the HIV sexual transmission rate in a population of PWID	Compartmental model/ deterministic differential equations	To reproduce the realistic seroprevalence of HCV among HIV-infected PWID, it is necessary to include sexual transmission Moreover, the level of co-infection seems to be a marker of HIV sexual transmission among PWID
Martin *et al.* [43]	United Kingdom Australia Canada	To estimate the effectiveness of future direct-acting antivirals on HCV chronic prevalence among PWID in three different settings (Edinburgh, Melbourne and Vancouver)	Compartmental model/ deterministic differential equations	The impact will be limited by current treatment coverage To halve the chronic prevalence of HCV within 15 years, the cost would be high, especially in Melbourne and Vancouver (~$50 million), where the chronic prevalence is highest
Corson *et al.* [46]	United Kingdom	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 eight 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.* [47]	United Kingdom	To estimate the cost–effectiveness of HCV case findings for PWID 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 becomes effective in prison
Martin *et al.* [48]	United Kingdom	To estimate the impact of combining opiate substitution therapy, high-coverage needle and syringe exchange programmes and HCV treatment on chronic prevalence and incidence	Compartmental model/ deterministic differential equations	HCV treatment is necessary to achieve a large reduction (>45%) in HCV chronic prevalence over 10 years. Opiate substitution therapy, high-coverage needle and syringe exchange programmes and new direct-acting antivirals should reduce the number of necessary treatments
Elbasha [49]	USA	To assess the impact of treatment on transmission of HCV in a PWID 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

(continued)

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Table 1 *(continued)*

Reference	Country (setting)	Objectives	Model/Approach	Main results
Rolls *et al.* [50]	Australia	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 network properties on incidence rates of primary infections and reinfections	Individual-based model on a simulated contact network of PWID/ 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 PWID and treat their contact are most effective and reduce the number of treatments needed to achieve a desired effect

HCV, hepatitis C virus; HRP, harm reduction policies; PWID, people who inject drugs; QALY, quality-adjusted life year.

among individuals. Thus, this approach takes into account the randomness of durations of the different health stages in the population. At each event, the transition that occurs is determined by probabilities induced by the global transition rates. When dealing with large populations, averaging of randomness leads to deterministic evolutions that can be described by ordinary differential equations [54]. For further explanation about the advantages and weakness of these two approaches, the reader can refer to Ball [55].

COMPARTMENTAL MODELS

Description

Compartmental models were the most frequently used class of models for HCV epidemic simulation among PWID with 31 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. [54–56]. Transitions from one state to another were based on rates that could be time dependent.

For instance, Fig. 2 presents a model we have recently developed for HCV transmission in PWID [57]. The population is distributed in eight compartments associated with HCV infection and care status. Susceptible PWID are separated into two categories: new and experienced injectors, as recently initiated injectors are at higher risk of infection [58]. When infected, they progress to acute hepatitis that can lead either to spontaneous recovery (and PWID become susceptible again) or to undiagnosed chronic hepatitis C. Infected patients could be diagnosed, and progress to diagnosed and nonlinked to care hepatitis C stages. They are then linked to care and lost to follow-up, or treated. When treated, patients may respond to treatment and return to a susceptible state, or not respond and progress to a non-SVR state. Transitions between different compartments or states are governed by annual transition rates that may be time dependent. For example, rates of infection depend on the current proportion of infected PWID in the population.

Other published models include more compartments or less compartments according to the objectives and available data. The most parsimonious models include only two compartments: susceptible and infectious [28,33,37–39]. Some authors included in their model the uncertain immunization [59] of previously infected PWID against re-infection [18,19,21,24,35,45]. Durier *et al.* [25] differentiated symptomatic and asymptomatic acute infection. Esposito *et al.* [29] and Cipriano *et al.* added compartments to model the use of intravenous drugs as an epidemic linked to the HCV epidemic. Martin *et al.* took into account the possibility of imprisonment. Additional compartments can

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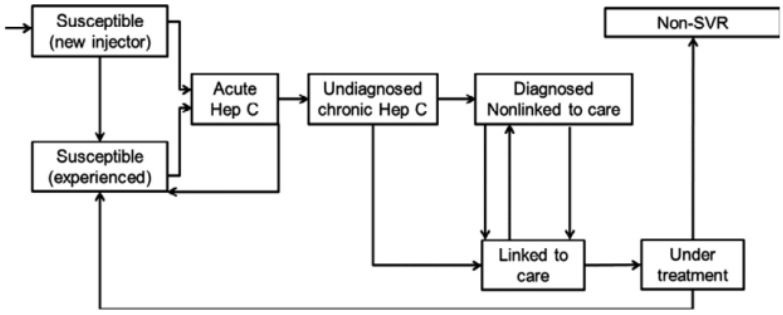

Fig. 2 Schematic representation of a compartmental model for the transmission of HCV in people who inject drugs (PWID) [57]. The model takes into account infectious status, acute hepatitis C, testing, linkage to care, loss to follow-up and treatment. We distinguished recently between initiated PWID and experienced PWID because of their different risk of infection [58]. Reinfections are possible, but no retreatment is allowed in the model. Transitions occur between the compartments at transition rates that can depend on time: the infection rate depends on the current number of infected PWID in the population.

allow including substitution therapies [27,47,48]. Finally, to estimate the cost of the infection or the consequences of HCV infection on the population's health, some authors included additional compartments of natural history of chronic hepatitis C [20,52].

Strengths and limits

Compartmental models have the advantage of not needing intensive computation time. In large populations, the trajectory of the epidemics can be described by a system of ordinary differential equations [55]. However, they are based on two important hypotheses.

First, the population of a compartment is supposed to be *homogeneous*. The only characteristic of an individual is the compartment in which he/she is located. Thus, parameters that define an individual are parameters that are derived from the overall population; they can be easily interpreted in terms of epidemiology and obtained from epidemiological studies. This is not necessarily the case for IBMs (see below). For example, the infection rate represents the force of infection in the population, for which estimations are available for HCV among PWID [58]. However, the PWID populations are highly heterogeneous. There is a variability of individual characteristics and behaviours, which can impact the risk of infection by HCV or HCV-infected patient care. Indeed, the high variations of infection risk among PWID are due to differences in injection frequency, numbers of syringe sharing and number of sharing partners [60]. Moreover, response rates to HCV treatment are different according to HCV genotypes. With a pegylated interferon + ribavirin regimen, SVR is around 75 for naïve patients infected with genotypes 2 or 3; and around 50% for naïve patients infected with genotype 1 [8–12]. One may hypothesize that this could lead to the selection of hard-to-treat genotypes and thus to a large proportion of prevalent cases infected with genotype 1. For simplicity, most of the published models do not differentiate genotypes and consider only an average duration of treatment and SVR rate in the population. The Cipriano *et al.* [52] study represents an exception, differentiating genotypes 1/4 from genotypes 2/3. Nevertheless, with the availability of highly effective pan-genotypic anti-HCV regimens not differentiating genotypes will no more be a problem. Some other characteristics are known to impact HCV transmission or treatment success: time since first injection, as the risk of transmission is higher in recent frequent injectors [58]; substitution therapy with reduced risk of transmission from those who receive substitution [61]; gender, as the spontaneous recovery rate is higher in women [62]; HIV–HCV co-infection, associated with lower treatment success [63]; imprisonment, as a history of injection in prison increases the risk of infection [64]; and even genetic characteristics, with the IL28B polymorphism impacting the treatment response [65]. Stratification of the population into different risk groups is a solution for relaxing the hypothesis of homogeneity of PWID [21–25,27,29,36,40–45]. Vickerman *et al.* [21–23] considered three levels of risk corresponding to no syringe sharing, low- and high-frequency syringe sharing. Corson *et al.* [36] structured their population by experience at injection: recent injectors were more likely to be infected than experienced injectors. Zeiler *et al.* [27] aimed at estimating the impact of methadone maintenance programmes and structured their population by methadone intake. However, stratification of the population is equivalent to introducing different compartments for each group, which can make the model highly complex. For example, the model by Cipriano *et al.* [52] has 756 compartments. Such models attempt to estimate much parameters, and data about PWID are often scarce due to the difficulty to reach this population by epidemiological studies.

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Secondly, the infection rate is often 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: in classical models, the infection rate per susceptible individual $\beta I(t)$ increases with the number of infected persons in the population. This hypothesis seems to be poorly suited for describing infectious contacts with a blood-borne pathogen among PWID. Indeed, it has been shown that PWID share their injection material with a restricted group of injection partners. Wylie *et al.* [60] found that PWID in Canada have few other PWID in their individual network: a median of 3.5 was found for a period of 30 days. Brewer *et al.* [66] 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 PWID in Seattle. Sacks-Davis *et al.* [67] reported, in Melbourne, a median number of three injection partners/Injecting drug user (IDU), with a median duration of 3 years for a partnership, and they found that HCV phylogeny was associated with the injection network. These results suggest that the number of potential infectious contacts is restricted to a small group for each infected PWID, which slows the transmission of the virus in the population. However, they are based on a snapshot and give no indication at a lifetime scale. In addition, Hahn *et al.* [30] suggest that because of the high number of injecting partners, the turnover of the injecting partners may be sufficiently high to consider that a totally mixed population is a valid hypothesis. An alternative approach chosen by several authors to relax this hypothesis in compartmental models is to include *assortative mixing*: they varied the mixing of the different risk groups. Fourteen articles in the present review among the 31 compartmental models took into account assortative mixing in the population according to risk groups [21–24,40,42–45,48], substitution therapies [25,27], experience as injector [46] or age [47]. However, this solution does not enable taking into account small subgroups at the individual or community scale (injecting partners groups), but only groups at a population scale.

INDIVIDUAL-BASED MODELS

Description

In 2001, Pollack already underlined that, while a simple model enables obtaining several important results, a homogeneous totally mixed population implies biases in the estimation of the effectiveness of HRP and does not assess effectiveness of targeting interventions [37–39]. A possibility to overcome these hypotheses is the use of IBMs. IBMs simulate the patients' trajectories 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 depend [68–70].

For HCV epidemic modelling among PWID, only a few authors have used IBMs. Mather *et al.* [51] considered a model taking into account isolated groups of individuals with possible immunization of individuals. De Vos *et al.* [41] 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. Hahn *et al.* [30] developed an IBM to take into account different behaviours and levels of risk exposure in the population. The authors distinguished two practices at risk: 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). Hutchinson *et al.* and Rolls *et al.* presented IBMs that took into account the social network of the population (see below) [26,31,50].

Modelling contact network

The network of contacts can be represented by a graph, that is a set of vertices representing individuals, and interconnected by a set of edges representing potentially infectious contacts between them (see example Fig. 3).

Various network models have been described in the literature ([71] and therein). The choice of these models depends on the expected characteristics of the network. Some simple graphs which are easily implemented have

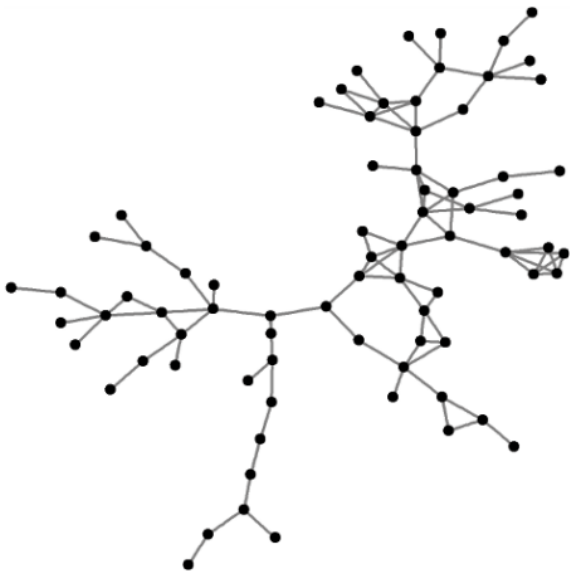

Fig. 3 Main component of an empirical network of people who inject drugs (PWID) in Melbourne from Rolls ***et al.*** [31]. Each node represents a PWID, and a tie is drawn between the injecting partners in the previous 3 months. Data courtesy of DA Rolls.

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unrealistic characteristics and neglect major aspects of the network structure, when focusing on the case of the PWID social networks. They are often based only on individual information such as the degree, that 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 [72,73]. Following this distribution, a degree is attributed to each member of the population, by giving half-edges to each individual. The half-edges are then connected to others at random.

Local information, for example the degree, can be obtained relatively easily using traditional epidemiological studies, by requesting the number of sharing partners or injection partners for each participant. More complex models such as *intersection graph models* [74–75], *household graph models* [76–77] and *stochastic block models* [78] have been proposed to reproduce characteristics of real networks, such as transitivity. The transitivity reflects the preferential association of two persons if they have a common relationship: two individuals are more likely to be friends if they have a common friend. In terms of the graph, this results in a large number of triangles in the network. These models 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 only provides information about the neighbourhood 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.* [79] to study the network of a population of PWID in New York City. In such surveys, new participants are recruited by previous participants among partners. The final result is a subgraph of the population's network.

In the case of HCV in PWID, Hutchinson *et al.* [26] used a configuration model. The number of partners for the PWID was generated by a geometric probability distribution with parameter $p \in (0,1)$, that is $P(X_i = k) = (1 - p)^{k-1}p$. This distribution was suggested by data on the distribution of degree in a population of PWID in Glasgow at the beginning of the 1990s. Rolls *et al.* [31] applied an IBM to a real network of 258 PWID in Melbourne, obtained using *chain-referral sampling*. This approach enabled the authors to obtain a very realistic network structure [80]. However, it was limited to a small sample due to the difficulty in tracing the contact network of different PWID. They compared results of their model with the empirical network and with a fully connected network (equivalent to the totally mixed hypothesis of compartmental models). 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. In more recent papers, they calibrated an exponential random graph model (ERGM) on these data [50,80]. ERGMs are statistical models aiming to reproduce some characteristics of the initial network (i.e. the number of edges, isolates, triangles, in particular). The ERGM used by Rolls *et al.* is based on the research of homophily in the network, which is the preferential attachment between PWID due to their similar characteristics: location, gender, age, frequency of drug use. This is an important part of the social component of the network.

Another research question in PWID is the dynamic of the network. Indeed, in a real population of PWID, the contact pattern may change: the identities of the different sharing partners change over time as relationships between PWID evolve [26]. A static network model, with identities of sharing partners fixed over time, may miss a crucial aspect of the social network. It 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 [81]. For HIV epidemics on sexual contact, the dynamic of the sexual partnership network has been proved to impact the epidemic trajectory [82–84]. For HCV in PWID, it is an open question. Only Hutchinson *et al.* have used a dynamic network model with a turnover of sharing partners for each individual each year. Two variants of turnover were tested: a turnover totally at random and a turnover with some stability in injecting partner groups, with few differences between the results in these two settings. These dynamic models are however not supported by data.

From another point of view, Hahn *et al.* [30] suggest that because of a high dynamic in the contact network, the population can be modelled as static and totally mixed. There is no evidence about this affirmation because it is only supported by the high number of reported injecting partners.

Further investigations should be conducted to clarify the necessity of dynamic models. Of note, Sacks-Davis *et al.* [67] reported in Melbourne a median number of three injection partners/IDU, with a median duration of 3 years for a partnership, suggesting a relative stability of the network.

MAIN RESULTS OF THE REVIEWED PAPERS

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

Vaccination

The potential effect of vaccination against HCV was evaluated in three articles. Mather *et al.* [51] showed that even immunizing half the population with a vaccine which has an 80% efficacy slows the spread of the infection in an Australian PWID population. For Dontwi *et al.* [32],

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potential vaccination must be carried out early and should cover a large portion of the population (>80%) so as to reduce the force of infection. Hahn *et al.* [30] tested scenarios that specifically target certain individuals in a population of PWID in USA. 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 programme in the USA [37–39]. His results suggested that, while such a programme may have an impact and could potentially eradicate the infection, the cost quickly becomes prohibitive for highly transmissible infections such as HCV (>250.000$ per averted infection). However, he suggested that the association of this programme 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 programmes. He stated that for HCV, a combination of different strategies is necessary to impact HCV transmission [39]. However, he underlined that the absence of heterogeneous behaviour and the totally mixed hypothesis could impact the results. Vickerman *et al.* [24] also found that widespread sustained coverage of syringe exchange in the population (reduction >40% of needle/syringe sharing) is necessary to obtain a significant reduction in prevalence after 10 years in Rawalpindi, Pakistan.

Hutchinson *et al.* [26] estimated the impact of HRP on HCV transmission, by varying the percentage of PWID who had shared per year, the mean number of needle/sharing partners and the percentage of injecting episodes. For the period 1988–2000, they estimated that 4500 infections would have been prevented in Glasgow with HRP. They also found that reducing the mean number of partners to one (*vs* between two and three partners in the baseline scenario) might prevent 5300 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 (5200 infections prevented): only 11–20% of PWID should be able to share a needle/syringe during that period.

Some authors suggested that the target of these interventions could be optimized. Vickerman *et al.* [21] suggested targeting recent injectors not reached by HRP and not already infected in the United Kingdom to reduce syringe sharing in this particular part of the population. They found that a significant reduction in seroprevalence could occur among recent PWID (<4 years) with a reduction in sharing frequency <25%, although among experienced PWID (>8 years), similar results would only occur with a reduction >50%. Similarly, Corson *et al.* [36] suggested that interventions in Scotland are most efficient during the first 5 years of the injecting career. Esposito *et al.* [29] in Italy showed a delay of 1 year between the peak of drug use and the peak of prevalence for HCV, suggesting also that interventions should occur early during the injecting drug career to impact HCV transmission.

In the context of limited resources, De Vos *et al.* [41] suggested that PWID at low risk (i.e. less frequent syringe sharing) should be targets for HRP (aiming at reducing the syringe sharing rate) so as to maximize their impact. 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 PWID population primarily explained the decrease.

Impact of harm reduction strategies on HIV and HCV infection among people who inject drugs

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 [28,39]. Vickerman *et al.* [23] estimated that reducing the injection risk by 30% would result in a reduction in the incidence/seroprevalence of 50%/28% for HIV and 37%/10% for HCV after 5 years in a population of PWID in the United Kingdom. De Vos *et al.* [42] found similar results. Murray *et al.* [33] 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 three partners/year for HCV in an Australian setting. They estimated the actual number of partners to be intermediate (≈6), which explains the success obtained against HIV and more questionable results for HCV. Bayoumi *et al.* [53] estimated the effectiveness and cost–effectiveness of supervised injection facilities in Vancouver. Their results suggest between $14 and $18 million gained and between 920 and 1175 life years saved after 10 years. However, the authors underlined that the cost saving is mainly due to HIV infections averted.

Hepatitis C virus treatment

The impact of HCV treatment on transmission is considered to be effective despite the risk of reinfection [17,19,25,34]. Some authors recommended specific targets and application modalities. Zeiler *et al.* [27] studied the impact of HCV treatment in Australia, taking into account methadone maintenance therapy. The main concern of that paper was to determine the optimal distribution of treatment in the population. The results suggested treating active PWID rather than PWID under methadone maintenance therapy, with the hypothesis of equal adherence to treatment in the

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two groups. The conclusion would be reversed only if adherence by active PWID was <44% of that of PWID under methadone maintenance therapy. Also in Australia, Hellard *et al.* [34] found that even a modest annual rate of treatment (25/1000 PWID) could have an impact on long-term HCV chronic prevalence (50% decrease after 30 years). Martin *et al.* [19] found similar results for the United Kingdom: for a baseline chronic prevalence of 20%, 40% and 60%, an annual treatment rate of 10/1000 PWID would achieve a reduction in chronic prevalence of 31%, 13% and 7%, respectively, after 10 years. Durier *et al.* [25], in Vietnam (with few HRP), found similar results. They estimated a strategy of treatment as prevention and suggested treating early (during the first year) to avoid a maximum of infections.

Martin *et al.* [20] estimated the cost–effectiveness of HCV treatment in the United Kingdom. Their results showed that treating active PWID and ex- or non-PWID was cost–effective, but for a chronic prevalence below 60%, treating active PWID was more cost–effective because of avoided re-infection. This result remained valid even with a SVR rate in active PWID that was 50% lower than that of ex- or non-PWID (which may reflect lower adherence to treatment).

Martin *et al.* [43] estimated the impact of a direct-acting antiviral, with treatment of shorter duration and with a higher tolerability. They compared efficiency and cost in three different geographic settings: Edinburgh, Melbourne and Vancouver. The study showed that halving the chronic prevalence after 15 years would be extremely expensive, particularly in Melbourne and Vancouver (around $50 million) where the chronic prevalence is high.

Finally, in Australia, Rolls *et al.* [50] targeted infected individual for treatment initiation according to their neighbours on the social network, with strategies including random treatment delivery, priority by node degree, treatment of the primary contacts of infected nodes, treatment of primary and secondary contacts of infected nodes, and treatment of treatment of the primary contact of uninfected nodes. They found that strategies including the treatment of primary and secondary contacts of some infected PWID randomly chosen for treatment ('ring' treatment) are the most effective for a similar number of treatment starts.

CONCLUSION

To date, several different models have been used to study transmission of HCV among PWID. Most of them were built to answer a specific question taking into account only the characteristics of PWID that pertained to that question, and thus averaging the nonrelevant 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 PWID (recent injectors, active PWID or PWID 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 programmes, substitution therapy), screening and treatment (efficacy of new treatments). Mathematical modelling can enable evaluating the cost associated with those different strategies and guiding optimal resource allocation.

Most models are compartmental and rely on strong assumptions. An individual-based approach could be an interesting alternative allowing, for example, to estimate the impact of strategies based on PWID characteristics and social networks. The most advanced research on this topic is that of Rolls *et al.* [50] showing that treatment strategies based on the social network have more impact on transmission than a random treatment distribution. But such studies are still few in numbers. One of the main difficulties lies in the lack of data for first calibrating and next to be used in the model. Data are difficult to obtain in particular regarding the risk of HCV transmission during an exchange, the frequency of material sharing, and social networks and their dynamics over time. As pointed out by Kretzschmar *et al.* [85], the construction of such models therefore requires multidisciplinary collaboration that includes clinical (transmission risk, treatment efficacy), epidemiological (current state of infection, screening, treatment), mathematical (modelling) and sociological (social network characteristics among PWID) components.

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STATEMENT OF INTERESTS

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3 Evaluation de l'impact d'une stratégie de « Treatment as Prevention » sur la transmission du VHC et la morbi-mortalité chez les UDI de la région parisienne

3.1 Résumé

Malgré l'accès au matériel d'injection stérile et aux TSO, la prévalence de l'infection chronique par le VHC chez les UDI reste élevée en France au début des années 2010, à environ 65% chez les injecteurs actifs dans le dernier mois (enquête ANRS-Coquelicot, données non-publiées). Avec l'arrivée des nouveaux AAD, plus efficaces et mieux tolérés que les traitements par la bithérapie peg-interféron/ribavirine, s'est posée la question de l'intérêt du traitement comme moyen de prévenir la transmission du VHC dans la population. Cette stratégie, dénommée « Treatment as Prevention » (ou TasP) repose sur l'idée qu'en traitant les malades rapidement après leur infection, on peut empêcher la transmission du VHC à leurs partenaires d'injection, les individus ne transmettant plus le virus après une RVS. L'efficacité de cette approche dépend de la cascade de soins de l'hépatite C chronique : le dépistage, les liens avec le système de soins et les critères d'initiation du traitement doivent permettre de traiter le plus rapidement possible ; et l'adhérence au traitement doit être optimisée afin d'obtenir le meilleur taux de RVS possible.

L'objectif de cette étude était d'évaluer, dans la population d'UDI en Île-de-France, l'impact d'améliorations dans la cascade de soins de l'hépatite C chronique sur la transmission de la maladie dans la population et la morbidité/mortalité associée.

Pour cela, nous avons développé un modèle dynamique de transmission du VHC chez les UDI. Il s'agit d'un modèle individu-centré à trois niveaux :

Niveau 1 : infection par le VHC et la cascade de soins de l'hépatite C chronique (dépistage, lien aux soins et perte de vue par le système de soins, initiation du traitement et adhérence au traitement)

Niveau 2 : histoire naturelle de l'hépatite C chronique. Cette partie du modèle détaille la progression de la fibrose hépatique chez les infectés, cette progression étant quantifié par le score Métavir de F0 à F4 (avec F4 la cirrhose). Deux complications de la cirrhose peuvent ensuite survenir : la décompensation de la cirrhose et le CHC, qui peuvent elles-mêmes conduire au décès.

Niveau 3 : le réseau social de la population UDI. Ce réseau est généré par un modèle de graphe aléatoire. Le modèle utilisé ici est un graphe d'Erdős–Rényi : chaque couple d'UDI est lié avec une probabilité fixe *p*.

Les paramètres nécessaires ont été évalués principalement à partir des résultats de l'enquête ANRS Coquelicot, une enquête de prévalence du VHC chez les utilisateurs de drogues en deux volets (un premier volet en 2004, l'autre en 2011) (Jauffret-Roustide et al. 2006; Jauffret-Roustide et al. 2009) ; ou à partir de la littérature scientifique. Les paramètres manquants ont été estimés par calcul bayesien approché (ABC pour Approximate Bayesian Computation), un algorithme qui permet d'estimer la valeur des paramètres manquants à partir d'informations connues sur la population (Marin et al. 2012).

Nous avons évalué l'impact de différents scénarios d'amélioration de la cascade de soins sur la prévalence et l'incidence après 10 ans de simulation, et sur le nombre de complications de la cirrhose (décompensation et CHC) évitées après 10 et 40 ans de simulation. Ces scénarios étaient :

Scénario 1 : le scénario de référence, avec la cascade de soins actuelle. Le diagnostic d'hépatite C chronique se fait en moyenne 1.25/1.45 ans après le passage à la chronicité (1.75/1.95 ans après l'infection) pour les injecteurs actifs (i.e. avant cessation de l'injection)/inactifs respectivement ; le lien aux soins 2.6 ans en moyenne après le diagnostic ; le taux de perte de vue est de 14%/an ; le traitement est initié chez les individus liés aux soins et dont le stade de fibrose se situe entre F2 et F4 ; et le taux de RVS au traitement est de 81% (le taux de RVS dans les essais cliniques était d'environ 90% pour les nouveaux AAD au moment de l'étude, mais nous avons diminué ce taux de 10% pour prendre en compte la différence d'adhérence au traitement entre un essai clinique et la « vraie vie »).

Scenario 2 : le scénario de l'amélioration du dépistage. Le diagnostic d'hépatite C chronique se fait en moyenne 6 mois après le passage à la chronicité (vs. 1.25/1.45 ans pour les UDI actifs/inactifs dans le scénario 1), conformément aux recommandations de l'EASL (European Association for the Study of the Liver 2015).

Scénario 3 : le scénario d'une amélioration des liens avec le système de soins. Nous avons supposé ici que le lien aux soins pourrait se faire rapidement après un test positif : 6 mois après celui-ci (vs 2.6 ans dans le scénario 1). De plus, nous avons diminué le taux de perte de vue à 5%/an. (vs. 14%/an dans le scénario 1).

Scénario 4 : la combinaison des scénarios 2 et 3. L'objectif de ce scénario est d'amener les UDI rapidement à une évaluation de l'avancée de leur fibrose hépatique, ce qui leur permet d'accéder au traitement en cas d'éligibilité (score de fibrose compris entre F2 et F4).

Scénario 5 : le scénario d'une amélioration de l'adhérence au traitement. Dans ce scénario, nous avons supposé qu'une amélioration de l'adhérence au traitement chez les UDI pourrait conduire à un taux de RVS similaire à celui obtenus lors des essais cliniques, c'est-à-dire 90% (vs. 81% dans le scénario 1).

Scénario 6 : le scénario d'un accès élargi au traitement. Dans ce scénario, le traitement est initié pour tous les individus avec un score de fibrose compris entre F0 et F4 (vs. F2 à F4 dans le scénario 1).

Scénario 7 : le scénario d'une amélioration de la cascade de soins dans sa globalité. Ce scénario combine les scénarios 4, 5 et 6.

De plus, une analyse de sensibilité déterministe univariée a été effectuée sur le scénario de référence pour estimer l'impact nos résultats de l'incertitude portant sur les estimations des paramètres. Pour cela, nous avons fait varier les valeurs des paramètres dans leur intervalle d'incertitude provenant de la littérature, en utilisant des valeurs provenant d'autres pays, ou dans un intervalle déterminé par des experts. Des analyses complémentaires ont également été faites en simulant l'ensemble des scénarios pour les paramètres présentant une incertitude importante : le nombre moyen de partenaires d'injection et l'incidence initiale des séroconversions. L'impact de variations du taux de réinfections après une RVS a également été évalué.

La prévalence initiale de l'infection chronique dans la population était de 42.8%. Dans le scénario de référence (scénario 1), la prévalence projeté à 10 ans était de 24.9% [intervalle de confiance à 95% : 24.8% ; 24.9%], et l'incidence à 10 ans de 0.84/100 personne-années (p.a) [0.81 ; 0.87]. Une initiation du traitement dès le stade F0 (scénario 6) était le seul moyen d'obtenir une réduction de la prévalence à 10 ans de plus de 2% par rapport au scénario de référence : la prévalence à 10 ans était de 11.6% [11.6% ; 11.7%] et l'incidence de 0.39/100 p.a [0.39-0.41]. Ce scénario n'avait toutefois qu'un impact limité sur le nombre de complications de la cirrhose : -0% [-1% ; +2%] après 10 ans et -7% [-9% ; -5%] après 40 ans. Le scénario combinant des interventions sur toute la cascade de soins (scénario 7) était le plus efficace, avec une prévalence à 10 ans de 7.0% [7.0% ; 7.1%] et une incidence à 10 ans de 0.23/100 p.a [0.22 ; 0.25], et permettait une diminution importante du nombre de complications : -15% [-17% ; -14%] et -29% [-30% ; -28%] après 10 ans et 40 ans respectivement. Ces résultats sont restés valides dans les différentes analyses de sensibilité.

On peut conclure de ces résultats qu'améliorer le dépistage de manière isolée aurait peu d'intérêt en France, celui-ci étant déjà performant par rapport à d'autres pays (Cornberg et al. 2011). Améliorer le lien aux soins ou l'adhérence au traitement aurait un impact modéré sur le nombre de complications de la cirrhose. Restreindre l'accès au traitement uniquement aux stades de fibrose F2 à F4 limiterait l'impact du traitement sur la transmission du virus, en retardant la mise sous traitement d'individus déjà diagnostiqués et liés au système de soins. Ces individus restent alors susceptibles de transmettre le VHC à leurs partenaires d'injection. Traiter dès le stade F0 aurait un impact important sur la transmission du virus, mais n'aurait en revanche qu'un faible impact sur le nombre de complications, car de ce point de vue, retarder le traitement jusqu'à ce que l'UDI ait atteint le stade F2 n'a pas d'importance. Le scénario le plus efficace, et le seul permettant une diminution à la fois de la transmission du virus et de la morbi-mortalité associée au VHC, serait une amélioration de l'ensemble de la cascade de soins. Ce scénario nécessiterait toutefois un nombre important de traitements (environ 4,000 traitements durant les 10 premières années de simulations) et impliquerait donc des coûts élevés. Toutefois, le nombre cumulé de traitements se stabilise rapidement (après 5 ans), contrairement aux autres stratégies, le nombre de patients en attente de traitement chutant rapidement. Mais même avec cette stratégie, une élimination du VHC à moyen terme (définie comme une incidence nulle dans la population après 10 ans) reste improbable.

Les résultats de cette étude ont fait l'objet d'une présentation orale à l'*International Liver Congress 2014, 49th Annual Meeting of the European Association for the Study of the Liver,* à Londres, Royaume-Uni ; et ont fait l'objet d'une publication acceptée à paraitre dans *Hepatology* en 2015.

3.2 Article 2 (accepté, Hepatology)

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HEPATITIS C TREATMENT AS PREVENTION OF VIRAL TRANSMISSION AND LIVER-RELATED MORBIDITY IN PERSONS WHO INJECT DRUGS

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Keywords: dynamic model, HCV elimination, treatment initiation criteria, cascade of care, direct-acting antiviral

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List of abbreviations

HCV: hepatitis C virus

PWID: people who inject drugs

DAA: direct-acting antiviral

SVR: sustained virological response

HCC: hepatocellular carcinoma

LTC: linkage to care

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ABSTRACT

Background: Hepatitis C virus (HCV) seroprevalence remains high in people who inject drug (PWID) populations, often above 60%. Highly effective direct-acting antiviral (DAA) regimens (90% efficacy) are becoming available for HCV treatment. This therapeutic revolution raises the possibility of eliminating HCV from this population. However, for this, an effective cascade of care is required.
Methods: In the context of the available DAA therapies, we used a dynamic individual-based model including a model of the PWID social network to simulate the impact of improved testing, linkage to care, and adherence to treatment, and of modified treatment recommendation on the transmission and on the morbidity of HCV in PWID in France.
Results: Under the current incidence and cascade of care, with treatment initiated at fibrosis stage ≥F2, the HCV prevalence decreased from 42.8% to 24.9% [95% confidence interval 24.8%–24.9%] after 10 years. Changing treatment initiation criteria to treat from F0 was the only intervention leading to a substantial additional decrease in the prevalence, which fell to 11.6% [11.6%–11.7%] at 10 years. Combining this change with improved testing, linkage to care, and adherence to treatment decreased HCV prevalence to 7.0% [7.0%–7.1%] at 10 years and avoided 15% [14%-17%] and 29% [28%–30%] of cirrhosis complications over 10 and 40 years respectively.
Conclusion: Major decreases in prevalent HCV infections occur only when treatment is initiated at early stages of fibrosis, suggesting that systematic treatment in PWID, where incidence remains high, would be beneficial. However, elimination within the 10 next years will be difficult to achieve using treatment alone, even with a highly improved cascade of care.

INTRODUCTION

Hepatitis C Virus (HCV) is responsible for more than 350,000 deaths every year worldwide worldwide (1). In high income countries, the main HCV transmission route is injection drug use (2, 3). In these countries, despite the introduction since the 80s of harm reduction measures, HCV prevalence among people who inject drugs (PWID) remains high, often above 60% (3).

Until recently, HCV treatment standard of care was a dual therapy combining peg-interferon and ribavirin that was moderately effective and with a high proportion of adverse events (4, 5). New direct-acting antiviral (DAA) based interferon-free regimens, associated with higher sustained virological response (SVR) rates, better tolerance profiles, and shorter durations are now available (6-11). These therapeutic improvements raise the question of using HCV treatment as a mean of preventing HCV transmission in PWID, and, in the longer-term of possibly eliminating the virus. However, the effectiveness of this strategy depends on several factors: time to diagnosis, patients' linkage to care, and treatment initiation criteria to achieve early treatment initiation; and adherence treatment, to achieve a high SVR rate.

Evaluating the impact of incoming treatments or improvements in the cascade of care on transmission in PWID through traditional epidemiological studies faces issues related to feasibility and costs. Dynamic modeling of HCV transmission in PWID is an interesting alternative allowing us to estimate the impact of various scenarios on the spread of HCV in this population. Numerous models have been proposed in the literature (12). However, most of them did not considered the social network of PWID, which impacts viral transmission (13); and they have often estimated strategies impacting only a specific point in the cascade of care (particularly treatment rate or treatment effectiveness), not the overall cascade.

The aim of this analysis was to estimate, in the context of incoming DAAs regimens, the impact of HCV testing, linkage to care, and treatment efficiency improvement, and of changes in treatment initiation criteria, on HCV transmission and HCV-related morbidity in PWID. For this purpose, we used a dynamic stochastic individual-based model with a social network model of PWID and natural history model of chronic hepatitis C.

METHODS

Here, we present the simulated population, the structure of the model, details of the different scenarios we evaluated, and the sensitivity analyses we performed. Supplementary Information S1 gives more details regarding the parameter values.

Population

We focused on a population with the characteristics of the PWID population in France. We considered that the size of the population was constant at 10,000 PWID – the order of magnitude of the drug user population in the main cities of France (14). Each PWID is characterized by 1) gender, to take into account differences of mortality between men and women (15): the gender of each new PWID is drawn following a probability p_M of being a man; 2) a set of injecting partners: we draw for each PWID a group of other PWID in the population according to a random graph model (see Supplementary Information S1) susceptible of infecting or becoming infected by the index PWID; 3) his/her status relating to injection: current or former injector, i.e. injector after cessation of drug injection; 4) his/her HCV-infection status; 5) if HCV-infected, his/her status regarding HCV infection knowledge and linkage to care, liver fibrosis stage, and treatment. In this analysis we considered HCV infected population in general; we did not explicitly considered HIV/HCV co-infections.

Model

Social network of injecting partners model

One of our objectives was to simulate possible pathways of HCV transmission in PWID. HCV is mainly transmitted by needles/syringes sharing in the PWID population; however paraphernalia sharing (e.g. filter, spoon) seems to play an important role too (16). To take into account the global risk of infection for a PWID, we chose, as previously described by Rolls *et al.*, to model the network of the injecting partners: two PWID are linked together if they inject together even without sharing needles/syringes (13).

The mathematical literature describes numerous models of networks (17). In the case of the injecting partners' network, the choice of a graph model is difficult, because no data are currently available on PWID social networks in France. Therefore, we used an Erdős-Rényi model where each PWID "couple" is linked with a fixed probability p (18). This model is simple to calibrate with only one parameter, which can easily be obtained with field studies: knowing $\bar{d}$, the mean number of injecting partners per PWID (i.e. the *degree*), and N, the size of the population, the parameter of the Erdös-Rényi model is . We assumed a static network, i.e. where there is no change in the links between PWID overtime. In addition, we hypothesized that each PWID who dies would be replaced by a new PWID.

Transmission and care model

We distinguished current injector and former injector. Each new PWID in the population is a current injector, and we attributed each one a duration for their injecting career, drawn from an exponential distribution of mean , where θ is the rate of drug use cessation. Only current injectors can transmit

HCV or be infected with HCV; sexual transmission was not considered, as the incidence rate is approximately one per 190,000 sexual contacts for heterosexual relationships (19).

Figure 1 describes the possible states through which PWID can progress. Briefly, new PWID start in "Susceptible (high risk)" for an average duration of one year, as there is a large amount of data showing that PWID are at higher risk of HCV infection during the first year of their injecting career (20-23). After a time determined by the rate η, they progress to "Susceptible (low risk)" , in which their risk of infection is lower. When Susceptible (high risk) each PWID k may be infected at rate $\beta I(k)$ ($\beta' I(k)$ when Susceptible (low risk)), with β (or β') the infection rate per infected partner, and $I(k)$ the PWID's number of infectious injecting partners. After infection, PWID progress to "Acute hepatitis C", in which they stay for a fixed time T_a. Acute hepatitis C can lead to a spontaneous recovery with a probability p_r, and the PWID returns in S'. Given the length of time between the beginning of the injecting career and the end of the acute hepatitis C, we consider PWID as Susceptible (low risk) after a spontaneous recovery. If spontaneous recovery does not occur, PWID progress from acute to "Undiagnosed chronic hepatitis C" with a probability equal to $1 - p_r$. A chronic hepatitis C is diagnosed at rate δ, which depends on the status of current/former injectors. We neglected the possibilities of diagnosis in acute hepatitis C because of the short and asymptomatic nature of the acute infection. When a PWID is diagnosed, he/she progress to "Diagnosed and non-linked to care chronic hepatitis C". A PWID is considered linked to care if he/she has one or more contact per year regarding his/her HCV-infection with a physician – general practitioner or other – able to refer him/her to a specialist that could initiate an antiviral treatment, i.e an hepatologist or an infectiologist. When a PWID is linked to care with a rate ϕ_{Link}, he/she progress . to "Diagnosed and linked to care chronic hepatitis C". However, he/she can be lost-to-follow at rate ϕ_{Lost}, and in this case the PWID returns to the "Diagnosed and non-linked to care" status. We considered that PWID with cirrhosis complications (i.e. decompensated cirrhosis and/or hepatocellular carcinoma (HCC), see "Natural history" below) are always linked to care because of the severity of their illness.

PWID linked to care and who have a Metavir score between F2 and F4 (see subsection "Natural history model") are immediately treated for chronic hepatitis C, according to French national guidelines in December 2014 (24), and progress to "Under treatment". Treatment has a fixed duration T_t, and can lead to SVR with a probability p_{SVR}: in this case, the PWID returns to the "Susceptible (experimented injector)" state; he/she can be re-infected in the same manner as PWID who have never been infected with HCV. If the PWID does not respond to treatment he/she progress to the "No SVR" state with probability $1 - p_{SVR}$. PWID cannot escape this state, as we did not include the possibility of retreatment for non-responders. A PWID can however be treated several times in case of reinfection after a SVR. The effectiveness of the DAAs in real-life and especially in PWID is not currently available. We therefore broke down p_{SVR} into two variables such as $p_{SVR} = r \times e$, where e is the treatment efficacy observed in clinical trials and r is the ratio of the effectiveness of treatment in real-

life to the efficacy in clinical trials. The inclusion of this ratio in the model allows us to take into account the impact of adherence to treatment in real-life compared with that in a clinical trial.
In each state of our model, we applied a mortality rate for deaths unrelated to HCV infection (i.e. to a cirrhosis complication). This rate, denoted μ, depends on the gender of the injector and the injector's status (current or former injector) (15). Mortality due to hepatitis C was taken into account in the natural history model described below.

Natural history model

The natural history model (Figure 2) describes the liver disease progression in HCV-infected PWID using the Metavir Score (25): F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = portal fibrosis with few septa, F3 = numerous septa without cirrhosis, F4 = cirrhosis. In this analysis we grouped F0 and F1, and F2 and F3 in unique states (F0/F1; F2/F3).
The second part of the model describes cirrhosis complications: decompensated cirrhosis and HCC. In the model, decompensated cirrhosis may progress to HCC. Finally, those complications lead to death related to HCV-infection.
In case of successful treatment, we considered that the PWID fibrosis regresses to F0, except if the patient has already developed cirrhosis (F4) (26). If so, we considered that cirrhosis complications may still occur (26) with the same rate as that with chronic hepatitis C.

Input Parameters

Input parameters were mainly derived from ANRS-Coquelicot study data, which was a HCV-seroprevalence cross-sectional survey conducted among drug users in France (27). The study was conducted in five French large cities selected to represent the diversity of drug addiction in France. Individual were recruited in high and low threshold structures for drug users: harm reduction centers, treatment centers and accommodation structures. Inclusion criteria were: being over 18 years old and having injected or snorted drug at least once during the lifetime, but due to our study population we estimated the parameters among injectors only, and among active injectors (i.e. injecting during the last month) when relevant. Other parameters were estimated from the medical literature using preferentially local data when available. Missing parameters were fitted by Approximate Bayesian Computation (see Supplementary Information S2) (28).
Supplementary Information S1, Table S1 gives a summary of parameters and their default values.

Tested scenarios

We simulated 7 scenarios, corresponding to different testing rates, linkage to care and loss to follow-up rates, treatment initiation criteria or SVR rates (see Table 1).

Scenario 1 (reference scenario) is the scenario with the parameter values presented in Table S1 in Supplementary Information, corresponding to the current cascade of care in the French PWID population. In the baseline analysis, for the nature of HCV treatment, we considered that patients received DAAs-based regimens. SVR for these regimens are estimated at e=90% in clinical trials and treatment duration at T_t=12 weeks (6-11). However, we decreased the efficacy rate of these treatments since they were derived from clinical trials in mostly non-IDUs population. To make these modifications, we applied the coefficient r derived from the ratio of the SVR in real life to the SVR in clinical trials for peg-interferon + ribavirin (r=0.903) (29).

Scenario 2 is scenario 1 with an improved testing rate. The mean time between the end of the acute hepatitis C phase and testing () is considered to be 0.5 years for all individuals (vs. 1.25/1.45 years for current/former PWID under scenario 1), to be in line with the EASL recommendations (30).

Scenario 3 is the same as scenario 1 with improved linkage to and retention in care: PWID are linked to care after an average duration of 0.5 years (vs. 2.6 years in scenario 1) and the loss to follow-up rate is 5%/year (vs. 13.8%/year in scenario 1).

Scenario 4 is a combination of scenarios 2 and 3 (improved testing, linkage to and retention in care).

Scenario 5 is scenario 1 with improved adherence to treatment. We considered that a better adherence could lead to a SVR rate similar to that of clinical trials, i.e.; r=1 (vs. 0.903 in scenario 1).

Scenario 6 is scenario 1 with changes in treatment initiation criteria. All PWID who are tested, linked to care and who have no complications of cirrhosis are treated, regardless of fibrosis stage.

Scenario 7 is the combination of scenarios 4, 5 and 6: improved testing, linkage to and retention in care; earlier treatment initiation criteria; and better adherence to treatment.

Implementation of the model and outcomes

For each scenario or sensitivity analysis, we performed 1,000 simulations. To ensure that results are comparable and to avoid the influence of the randomness in the network or population structure, we matched the simulations: each scenario was simulated on the same 1,000 simulated networks and PWID populations.

The impact of the scenarios on the prevalence and the incidence at 10 years, and on the difference in the number of new complications of cirrhosis in the population after 10 and 40 years was calculated and compared to the reference scenario. This time horizon for the number of cirrhosis complications was chosen because of the long delay before the occurrence of the complications in HCV infections. In addition, given the current high costs associated with new DAAs and questions regarding the feasibility of treating patients without any restriction on their fibrosis stages severity, the cumulative number of treatments initiated was estimated for each scenario as a measure of the resource needed and budgetary impact. The average number of infections avoided after 10 years was also estimated.

Sensitivity analysis

We first performed a global deterministic sensitivity analysis to determine the parameters that have the most important impact under the reference scenario on the outcomes. We varied the values of the following parameters over the range of their uncertainty intervals, using data from other high income countries, or using estimates from expert opinion: the infection rates β', the relative risk of infection when Susceptible (high risk), the testing rate δ, and the linkage to care rate and lost to follow-up rate ϕ_{Link} and ϕ_{Lost}, the transitions rates of the natural history model, and the initial distribution in the natural history model (Supplementary Information S5, Table S4).

We also performed specific sensitivity analysis about the parameters where uncertainty was important. First, when the parameter's estimate was uncertain because of the data source: the average number of injecting partners, which was fixed at 6 by hypothesis according to limited information from other countries (see Supplementary Information S1, Table S1). We also varied the values of the parameter for which the situation could change – or had already changed – compared to our estimates: the infection rate β', as some evidence from different French sociological surveys show an increase in at-risk practices among PWID in France in recent years; the risk of reinfection after a SVR to assess the impact of possible increase in reinfections with the arrival of highly effective and well tolerated treatments; and the risk of reinfection after a spontaneous recovery, which can be higher than the primary infection rate (31, 32). Thus, we estimated the impact of a drop to an average of 3 partners or an increase to an average of 15 partners per PWID; and the impact of increasing the reference infection rate 5 ($\beta' = 0.05$) and 10 times ($\beta' = 0.1$) on all the simulated scenarios. As HCV treatment may not be initiated in a non-negligible proportion of PWID eligible due to medical criteria (e.g. uncontrolled drug consumption or psychiatric disorders) or patient reluctance, we estimated the outcomes of the different scenarios when only 10% of eligible (according to fibrosis stage) PWID effectively initiate a treatment each year (vs. 100% in the base case analysis).

RESULTS

Impact of different interventions on the HCV-prevalence, incidence and related complications

Figure 3 illustrates the impact of different interventions on the HCV infection prevalence and incidence at 10 years, and Figure 4 the impact on the number of complications of cirrhosis over 10 and 40 years. Tables S3 and S4 in Supplementary Information present more details.

The HCV prevalence was set at 42.8% at the beginning of the simulation. With scenario 1 reflecting the current situation of HCV treatment, the mean prevalence decreased to 24.9% [95% confidence interval: 24.8%–24.9%] at 10 years. An improved testing performance (scenario 2) and/or linkage to care (scenario 3 and 4) or an improved adherence to treatment had a small impact on the results. Treating HCV-infected patients at the F0/F1 stage (scenario 6) decreased the prevalence at 10 years to

11.6% [11.6%–11.7%]. Finally, when combining improved testing, linkage to care, and adherence to treatment (scenario 7), we obtained a prevalence of 7.0% [7.0%–7.1%]. Impact on the HCV incidence at 10 years followed comparable trends (see Figure 3).

Compared with the reference scenario (scenario 1), scenario 2, which includes improved testing, had a small impact on the number of cirrhosis complications avoided after 10 and 40 years. Scenario 3, with an improved linkage to care, led to a decrease of 10% [9%–11%] and 12% [10%–13%] over 10 and 40 years respectively. In scenario 5, the improved adherence to treatment led to a decrease of 3% [2%–5%] and 12% [10%–13%]. Treating infected PWID from F0/F1stage in scenario 6 did not have any impact on the number of cirrhosis complications. In scenario 7, with improved testing, linkage to care, adherence to treatment and early treatment the number of cirrhosis complications decrease was at 15% [14%–17%] and 29%; [28%;30%] over 10 and 40 years respectively.

Impact of different strategies on the number of HCV infections

The average number of infections avoided during the first 10 years compared with the reference scenario (Figure 5) were high when treating from F2. In scenario 6, 29% of the infections are avoided, and when combining with improved testing, linkage to care and adherence to treatment in scenario 7, this decrease reached 56%.

Impact of different strategies on the cumulative number of treatments initiated

The average cumulative number of treatment courses initiated during the first 20years (Figure 6) is higher in scenarios 6 and 7, when HCV treatment is initiated early, with 3,978 and 4,066 treatments initiated, respectively, vs. scenarios 1 to 5, when treatment is initiated at liver fibrosis stages >F2, with 2,349 and 2,404 treatments initiated, respectively. In addition, the distribution of the number of treatments initiated over time is different under different scenarios. In scenarios 3, 4, 6, and 7, more treatments were used at the beginning of the simulation period compared to scenarios 1, 2, and 5.

Sensitivity analysis

The detailed results of the deterministic sensitivity analysis of the model under the reference scenario are presented in the tornado diagrams Figure 7. The infection rate per partner, the transition rate between F0/F1 and F2/F3, the linkage to care/lost to follow-up rates are the parameters with the most important impact on HCV prevalence at 10 years, with variations of -3.1% to +4.7%, -2.2% to +2.6%, and -1.5% to +2.7%, respectively. The fourth parameter in order of importance is the average time to diagnosis, with variations of -0.2% to +2.5%. For the incidence at 10 years, the infection rate per partner, the average time to cessation and the relative risk of infection for Susceptibles (high risk) are

the most sensitive parameters with variations of respectively -0.6/100PY to +1.2/100PY, -0.2/100PY to +0.1/100PY and -0.06/100PY to 0.16/100PY. The transition rate between F2/F3 and F4, the initial fibrosis distribution and the linkage to care/loss to follow-up rates are the most sensitive parameters regarding to the cirrhosis complications over 10 years.

In the other sensitivity analyses, results were robust to variations in the average number of injecting partners (3 or 15 vs. 6, see Table S5). When we increased the infection rate (see Figure S2 and S3) to $\beta' \times 5$ to take into account a possible increase in the PWID risk-taking behaviors, prevalence at 10 years was stable in the reference scenario, varying only from 42.8% to 43.7% [43.6%–43.8%] despite DAA use. When we increased the infection rate to $\beta' \times 10$, the prevalence at 10 years increased to 60.5% [60.4%–60.6%]. In these two cases, results were similar than in the base case analysis. When only 10% (Figure S4 in Supplementary Information) of the PWID eligible to treatment effectively initiate the therapy, the results were similar than in the base case analysis, except for the number of complications of cirrhosis avoided after 40 years in scenario 6 (-17% vs -7% in the base case).

DISCUSSION

The proposed model allows comparing different scenarios impacting every step of the cascade of care (testing, linkage to care, treatment) on both the HCV transmission and on the HCV-related morbidity. The results of the simulations showed several important points.

First, improving linkage to care or increasing the SVR rate to match that achieved with new DAAs in clinical trials decreased the number of cirrhosis complications by 10% on average after 40 years compared to the current situation. The benefit is relatively fast when improving linkage to care (10% after 10 years), meanwhile increasing the SVR rate had a more long-term impact. However, changing these parameters only had a small benefit on transmission, and, therefore, on the reduction in HCV prevalence (less than a 2% decrease in prevalence at 10 years). Second, the impact of improved testing was low on both transmission and morbidity despite the highly optimistic value we used in scenario 2. This trend is observed because, in France, HCV testing rate is already high: France has one of the highest rate of infection awareness in Europe (2, 33) with 93.7% of PWID or ex-PWID aware of their infection (34). In the sensitivity analysis, using testing rates observed in the UK, where the time between chronic infection and diagnosis is estimated to be 7.8 years (vs. 1.25/1.45 years in our model), we obtained for example a 10.4% increase of cirrhosis complications after 40 years. Thus, improved HCV testing could lead to a larger benefit in other settings. Third, initiating HCV treatment earlier, at F0/F1 fibrosis stage, had an important impact on prevalence. The impact on morbidity was relatively moderate. From an individual perspective, treating early is not associated with an important benefit because a large proportion of the infected population never develop a liver complication (35). Those who do progress to later HCV fibrosis stages are usually detected and treated before developing

complications using HCV fibrosis monitoring tools. Although, in our analysis we considered that we had perfect tools, which may be an optimistic hypothesis (36). In contrast, from a population perspective, treating patients early does prevent HCV transmission. Finally, improvements in testing, linkage to care, and adherence to treatment in addition to early treatment initiation allowed for a substantial decrease in both HCV transmission and morbidity.

All treatment naïve and experienced patients with compensated or decompensated chronic liver disease related to HCV, who are willing to be treated and who have no contra-indications to treatment, should be considered for therapy. However, because not every HCV-infected patient can be treated within the next year or so (cost and logistical issues), prioritization is necessary (30). In France, the treatment is currently reimbursed only for patients who have reached a moderate to severe liver disease (24). The model shows that if the objective of policy-makers is the elimination of HCV infection, treating PWID from F0, in settings where the incidence remains high, is necessary. However, even in this case, elimination will be difficult to achieve and only important improvements on the cascade of care allowed decreasing the prevalence at 10 years below 10%.

The availability of a highly effective and well-tolerated treatment could potentially cause an increase in risky practices (i.e. needle sharing or some other example), as for HIV, for which the belief about highly active antiretroviral therapy had an impact on sexual risk behaviors, even if sexual behaviors and injection practices are not easily comparable due to different social practices (37). However, in our sensitivity analysis, we showed that our conclusions remained valid with an incidence 5 to 10 times greater than the base case. Since treatment regimens are expensive, the question of reinfection is an important one. In our model, using a re-infection rate per partner 2 times higher after a SVR than the primary infection rate only had a low impact on the prevalence at 10 years, with less than 1% increase.

This study presents several limitations. First, we didn't explicitly considered HIV-coinfections and alcohol consumption, which are two common conditions among PWID (38) that could impact liver fibrosis progression (39). However, in our analysis we used transition rates from (39) estimated specifically for PWID and thus taking into account a part of HIV-coinfected and alcohol consumers in the estimates. Next, the lack of data on the PWID social network in France constrained us to use a network model but with basic properties. The model we used, in particular, shows no community structures (i.e. strongly linked and relatively isolated groups) and neglects the network dynamic (i.e. the network turnover). Further data are needed to build a more sophisticated model. However we still believe that the model used better captures the dynamic of the epidemic than compartmental models (12). We also placed our model in an ideal setting where the treatment regimens are given according to the national recommendations: PWID cannot decide or be told to reject treatment for any reason. In real life, because of the assumed risk of reinfection and poor "compliance" of PWID there is resistance to treatment initiation. As a result, we performed a sensitivity analysis where we showed that overall, our conclusions remained valid when only 10% of eligible PWID were treated annually. Moreover under this scenario, unlike the base case analysis, treatment initiation without restriction on the

severity of the fibrosis may also decrease the number of cirrhosis complications over 40 years. Nevertheless, with the arrival of well-tolerated, injection-free treatments, with shorter durations, one may suppose that the treatment compliance will increase and eligible patients will more frequently receive treatment. Moreover, we hypothesized that there was no retreatment after first treatment failure. We did not account for possible behavioral changes in PWID upon learning their hepatitis status (40), although they could impact the results. In this analysis, we did not limit the number of available treatment slots. Treating patients early (scenarios 6 and 7) sharply increased the cumulative amount of treatment used during the first years, which quickly reached 4,000 treatment courses after a few years, but remained stable thereafter. Given the current high costs associated with new DAAs (between 41,000 and 48,000 euros for a 12-week treatment course in France), budgetary impact will be an important issue especially when we consider treating patients early. In addition to costs, early treatment may have an important logistical and organizational impact for the medical system.
In conclusion we built an individual-based model taking into account the HCV infection, social network, natural history and cascade of care of chronic hepatitis C. We showed that to make the elimination of HCV possible, highly effective treatments are not sufficient in PWID, but an unconditional treatment, ideally associated with an improvement of access to care, is required. Several research pathways are offered by this model. In this context of costly treatment, a cost-effectiveness analysis should be considered in the future. In particular, we should evaluate the cost-effectiveness of strategies targeting PWID in the population according to their social network, that were shown to be more optimal in term of number of treatments needed (41). In addition, harm-reduction strategies such as supervised consumption rooms, improvement of needles/syringes exchange programs or substitution therapies, represent another way to impact the HCV epidemic. HCV treatment and care is not the only efficient strategy to decrease HCV transmission and the impact of these harm-reduction strategies along with treatment should be considered in the future to eliminate HCV infection.

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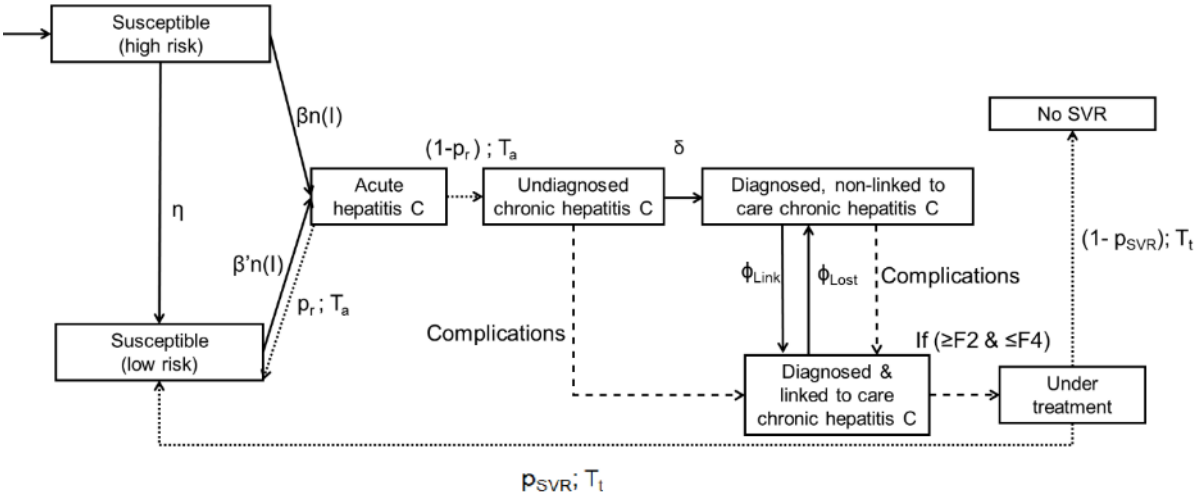


Figure 1 Individual-based model for HCV infection and cascade of care. SVR: sustained virological response. The Greek letters correspond to annual rates and the transitions occur according to exponential laws. n(I) is the number of current infected injecting partners of the PWID. The time spent with acute hepatitis C T_a or on treatment T_t is deterministic. After these compartments, the individual progress to "Undiagnosed chronic hepatitis C" or "Susceptible (high risk)" in acute hepatitis C, and "No SVR" or "Susceptible (low risk)" after the treatment, according to Bernoulli draws of parameter p_r and p_{SVR} respectively. In each state of the model, cessation of injections or death non-related to HCV occurs according to exponential laws.

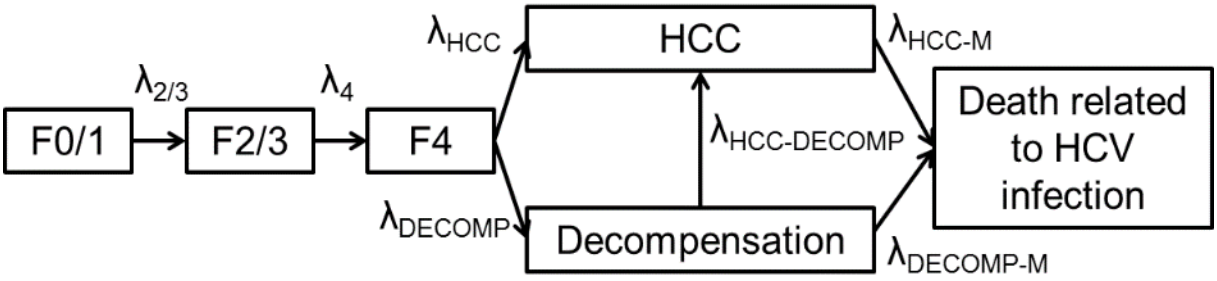


Figure 2 Natural history model for chronic hepatitis C. We grouped Metavir score F0 and F1 (F0/1), and F2 and F3 (F2/3) for simplicity. The transitions times between the different states are drawn in exponential distributions.

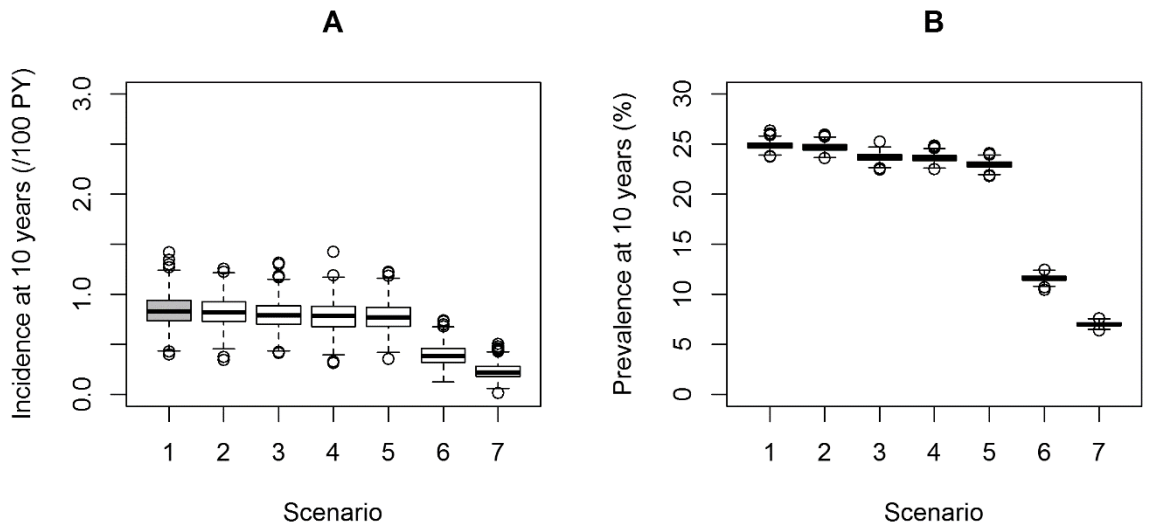


Figure 3 Boxplots of the outcomes of the model according to the different scenarios. A. Prevalence at 10 years; B. Incidence at 10 years. The black line represents the median, the box represents the interquartile range. Whiskers maximum distance is 1.5 times the interquartile range. The scenarios are: 1- Current cascade of care (reference), 2 – Improvement of HCV testing, 3 – Improvement of linkage to care, 4 – Improvement of testing and linkage to care, 5 – Improvement of adherence to treatment, 6 – Treatment initiated from F0, 7 –Improvement of the entire cascade of care (combination of scenarios 4, 5 and 6).

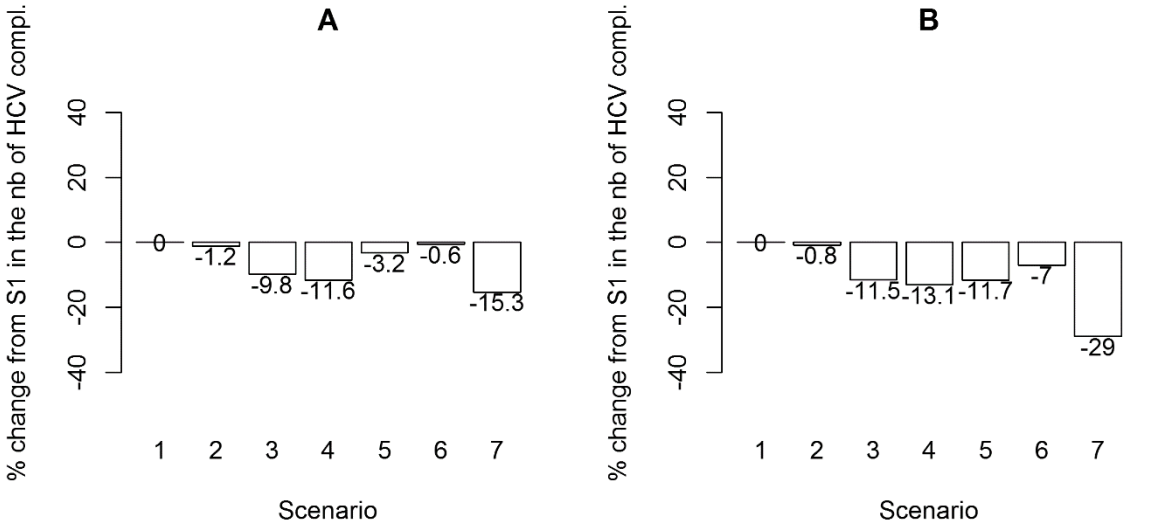


Figure 4 Average percentage of cirrhosis complications avoided over A. 10 years and B. 40 years for each scenario, compared to scenario 1. The scenarios are: 1- Current cascade of care (reference), 2 – Improvement of HCV testing, 3 – Improvement of linkage to care, 4 – Improvement of testing and linkage to care, 5 – Improvement of adherence to treatment, 6 – Treatment initiated from F0, 7 – Improvement of the entire cascade of care (combination of scenarios 4, 5 and 6).

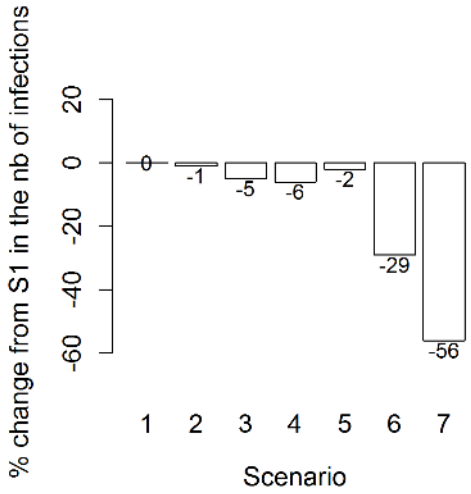


Figure 5 Average number of infections avoided over 10 years for each scenario, compared to scenario 1. The scenarios are: 1- Current cascade of care (reference), 2 – Improvement of HCV testing, 3 – Improvement of linkage to care, 4 – Improvement of testing and linkage to care, 5 – Improvement of adherence to treatment, 6 – Treatment initiated from F0, 7 –Improvement of the entire cascade of care (combination of scenarios 4, 5 and 6).

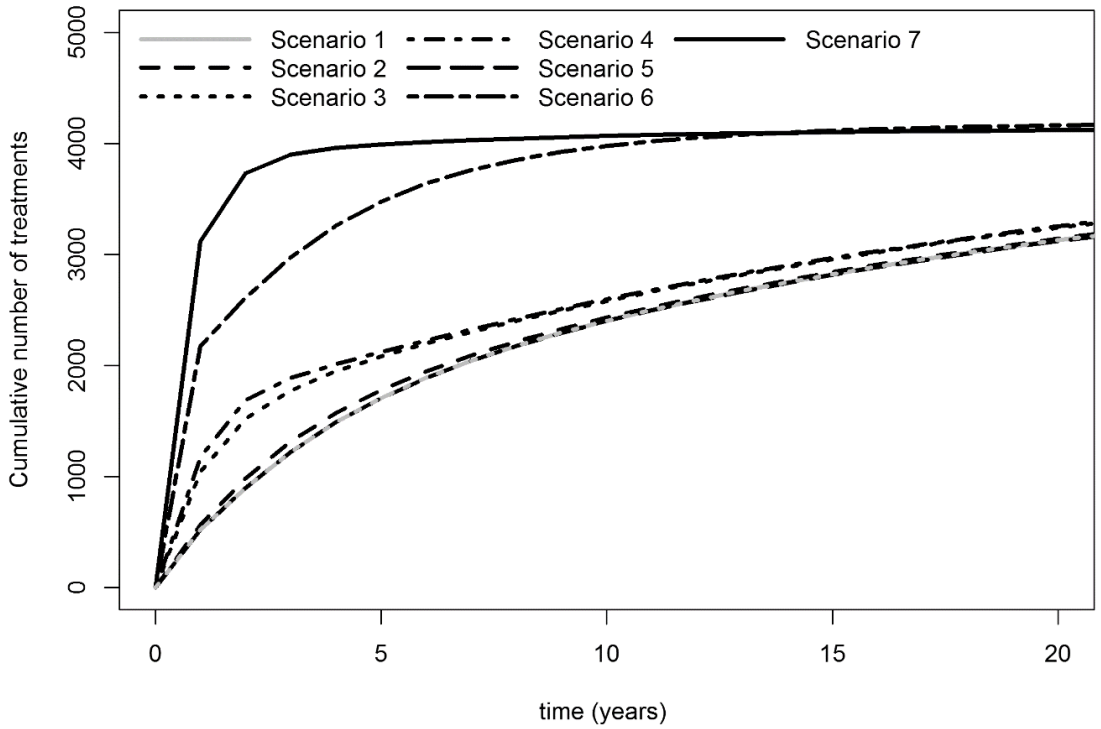


Figure 6 Cumulative number of treatment courses initiated over the 10 years of simulations, for each scenario. The scenarios are: 1- Current cascade of care (reference), 2 – Improvement of HCV testing, 3 – Improvement of linkage to care, 4 – Improvement of testing and linkage to care, 5 – Improvement of adherence to treatment, 6 – Treatment initiated from F0, 7 –Improvement of the entire cascade of care (combination of scenarios 4, 5 and 6).

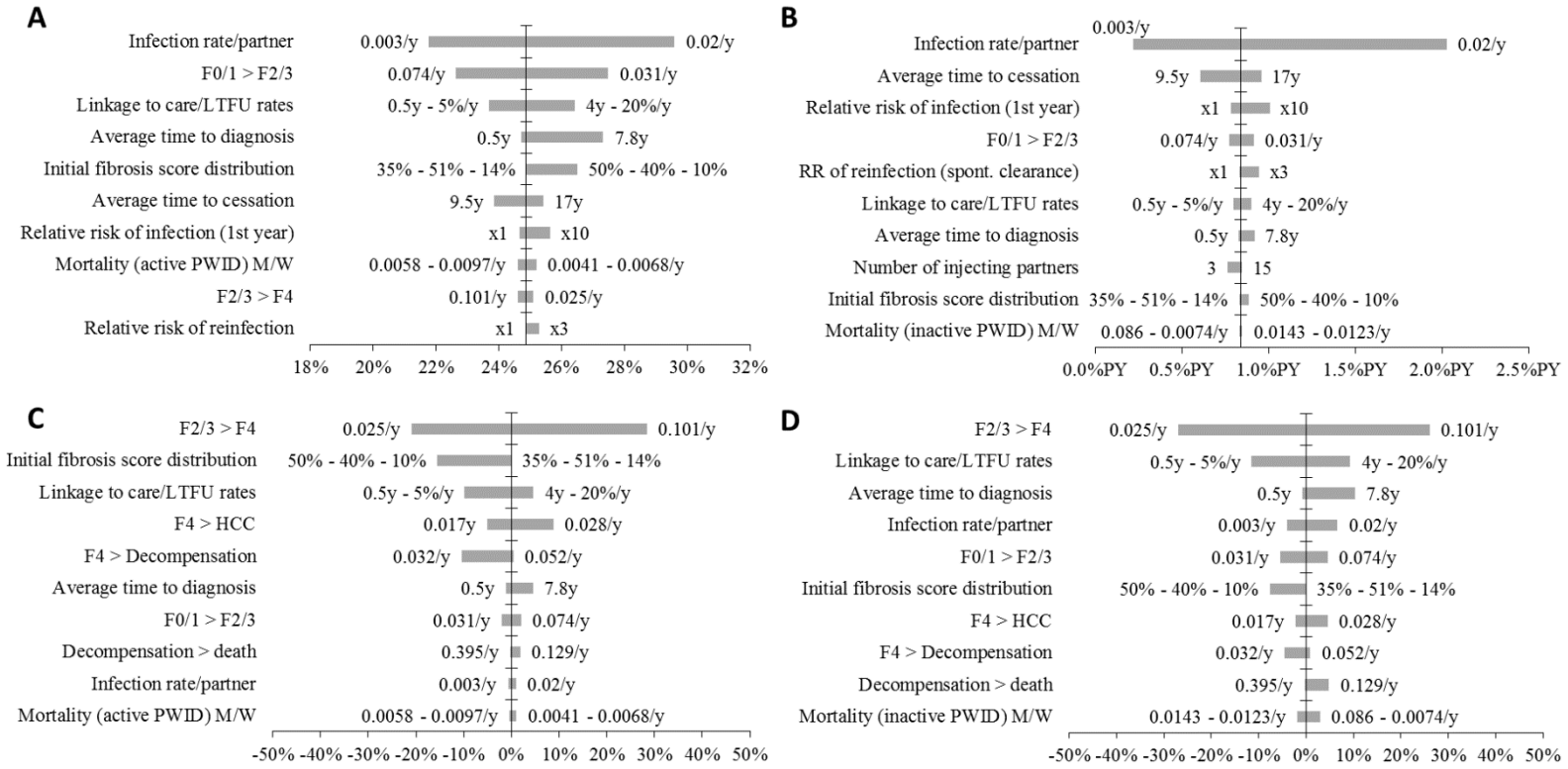


Figure 7 Tornado diagrams for the sensitivity analysis of A. prevalence at 10 years; B. incidence at 10 years; C. cirrhosis complications avoided over 10 years; D. change in the number of cirrhosis complications occurring over 40 years. The diagrams represent the change in the outcomes for each parameter varied. Parameters are sorted according to the magnitude of variation of the outcome. Only the 10 most sensitive parameters were plotted. The values on the graph indicate the parameters' values used.

Table 1 Description of the scenarios

	Scenario	Average time to diagnosis in chornic hepatitis C (current/former PWID)	Average time to LTC	Loss to follow-up rate ϕ_{Lost}	Treatment initiation criteria	%SVR e
1 (reference)	Incoming DAAs regimens	1.25 y / 1.45 y	2.6 y	14%/y	F2 →F4	81.30%
2	Incoming DAAs regimens + improved testing	0.5 y	2.6 y	14%/y	F2 →F4	81.30%
3	Incoming DAAs regimens + improved LTC	1.25 y / 1.45 y	0.5 y	5%/y	F2 →F4	81.30%
4	Incoming DAAs regimens + improvement of testing + improvement of LTC	0.5 y	0.5 y	5%/y	F2 →F4	81.30%
5	Incoming DAAs regimens + improved adherence to treatment	1.25 y / 1.45 y	2.6 y	14%/y	F2 →F4	90.00%
6	Incoming DAAs regimens + earlier treatment initiation	1.25 y / 1.45 y	2.6 y	14%/y	F0 →F4	81.30%
7	Incoming DAAs regimens + Changes in recommendations to treat earlier + improvement of testing + improvement of LTC + improvement of adherence to treatment	0.5 y	0.5 y	5%/y	F0 →F4	90.00%

SVR: Sustained virological response; PWID: People who inject drugs; DAA: Direct-acting antiviral; LTC: Linkage to care

3.3 Annexes

Manuscript number: HEP-15-0777

SUPPLEMENTARY INFORMATION

S1: MODEL DETAILS AND PARAMETERS ESTIMATIONS

Table S1 summarizes the values of the parameters we used in the model and the hypotheses we made.

Network

For the Erdös-Rényi graph, the only parameter needed is the average number of injecting partners. Wylie *et al.* found that Canadian PWID had a median of 3.5 injecting partners for a period of 30 days (1). Sacks-Davis *et al.* reported a median number of 3 injecting partners/PWID, in Melbourne, with a median duration of 3 years for a partnership (2). Murray *et al.* estimated the annual number of injecting partners to be 6 in Australia (3). Due to the lack of data about network dynamics over the long term, we assumed that PWID had an average of 6 injecting partners for the whole period. We varied this parameter from 3 to 15 in a sensitivity analysis.

Population

Size of the population: we assumed a population of 10,000 PWID.

Proportion of current PWID: we considered a population that consisted exclusively of current PWID, at the beginning of each simulation.

From this point forward, we use the name of the state of the model in Figure 1 to describe the percentage of people in this state.

Initial distribution in the model: from ANRS-Coquelicot study for the year 2011 (unpublished). Throughout the text we use the following notations to denote the initial proportion of individual in each compartment: S: Susceptible (high risk), S': Susceptible (low risk), A: Acute hepatitis C, UC: Undiagnosed chronic hepatitis C, DNLC: Diagnosed and non-linked to care chronic hepatitis C, DLC: Diagnosed and linked to care chronic hepatitis C, T: Under treatment, No SVR: No-SVR. We estimated the seroprevalence in PWID to be 65.9%. Knowing that viral ARN is present in 65% of seropositive individuals PWID (4), we had a viral prevalence of 42.8%. Thus the percentage of uninfected PWID initially is S+S'=57.2%. In our population, 5.4% of individuals were in their first year of injection, and we assumed that they were all susceptible to infection. Since S+S'=57.2%, Thus S=5.4% and S'=51.8%. Due to the short duration of acute hepatitis C (6 months), we assumed that the number of acute hepatitis C cases at a given moment was negligible: A=0%. In ANRS-Coquelicot, 21.4% of infected people, which represent 42.8% of the whole population, were unaware of their

infection, thus UC=9.2%. 33.7% of those who were aware of their infection, i.e. the remaining 33.6% of the whole population, were not linked to care, thus DNLC=11.3%; 47.6% were linked to care, but not treated, so UC=16.0%; 6.4% were linked and currently undergoing treatment, thus T=2.2%; and 12.3% had a previous unsuccessful or interrupted treatment, so No-SVR=4.1%.

To avoid that all the initially treated people stop their treatment at the same time and ensure a smooth trajectory at the beginning of the simulations, we drew a past time under treatment for individual in T in a uniform distribution (between 0 and T_t).

Distribution in the natural history model: we found no estimation of the distribution of chronically infected PWID according to Metavir Score for the whole infected group for the French PWID population. However, Melin *et al.* provide an estimate at the initiation of treatment, so we assumed that these two distributions were similar (5).

We assumed that at the beginning of each simulation, the number of cirrhosis complications was negligible.

We required that in the initial population an individual in a state had a fibrosis score coherent with his state, i.e. no cirrhosis complications in "undiagnosed chronic hepatitis C", "diagnosed and non-linked to care chronic hepatitis C" or "diagnosed and linked to care chronic hepatitis C" (as we assumed that any individual with complications would always be linked to care), no F2-F3-F4 in "diagnosed and non-linked to care chronic hepatitis C" (because we assumed people in these stages would get treated); and no fibrosis score <F2 in Under Treatment" and "No SVR" because in the base case PWID were only treated according to current guidelines - between scores F2 and F4.

Proportion of men, p_M: the proportion of men in PWID, 74.5%, was given by ANRS-Coquelicot study.

Transmission and care

Infection rate per infectious contact in Susceptible (high risk), β, and in Susceptible (low risk) β': We fitted these rates using approximate Bayesian computation (ABC) from some statistics calculated on the ANRS-Coquelicot population. The detailed methods are given in Supplementary Information S2.

Duration of acute hepatitis, T_a, and probability of spontaneous recovery, p_r: Micallef *et al.* provided an estimated p_r=26% of spontaneous recovery during the T_a=0.5 years of acute hepatitis (6).

Testing rate in chronic hepatitis C, δ: We found no direct estimation of the testing rate in the literature. However, the ANRS-Coquelicot study contains data sufficient to derive the rates for active PWID and inactive PWID. From this point forward, we define "active PWID" as the PWID that injected in the past month, and "inactive PWID" as the PWID that did not inject in the past month. We used these two groups as a proxy for current PWID, and former PWID (see Supplementary Information S3). We found a mean duration between the end of acute hepatitis phase and diagnosis of =1.25 years for current PWID and =1.45 years for former PWID.

Linkage to care rate, ϕ_{Link}, and loss to follow up rate, ϕ_{Lost}: we found no data about loss to follow-up for chronically HCV-infected PWID in France. However, the doctoral thesis work of Dr. Bakhao Ndiaye provides this rate among HIV-infected PWID (7). We assumed that the rate was similar for both HIV and HCV. Therefore, the annual probability of loss to follow up was 13.8/100 person-year. The linkage to care rate, ϕ_{Link}, was estimated at 0.39 by ABC (see Supplementary Information S2), corresponding to an average duration of 1/0.39=2.6 years before an individual links to care.
Treatment: For incoming DAAs regimens, we used a e=90% SVR rate for a 12-week treatment (8-15). In order to take into account the lower effectiveness of treatment in real life compared to the efficacy of the same regimen in clinical trials, we applied a ratio r=90.3% to the SVR rate. This ratio corresponds to the ratio of the effectiveness in an observational study to the efficacy in clinical trials of the dual therapy in Melin *et al.* (5) (if we consider a SVR rate of 50% for genotype 1 and 80% for genotype 2/3 in clinical trials (16) in bitherapy peg-interferon + ribavirin).
Cessation of drug use rate, θ: in the absence of data on a French PWID population, we used Scottish data to get the mean duration between first injection and cessation of drug use: 1/ θ=13.9 years (17, 18).
Non-HCV mortality, μ: For mortality of PWID, Lopez *et al.* estimate the annual mortality rate to be 0.0077 per years (y^{-1}) for men and 0.0054 y^{-1} for women among heroin, cocaine and crack cocaine users (19).
For former-PWID, we found no data. We hypothesized that mortality among former-PWID was similar to the mortality of adults >20 years in the general population, which was μ=0.0113 y^{-1} for men and μ=0.0098 y^{-1} for women in 2011 (20, 21).

Natural history parameters

Estimates of the transition rates between stages F0/1, F2/3 and F4 specific to PWID were available in Thein *et al.* (22). For complications and HCV-related death rates, we found no estimate for a PWID population, but Salomon *et al.* provided an estimate of HCV-related cirrhosis rates for the general population (23, 24). We found no estimate of the HCC rate in decompensated cirrhosis $\lambda_{HCC-Decomp}$, so we assumed that $\lambda_{HCC-Decomp} \approx \lambda_{HCC}$.

Table S1 Parameters for the model

Parameter	Value	References
Population size	10,000*	
Initial distribution for HCV infection and care		
Susceptible (high risk) (S)	5.4%	ANRS-Coquelicot
Susceptible (low risk) (S')	51.8%	
Acute hepatitis C (A)	0%*	
Undiagnosed chronic hepatitis C (UC)	9.2%	ANRS-Coquelicot
Diagnosed, non-linked to care chronic hepatitis C (DNL)	11.3%	
Diagnosed and linked to care chronic hepatitis C DLC)	16.0%	
Under treatment(T)	2.2%	
No SVR (No-SVR)	4.1%	
Initial distribution in the natural history model		
F0/F1	35%	(5)
F2/F3	51%	
F4	14%	
Decompensated cirrhosis	0%*	
HCC	0%*	
% Men among current PWID (p_M)	75.5%	ANRS-Coquelicot
Number of injecting partners per PWID ($\bar{d}$)	6*	See Supplementary Information S1
Infection rate by injecting partner (Susceptible (high risk) (β'))	0.01 y^{-1}partner^{-1}	See Supplementary Information S2
Relative risk of infection if Susceptible (low risk) ()	3	(25)
Duration of high risk period ()	1 y	
Duration of acute hepatitis C (T_a)	0.5 y	(6)
Probability of spontaneous recovery (p_r)	26%	
Average time from the end of acute hepatitis C phase to diagnosis ()		
Current PWID	1.25 y	Derived from ANRS-Coquelicot data (See Supplementary Information S3)
Former PWID	1.45 y	
Average time before linkage to care ()	2.6 y	See Supplementary Information S2
Loss to follow-up rate (ϕ_{Lost})	14%/y	(7)
Treatment: incoming DAAs regimens		
Duration (T_t)	12 weeks	(8-10, 12-14, 26-28)
SVR rate (p_{SVR}) – *treatment naive - all genotypes- clinical trials*	90%	
Ratio of the effectiveness in real life to the efficacy in clinical trials (r)	0.903	(5)

Mortality (μ)		
Current PWID - men	0.0077 y^{-1}	(19)
Current PWID - women	0.0054 y^{-1}	
Former PWID - men	0.0114 y^{-1}	(20, 21)
Former PWID - women	0.0098 y^{-1}	
Duration of injecting career ()	13.9 y	(17, 18)
Transition rate F0/F1→ F2/F3 ()	0.052 y^{-1}	(22)
Transition rate F2/F3→ F4 (λ_{4})	0.054 y^{-1}	
Transition rate F4→Decompensated cirrhosis (λ_{Decomp})	0.04 y^{-1}	(23, 24)
Transition rate F4→HCC (λ_{HCC})	0.021 y^{-1}	
Transition rate Decompensated cirrhosis→Death related to HCV ($\lambda_{Decomp-M}$)	0.306 y^{-1}	
Transition rate HCC→Death related to HCV (λ_{HCC-M})	0.433 y^{-1}	
Transition rate Decompensated cirrhosis→HCC ($\lambda_{Decomp-HCC}$)	0.021 y^{-1}	

* Hypothesis
SVR: Sustained virological response
PWID: People who inject drugs
y^{-1} : per year
HCC: Hepatocellular carcinoma
DAA: Direct-acting antiviral
HCV: Hepatitis C virus

S2: ESTIMATING THE INFECTION RATE β AND THE LINKAGE TO CARE RATE ϕ_{Link} BY APPROXIMATE BAYESIAN COMPUTATION (ABC)

For sophisticated models where likelihood can be numerically intractable, methods based on likelihood fail to provide good estimates for parameters. Approximate Bayesian Computation (ABC) is a computational method used to infer some parameters without likelihood estimation (29).
We denote by θ the set of parameters to derive and X the set of observed data.

Reminder: Bayesian inference

To clearly understand the motivation of ABC, we begin with a quick reminder about the main principle of Bayesian inference. The main idea of the Bayesian inference is to consider θ as a random variable with a probability distribution.
Let $\pi(\theta)$ be the *prior distribution* of the parameters. The prior distribution is chosen to reflect the uncertainty around θ *before* any data is observed. Ideally, the variable must be the most informative possible (for example, a choice for the parameter p of an Erdős–Rényi model can be a beta distribution).
Let $L(\theta, X)$ be the likelihood of θ given the data X in the model. This likelihood corresponds to the information given by the data.

The *posterior distribution* of the parameters is defined as the distribution of θ taking into account the available data, i.e. $p(\theta|X)$. According to Bayes theorem, it is given by:

$$p(\theta|X) \propto L(\theta, X)\pi(\theta)$$

Where $\propto$ means that the two quantities are proportional. The posterior distribution is more informative than the prior distribution and we expect a tighter distribution. Bayesian inference aims at estimating this distribution and its mean or median can be chosen as estimates of the parameter θ.

Main idea of ABC

The key point of Bayesian inference is the computation of the likelihood $L(\theta, X)$. However, for a complex model, this may be intractable. The main idea of ABC is to 1) catch information from the observed data by replacing the posterior distribution by the target distribution $p(\theta|S(X))$ (called the *partial posterior distribution*), where S is a vector of summary statistics of the data (for example, the number of edges or the number of triangles of the graph); and 2) use the generative model to avoid any likelihood-like computation.

Let s_{obs} be the value of $S(X)$ in the data. ABC aims to approximate $L(\theta|\mathrm{s_{obs}})$ by considering simulations for which S is closed to s_{obs}.

The basic form of the ABC is thus based on a rejection algorithm, and implemented as follows:

1. Generate *N* random draws $(\theta_i, s_i), i = 1, \dots, N$ in the joint law of (θ, S). The parameter θ_i is generated from the prior distribution π, and the vector of summary statistics s_i is calculated for the *i*th data set that is simulated from the model with parameter θ_i.
2. Associate to the *i*th simulation, the weight $W_i = K_\delta(s_i - s_{obs})$, where δ is a tolerance threshold and K_δ a (possibly multivariate) smoothing kernel.
3. The distribution in which δ_θ denotes the Dirac mass at θ, approximates the target distribution.

In our study, we used an improved version of this rejection algorithm, based on linear adjustments of the parameters: we assumed a linear link between θ and S for observations under the tolerance threshold, i.e. θ can be approximated by a function of the form $a + bS$, and θ_i is replaced by:

$$\theta_i^* = \theta_i - \mathrm{b}(s_i - s_{obs}),$$

The slope b is estimated by regressions of θ_i on $s_i$with *N* simulations, using the package "abc" (30) of the statistical software R (31).

Application of ABC

We have two parameters of interest: β' the injection rate per infectious edge in the network for a Suscpetible (low risk) PWID, and ϕ_{Link} the rate of linkage to care. We have also nuisance parameters (i.e. parameters necessary for the model): the distribution in "Undiagnosed chronic hepatitis C", "Diagnosed and non-linked to care chronic hepatitis C", "Under treatment" and "No SVR" in 2004. These parameters are estimated from the following data of ANRS Coquelicot study:

- Prevalence among active PWID in 2011: 42.8%
- Distribution of inactive PWID in "Diagnosed and non-linked to care chronic hepatitis C": 11.3%
- Distribution of inactive PWID in "Undiagnosed chronic hepatitis C": 16%
- Distribution of inactive PWID in "Under treatment": 2.2%.

Since the Coquelicot study allowed us to have the prevalence in the model in 2004, we performed simulations over the 2004-2011 period. We used specific data available for this period about the mortality among former PWID, the testing rate, and the distribution in "Susceptible (high risk)", "Susceptible (low risk)" and "Undiagnosed chronic hepatitis C" instead of the parameters we used in the base case (see Table S2).

Concerning the parameters of ABC, we performed 25,000 simulations, the tolerance threshold δ was 0.1 and we used an Epanechnikov kernel, i.e. for all u in $\mathbb{R}$:

$$K_\delta(u) = \frac{3}{4\delta}\left(1 - \frac{u^2}{\delta^2}\right)1_{u\leq\delta}$$

To ensure positivity of β and ϕ_{Link}, these parameters were log-transformed and the distribution in 2004 of infected and diagnosed individuals was logit-transformed to ensure it corresponded to a distribution and summed to 100%. The prior law distributions were: $\log(\beta) \sim U[0.003; 0.3]$; $\log(\phi_{Link}) \sim U[0.1; 15]$ where $U[\text{a; b}]$ is a uniform law on [a; b]. The prior law distributions of "Susceptible (high risk)", "Susceptible (low risk)" and "Undiagnosed chronic hepatitis C" and "No SVR" were uniform distributions (renormalized so that the distribution in the model summed to 100% with respective means of 14%, 8.8%, 2.1%. and 4.5% for the afore-mentioned states).

Table S2 - parameters for ABC implementation

Parameter	Value	References
Distribution in 2004		
Susceptible (high risk)	3%	ANRS-Coquelicot
Susceptible (low risk)	43%	
Undiagnosed chronic hepatitis C	16.7%	
% Men (current PWID)	80.7%	
Duration of treatment (bitherapy)	36 weeks	(16)
%SVR bitherapy (naïve, all genotypes)	58%	(5)
Former PWID mortality (Men -Women)	11.3 - 9.6/1000 PY	(20, 21)

PWID: People who inject drugs
SVR: sustained virological response
PY: person-year

Results

We found the following results (with 95% confidence intervals), depending on the average number of injecting partners: 6 partners is the value assumed in the base case analysis, while 3 partners and 15 partners were used in sensitivity analyses.

Table S3 Infection rate per partner β' and time to linkage to care estimates by Approximate Bayesian Computation, according to the average number of injecting partners (with 95% confidence intervals)

Average number of injecting partners	Infection rate per partner β' (y^{-1})	Time to linkage to care (y)
3	0.019 (0.004-0.045)	2.6 (2.3-2.9)
6	0.01 (0.003-0.02)	2.6 (2.3-2.9)
15	0.004 (0.002-0.008)	2.6 (2.3-2.9)

S3: ESTIMATING THE TIME BEFORE DIAGNOSIS BY MAXIMUM LIKELIHOOD FROM THE DATA OF THE ANRS COQUELICOT STUDY

We wanted to estimate the test rate δ using the data available in the Coquelicot study. PWID undergo test until they are diagnosed with HCV. We assume that to each PWID without HCV diagnosis is associated a Poisson process of rate δ, that is to say that intervals between successive tests follow exponential distribution with parameter δ.

Let's assume that we observed n PWID without HCV diagnosis, i.e. people non-infected or unaware of their infection.

For each PWID i, we observed :

• T the delay between the beginning of his/her injecting career (i.e. the first injection) and the time of the Coquelicot study

• C indicator of the presence of a HCV test before the survey

• S the time of the last test done before the survey

We denote by $(t_i, c_i, s_i)_{1\leq i\leq n}$ the observations of (T, C, S) for the n PWID, and $N_c = \sum_{1\leq i\leq n} c_i$ the number of PWID in the survey with a previous HCV test.

We define the likelihood of $\delta, (c_i, s_i)_{1\leq i\leq n}$ conditionnally to the $(t_i)_{1\leq i\leq n}$as

$$L(\delta, (c_i, s_i)_{1\leq i\leq n} | (t_i)_{1\leq i\leq n}) \propto \prod_{i|c_i=0} P(N(t_i) = 0 | T = t_i) \prod_{i|c_i=1} f_{t_i}(s_i) P(C = 1 | T = t_i)$$

With $N(t_i)$ be the number of tests done on the interval $[0, t_i]$ for the individual i, and f_{t_i} the density of S knowing that and $T = t_i$ and $C = 1$

Proposition: The maximum-likelihood estimator of δ is

$$\hat{\delta} = \frac{N_c}{\sum_{i|c_i=0} t_i + \sum_{i|c_i=1} s_i}$$

Proof: $N(t)$ follows a Poisson distribution of parameter δt.

We have:

1) $P(N(t) = 0|T = t) = e^{-\delta t}$
2) $P(C = 1|T = t) = 1 - P(N(t) = 0) = 1 - e^{-\delta t}$
3) Knowing $T = t$ and $C = 1$, the survival function of S is, $\forall s < t$

$$P(S > s|T = t, C = 1) = \sum_{k>0} P(X_k < t - s|T = t, N(t) = k) P(N(t) = k|T = t, N(t) \geq 1)$$

With X_k the elapsed time between the first injection and the k[th] test of the PWID. Knowing that he/she had had k tests, , the tests repartition on $[0, t]$ follows a uniform distribution on the injecting period, as the PWID are tested following a Poisson process. Thus, if for $1 \leq l \leq k$, U_l follows an uniform distribution on $[0, t]$ we have :

$$P(X_l < t - s|T = t, N(t) = k) = P\left(\max_{1 \leq l \leq k} U_l < t - s\right) = \prod_{1 \leq l \leq k} P(U_l < t - s) = \left(\frac{t - s}{t}\right)^k$$

Moreover,

$$P(N(t) = k|T = t, N(t) \geq 1) = \frac{P(N(t) = k|T = t)}{P(N(t) \geq 1|T = t)} = \frac{e^{-\delta t}(\delta t)^k}{k!\,(1 - e^{-\delta t})}$$

Thus,

$$P(S > s|T = t, C = 1) = \sum_{k>0} \left(\frac{t - s}{t}\right)^k \frac{e^{-\delta t}(\delta t)^k}{k!\,(1 - e^{-\delta t})}$$

$$= \frac{e^{-\delta t}}{(1 - e^{-\delta t})} \sum_{k>0} \frac{\delta^k (t - s)^k}{k!} = \frac{e^{\delta(t-s)} - 1}{e^{\delta t} - 1}$$

Then,

$$P(S > s|T = t, C = 1) = \frac{e^{-\delta s} - e^{-\delta t}}{1 - e^{-\delta t}}$$

Therefore,$\forall s < t_i$

$$f_t(s) = \frac{e^{-\delta s}}{1 - e^{-\delta t}}$$

And the likelihood for a sampling:

$$L(\delta, (c_i, s_i)_{1 \leq i \leq n} | (t_i)_{1 \leq i \leq n}) \propto \prod_{i|c_i=0} e^{-\delta t_i} \prod_{i|c_i=1} \delta e^{-\delta s_i} = \lambda^{N_c} e^{-\delta(\sum_{i|c_i=0} t_i + \sum_{i|c_i=1} s_i)}$$

Therefore,

$$ln(L(\delta, (c_i, s_i)_{1 \leq i \leq n} | (t_i)_{1 \leq i \leq n})) = N_c ln(\delta) - \delta \left(\sum_{i|c_i=0} t_i + \sum_{i|c_i=1} s_i \right) + A$$

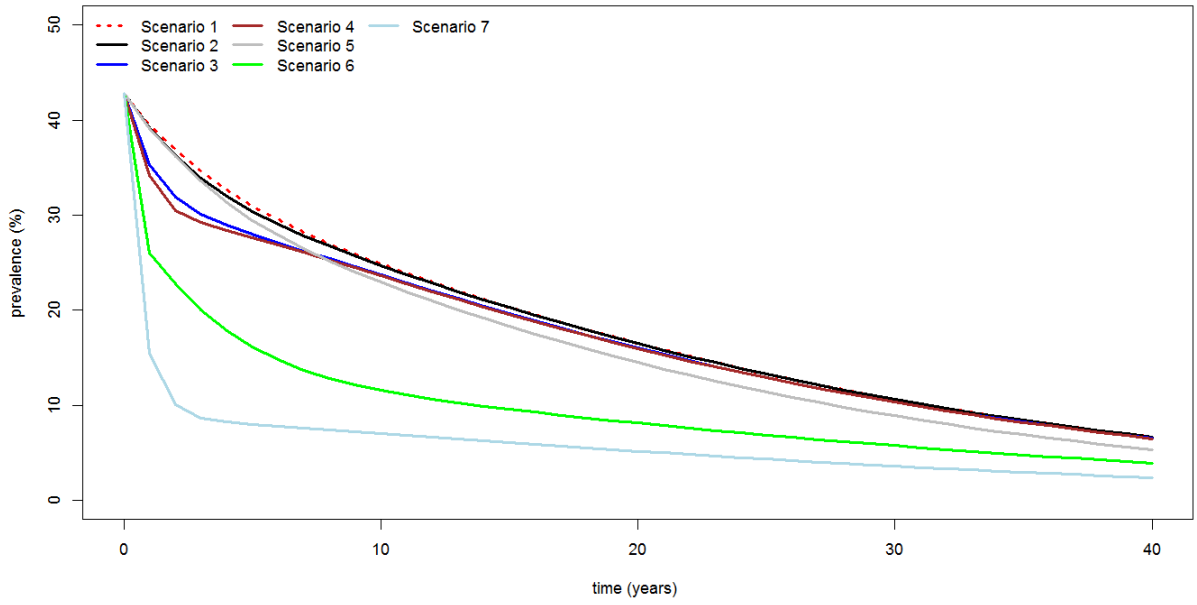
Where A is a constant. It follows that the maximum-likelihood estimator of δ be that proposed above.

Results

Using the data of the ANRS Coquelicot survey, we found an estimate of 0.80 $years^{-1}$ for active PWID and 0.69 $years^{-1}$ for inactive PWID (PWID after cessation of drug use), corresponding to an average duration of 1.25 and 1.45 years before diagnosis.

S4: EVOLUTION OF THE PREVALENCE, INCIDENCE, AND THE NUMBER OF CIRRHOSIS COMPLICATIONS OVER THE FIRST 40 YEARS

A.



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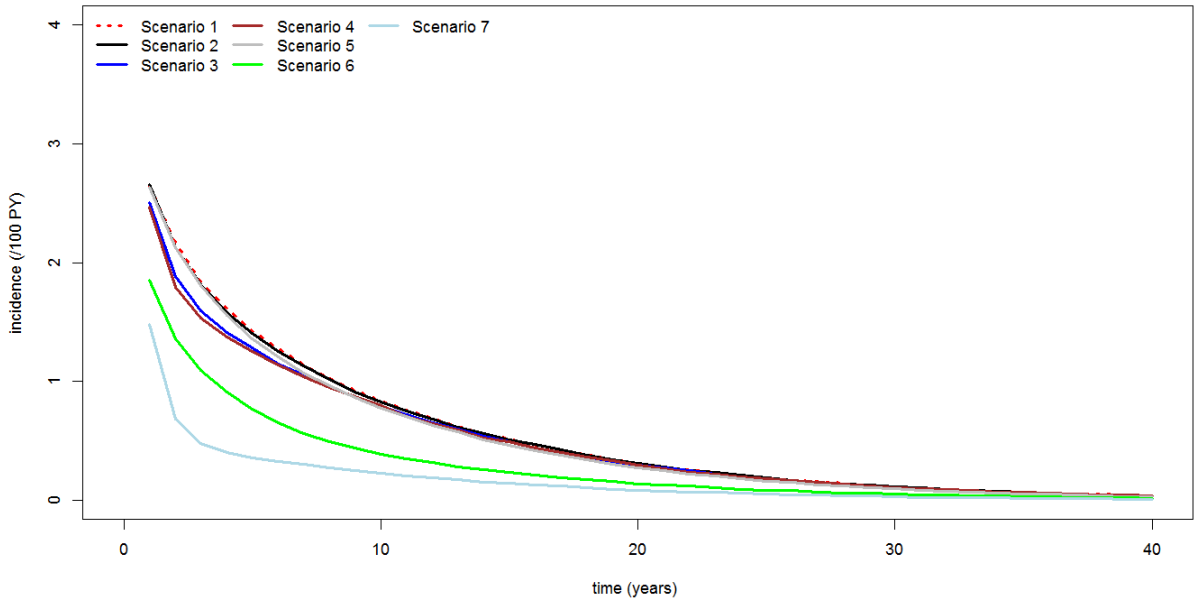

C.

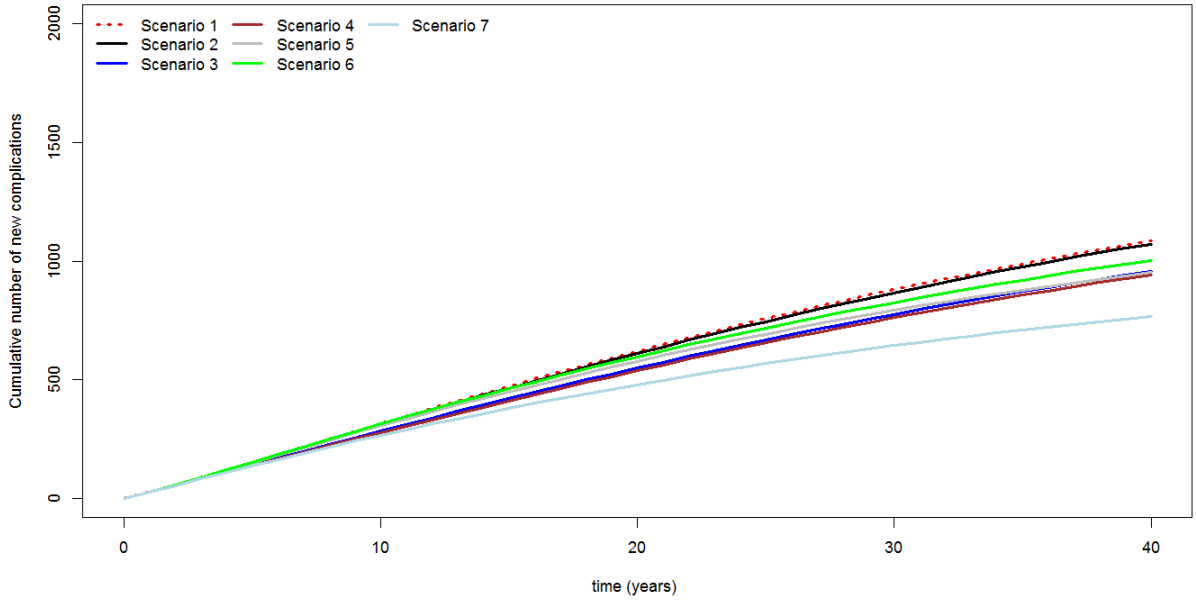

Figure S1 evolution of A) the prevalence of HCV in the population, B) the incidence of HCV infection and C) the number of new cirrhosis complications over the first 40 years.

S5: SENSITIVITY ANALYSIS

We present the results of some sensitivity analyses. First, the parameters' values used in the deterministic sensitivity analysis are summarized in Table S4. Table S5 gives the results for settings with an average of 3, 6 (base case), and 15 injecting partners. The results show similar incidence and prevalence at 10 years, and number of new complications in the population at 40 years.

Figures S2 and S3 presents the results when we increased β to 5 and 10 times the base case. Base case analysis results also presented for comparison. These three settings correspond respectively to a stable, increasing and decreasing prevalence at 10 years in the reference scenario. The conclusion of the base case remains valid in these other two settings. The clinical benefits are even better in setting with higher infection rates.

Figure S4 presents the results when only 10% of the PWID eligible to treatment effectively initiate the therapy. The conclusions of the base case analysis remain valid, with the exception of the results on the number of complications of cirrhosis avoided after 40 years in scenario 6, i.e. when the treatment initiation criteria is a fibrosis score between F0 and F4. Indeed, in the base case analysis treatment from F0 had a small impact on the probability of progression to liver disease for people who have reached the "diagnosed and linked to care chronic hepatitis C" state before reaching F2. In this

sensitivity analysis, when we introduce in the model the fact that not all individuals initiate treatment immediately at F2 diagnosis and therefore an annual rate of transition to treatment for eligible individuals, treating early is associated with an individual benefit because it increases each patient chances to initiate the treatment.

Table S4 Description of the sensitivity analysis

Parameters	Base case value	Sensitivity analysis	References
Initial distribution in the natural history model			
F0/F1	35%	50%	Assumption
F2/F3	51%	40%	
F4	14%	10%	
Number of injecting partners/PWID ($\bar{d}$)	6	3 – 15	Assumption
Infection rate in Susceptible (low risk) per infected injecting partner (β')	0.01 y^{-1}partner^{-1}	0.003 – 0.02	See Supplementary Information S2
Relative risk of infection in Susceptible (low risk) ()	3	1-3	Assumption
Relative risk of reinfection after spontaneous recovery per infected partner	1	1-2	(32)
Relative risk of reinfection after SVR per infected partner	1	1- 2	Assumption
Time between chronic infection and diagnosis (current PWID/former PWID) ()	1.25/1.45 years	0.5 – 7.8	Scenario 2 -Value in UK (33)
Average time before linkage to care ()/ Loss to follow-up rate (ϕ_{Lost})	2.6 y / 14%/year	0.5 - 4 / 5 – 20	Scenario 3 – Assumption
Current PWID mortality (Men/Women) (μ)	0.0077 y^{-1}/ / 0.0054 y^{-1}	0.0058 - 0.0097 / 0.0041 - 0.0068	Assumption
Former PWID mortality (Men/Women) (μ)	0.0114 y^{-1} / 0.0098 y^{-1}	0.0086 - 0.0143 / 0.0074 - 0.0123	Assumption
Average duration of injecting career ()	13.9 years	9.5 – 17	(17, 18)
Transition rate F0/F1→ F2/F3 ()	0.052 y^{-1}	0.031 - 0.074	(22)
Transition rate F2/F3→ F4 (λ_{4})	0.054 y^{-1}	0.025 – 0.101	
Transition rate F4→Decompensated cirrhosis (λ_{Decomp})	0.04 y^{-1}	0.032 – 0.052	(23, 24)
Transition rate F4→HCC (λ_{HCC})	0.021 y^{-1}	0.017 – 0.028	
Transition rate Decompensated cirrhosis→Death related to HCV ($\lambda_{Decomp-M}$)	0.306 y^{-1}	0.129 – 0.395	
Transition rate HCC→Death related to HCV (λ_{HCC-M})	0.433 y^{-1}	0.319 – 0.499	
Transition rate Decompensated cirrhosis→HCC ($\lambda_{Decomp-HCC}$)	0.021 y^{-1}	0.017 – 0.028	

PWID: People who inject drugs
y^{-1} : per year
HCC: Hepatocellular carcinoma
HCV: Hepatitis C virus
SVR: Sustained Virological Response

Table S5 Results per scenario for an average number of 3, 6 and 15 injecting partners.

Scenario	Average number of injecting partners	Prevalence at 10 years (%)	Incidence at 10 years (/100 PY)	% cirrhosis complications avoided compared to Scenario 1 over 10 years	% cirrhosis complications avoided compared to Scenario 1 over 40 years
		mean (95% CI)	mean (95% CI)	mean (95% CI)	mean (95% CI)
Scenario 1	3	**24.6 (24.5;24.7)**	**0.77 (0.74;0.79)**	/	/
	6	**24.9 (24.8;24.9)**	**0.84 (0.81;0.87)**	/	/
	15	**24.9 (24.9;25)**	**0.85 (0.82;0.88)**	/	/
Scenario 2	3	24.4 (24.3;24.5)	0.75 (0.73;0.78)	-1 (-3 ; 0)	-1 (-3;1)
	6	24.7 (24.6;24.8)	0.83 (0.8;0.86)	-1 (-3 ; 0)	-1 (-3;1)
	15	24.8 (24.7;24.8)	0.86 (0.83;0.89)	-1 (-3 ; 0)	-2 (-3;1)
Scenario 3	3	23.4 (23.4;23.5)	0.72 (0.69;0.74)	-10 (-11;-8)	-12 (-13;-10)
	6	23.7 (23.6;23.8)	0.8 (0.77;0.83)	-10 (-11;-8)	-12 (-13;-10)
	15	23.8 (23.7;23.8)	0.81 (0.79;0.84)	-10 (-11;-8)	-12 (-13;-10)
Scenario 4	3	23.3 (23.2;23.4)	0.72 (0.69;0.74)	-12 (-13;-10)	-13 (-15;-12)
	6	23.6 (23.5;23.7)	0.78 (0.76;0.81)	-12 (-13;-10)	-13 (-15;-12)
	15	23.7 (23.6;23.7)	0.81 (0.78;0.84)	-12 (-13;-10)	-13 (-15;-12)
Scenario 5	3	22.7 (22.6;22.7)	0.71 (0.69;0.74)	-3 (-4 ;-1)	-12 (-14;-11)
	6	22.9 (22.9;23)	0.78 (0.75;0.81)	-3 (-5 ;-2)	-12 (-13;-10)
	15	23 (22.9;23.1)	0.79 (0.77;0.82)	-3 (-4 ; -2	-12 (-14;-11)
Scenario 6	3	11.5 (11.5;11.6)	0.36 (0.34;0.38)	0 (-2;1)	-8 (-9;-6)
	6	11.6 (11.6;11.7)	0.39 (0.37;0.41)	0 (-2;1)	-7 (-9;-5)
	15	11.6 (11.6;11.7)	0.4 (0.38;0.42)	0 (-2;1)	-7 (-9;-6)
Scenario 7	3	7 (7;7.1)	0.21 (0.2;0.23)	-15 (-17;-14)	-29 (-30;-28)
	6	7 (7;7.1)	0. 23 (0.22;0.25)	-15 (-17;-14)	-29 (-30;-28)
	15	7 (7;7.1)	0. 23 (0.22;0.25)	-15 (-17;-14)	-30 (-31;-28)

CI: Confidence interval
PY: person-year

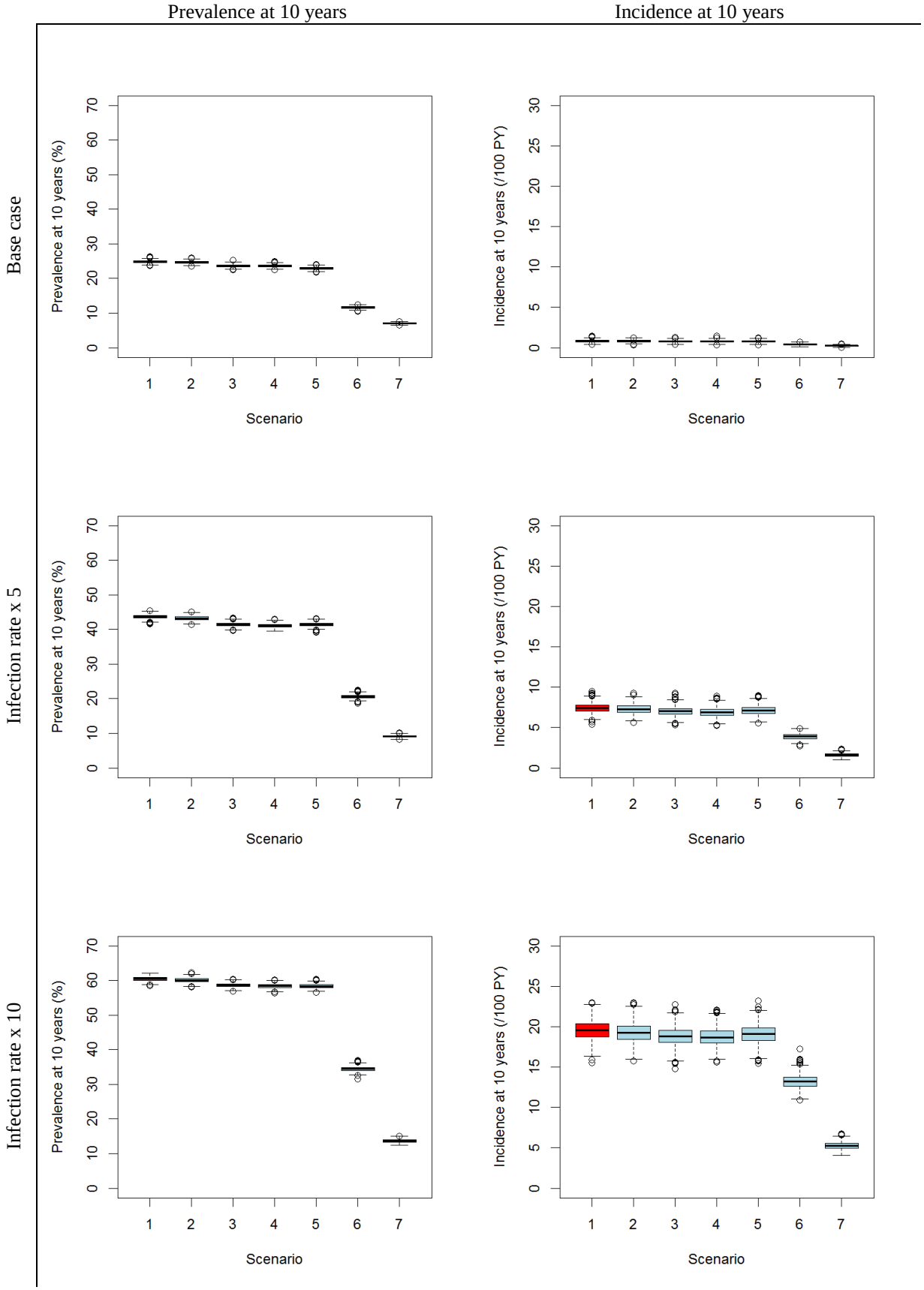

Figure S2 Boxplots of the prevalence and incidence at 10 years according to the scenario in three settings: base case rate, infection rate/infected partners x 5 and infection rate/infected partners x 10**.** The scenarios are: 1- Current cascade of care (reference), 2 – Improvement of HCV testing, 3 – Improvement of linkage to care, 4 – Improvement of testing and linkage to care, 5 – Improvement of adherence to treatment, 6 – Treatment initiated from F0, 7 –Improvement of the entire cascade of care (combination of scenarios 4, 5 and 6).

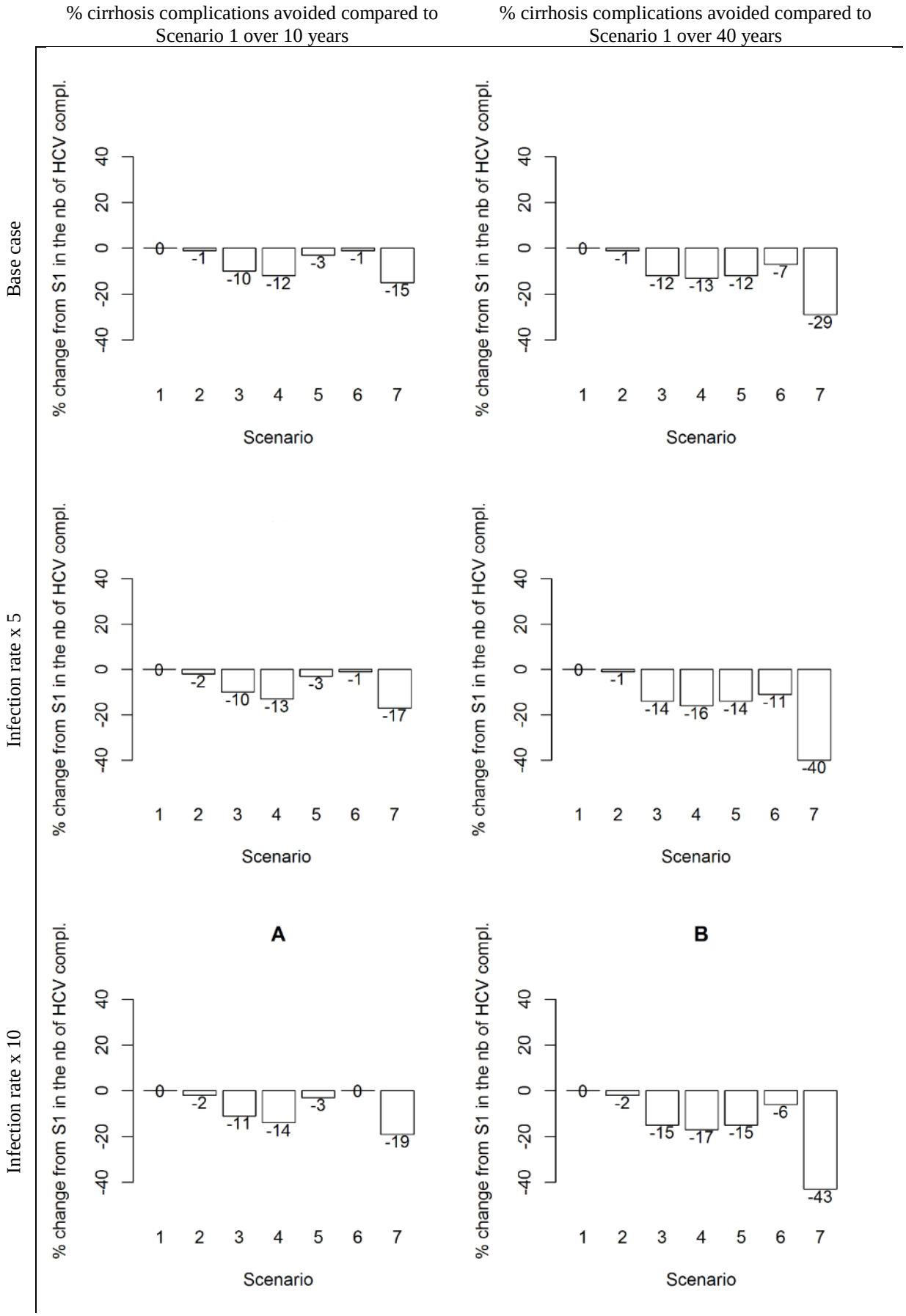

Figure S3 Average percentage of cirrhosis complications avoided over 10 and 40 years according to the scenario in three settings: base case, infection rate/infected partners x 5 and infection rate/infected partners x 10**.** The scenarios are: 1- Current cascade of care (reference), 2 – Improvement of HCV testing, 3 – Improvement of linkage to care, 4 – Improvement of testing and linkage to care, 5 – Improvement of adherence to treatment, 6 – Treatment initiated from F0, 7 –Improvement of the entire cascade of care (combination of scenarios 4, 5 and 6).

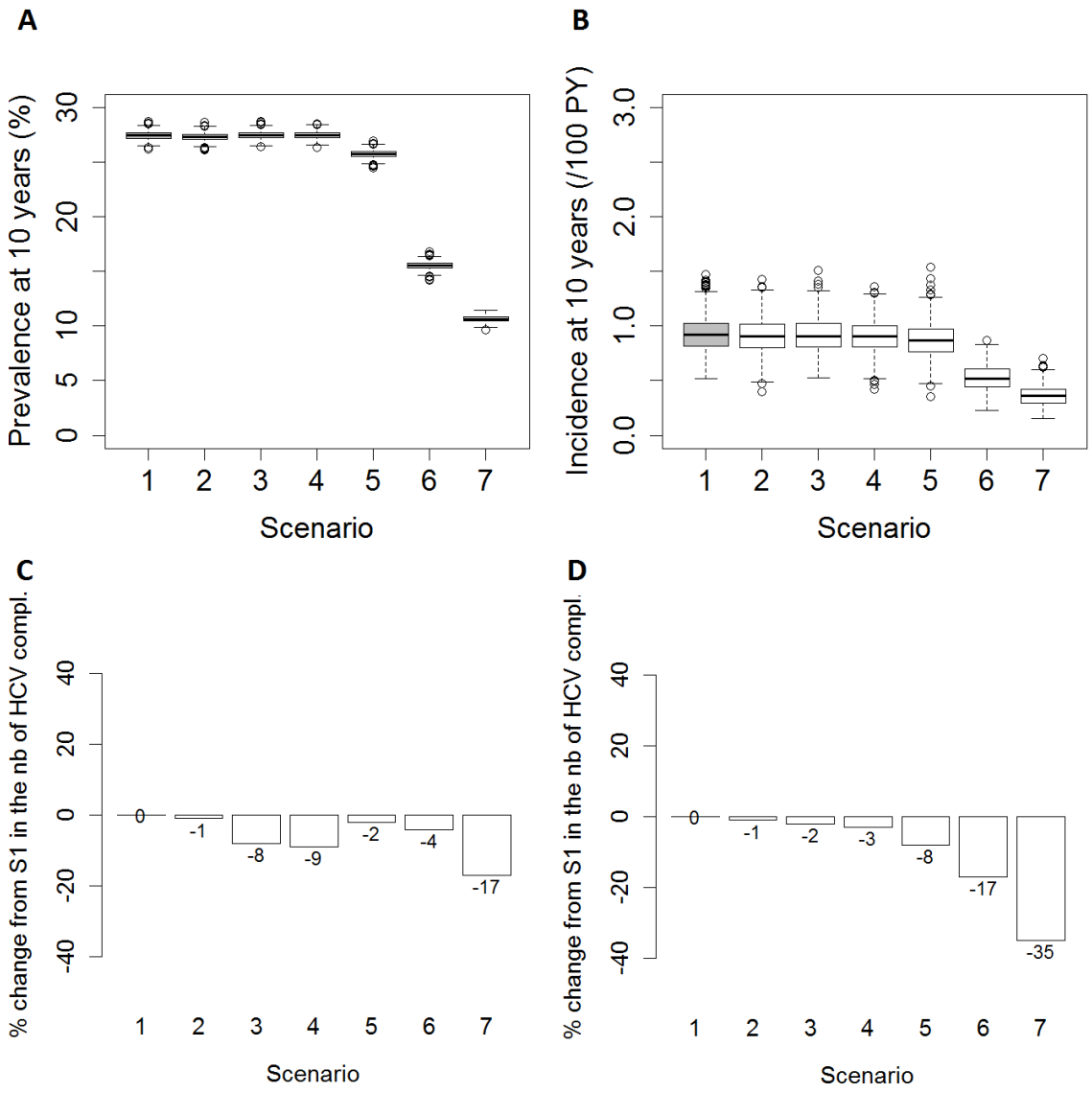

Figure S4 Boxplots of the prevalence (A) and incidence (B) at 10 years and average percentage of cirrhosis complications avoided over 10 (C) and 40 years (D) when the annual treatment delivery rate among eligible PWID is set to 10%, according to the scenario. The scenarios are: 1- Current cascade of care (reference), 2 – Improvement of HCV testing, 3 – Improvement of linkage to care, 4 – Improvement of testing and linkage to care, 5 – Improvement of adherence to treatment, 6 – Treatment initiated from F0, 7 –Improvement of the entire cascade of care (combination of scenarios 4, 5 and 6).

S6: CORRESPONDENCE BETWEEN THE MEAN TIME TO DIAGNOSIS/TIME TO LINKAGE TO CARE AND THE ANNUAL PROBABILITY OF OCCURRENCE OF THE CORRESPONDING EVENT

Table S6 Correspondence between the mean time to diagnosis/time to linkage to care and the annual probability of occurrence of the corresponding event

Event	Average time to event	Annual probability of the event	Scenario
Diagnosis	1.25/1.45 years (active/inactive PWID)	55%/50%	1 (reference)
	0.5 years	86%	2,6
Linkage to care	2.6 years	32%	1 (reference)
	0.5 years	86%	2,6

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4 Evaluation de l'impact d'une stratégie de « Treatment as Prevention » sur la transmission du VHC et la morbi-mortalité chez les UDI de Montréal, Canada

4.1 Résumé

A Montréal, l'incidence des infections par le VHC reste élevée : pour la période 2010-2013, l'incidence des séroconversions chez les UDI actifs (i.e. s'étant injectés durant les six derniers mois) est estimée à 22.1/100 p.a d'après les données du volet montréalais du réseau SurvUDI, un réseau de surveillance épidémiologique chez les UDI au Canada existant depuis 1995 (Leclerc et al. 2011). Les recommandations actuelles de traitement de l'hépatite C chronique préconisent une décision au cas par cas, et le remboursement du traitement n'est pas conditionné à la sévérité de la fibrose hépatique (Extrait du ministère de la Santé et des Services sociaux 2014). Le nombre d'individus traités reste cependant très faible : sur la période 2003-2011, parmi les UDI se sachant infectés par le VHC, seuls 12% avaient déjà reçu un traitement pour leur infection. Comme en France, l'arrivée des nouveaux AAD soulève la question de l'utilisation du traitement antiviral pour prévenir la transmission du VHC dans cette population, et donc, des forces et des faiblesses de la cascade de soins de l'hépatite C chronique à Montréal.

L'objectif de cette étude était donc d'évaluer, chez les UDI de Montréal, l'impact d'améliorations dans la cascade de soins de l'hépatite C chronique sur la transmission de la maladie dans la population et la morbidité/mortalité associée.

Nous avons pour cela réutilisé le modèle développé pour la population d'UDI en Île-de-France. Le critère d'initiation du traitement utilisé pour le contexte français (score Métavir entre F2 et F4 dans le scénario de référence) a ici été remplacé par un taux annuel de traitement des UDI liés au système de soins (5%/an dans le scénario de référence).

Les paramètres du modèle ont été estimés à partir des données de l'enquête SurvUDI, du registre des Maladies A Déclaration Obligatoire (MADO) de la Direction de la Santé Publique de Montréal, et des nombreuses études épidémiologiques publiées dans la littérature (Bernier et al. 1996; Roy et al. 2004; De 2007; Roy et al. 2009; Leclerc et al. 2014). Le taux de transmission a été estimé par calcul bayésien approché à partir de l'incidence des séroconversions chez les UDI de Montréal entre 2010 et 2013, qui est de 22.1/100 p.a (enquête SurvUDI, données non-publiées).

Comme dans le cadre de l'étude sur la population d'UDI en France, le modèle a été utilisé afin d'évaluer l'impact de scénarios d'améliorations de la cascade de soins sur l'incidence des séroconversions et la prévalence du VHC dans la population après 10 ans, et sur le nombre de complications de la cirrhose (décompensation et carcinome hépatocellulaire) évités après 10 et 40 ans. Les scénarios évalués étaient les suivants :

Scénario 1 : le scénario de référence, avec la cascade de soins actuelle. Le diagnostic d'hépatite C chronique se fait en moyenne 2 ans après le passage à la chronicité (2.5 ans après l'infection) ; le lien

aux soins 1.7 ans en moyenne après le diagnostic ; le taux de perte de vue est de 10.2%/an ; le traitement est initié chez les individus liés aux soins au taux de 5%/an ; et le taux de réussite du traitement est de 81% (le taux de RVS dans les essais cliniques était d'environ 90% pour les nouveaux AAD au moment de l'étude, mais nous avons diminué ce taux de 10% pour prendre en compte la différence d'adhérence au traitement entre un essai clinique et la vie réelle).

Scenario 2 : le scénario de l'amélioration du dépistage. Le diagnostic d'hépatite C chronique se fait en moyenne 6 mois après le passage à la chronicité, conformément aux recommandations de l'EASL (European Association for the Study of the Liver 2015) (vs. 2 ans dans le scénario 1).

Scénario 3 : le scénario d'une amélioration des liens avec le système de soins. Nous avons supposé ici que le lien aux soins pourrait se faire 6 mois après la détection (vs. 1.7 ans dans le scénario 1). De plus, nous avons diminué le taux de perte de vue à 5%/an (vs 10.2%/an dans le scénario 1).

Scénario 4 : le scénario d'une amélioration de l'adhérence au traitement. Dans ce scénario, nous avons supposé qu'une amélioration de l'adhérence au traitement chez les UDI pourrait conduire à un taux de RVS similaire à celui obtenus lors des essais cliniques, c'est-à-dire 90% (vs. 81% dans le scénario 1).

Scénario 5 : le scénario d'une amélioration de l'accès au traitement. Le taux de traitement a été augmenté à 10%/an chez les individus liés aux soins (vs. 5%/an dans le scénario 1).

Scénario 6 : le scénario d'une amélioration importante de l'accès au traitement. Le taux de traitement a été augmenté à 20%/an chez les individus liés aux soins (vs. 5%/an dans le scénario 1).

Scénario 7 : le scénario d'une amélioration de l'ensemble de la cascade de soins. Il s'agissait de la combinaison des scénarios 2, 3, 4 et 6.

Scénario 8 : le scénario d'un traitement conditionné au stade de fibrose. Le taux d'initiation du traitement a été remplacé par une condition d'accès liée à la sévérité de la fibrose hépatique : seuls les individus avec un score Métavir compris entre F2 et F4 étaient traités, et le traitement était initié de manière systématique chez ces individus (pas de limitation à un taux de traitement annuel comme dans les précédents scénarios).

Une analyse de sensibilité déterministe a également été effectuée en faisant varier les paramètres dans un intervalle d'incertitude (ou en utilisant les données d'autres études). De plus l'ensemble des scénarios ont été simulés en faisant varier le nombre de partenaires d'injection, sur lesquels l'incertitude est élevée. Dans le scénario de référence (scénario 1), l'incidence à 10 ans était estimée à 9.4/100 p.a [intervalle de confiance à 95% : 9.2 ; 9.7] et la prévalence à 10 ans à 55.8% [55.6% ; 55.9%]. Améliorer le dépistage, le lien aux soins ou l'adhérence au traitement de manière isolée (scénarios 2, 3 et 4) aboutissait à des diminutions modestes de l'incidence (entre 9.1 et 9.3/100 p.a en moyenne), de la prévalence (entre 53.2% et 54.7%), et du nombre de complications de la cirrhose (entre 0% et -2% après 10 ans, et entre -1% et -6% après 40 ans). Augmenter l'accès au traitement était la seule intervention permettant une diminution importante de la transmission du VHC dans la population : lorsque ce taux était augmenté à 20%/an (scénario 6), l'incidence à 10 ans obtenue était de 6.4/100 p.a [6.2 ; 6.6], la prévalence à 10 ans de 36.6% [36.4% ; 36.6%], et 37% [36% ; 38%] des complications de la cirrhose avaient été évitées

après 40 ans. Traiter uniquement les stades de fibroses F2 à F4, même en traitant tous les individus éligibles (scénario 8) ne permettait pas une réduction aussi importante de la transmission du virus, avec une incidence de 7.3/100 p.a [7.1 ; 7.5] et une prévalence de 44.3% [44.1% ; 44.5%] après 10 ans. Le scénario 7, correspondant à une amélioration de l'ensemble de la cascade de soins, était le plus efficace, avec une incidence de 4.3/100 p.a [4.2 ; 4.4], une prévalence de 24% [23.9% ; 24.2%] et 54% [53% ; 54%] de complications évitées après 40 ans.

Les analyses de sensibilité ont montré un impact important sur l'incidence et la prévalence à 10 ans du temps moyen avant cessation des injections lorsque celui-ci variait dans un intervalle de valeurs issues de la littérature (de 4.7 ans à 14 ans, contre 9.5 ans dans le scénario de référence (Fazito et al. 2012)). Toutefois, les tendances de l'analyse principale sont restées inchangées en simulant l'ensemble des scénarios avec ces deux valeurs de paramètres.

On peut donc conclure des résultats de ces analyses que, dans la situation actuelle, le faible nombre de traitements initiés chez les UDI de Montréal déjà diagnostiqués et liés au système de soins limite une diminution massive à la fois de la transmission du VHC et de la morbidité/mortalité associée par l'utilisation du traitement. En effet, en l'absence de traitement ces individus restent susceptibles de transmettre l'infection malgré leur détection par le système de santé. Ce n'est qu'une fois cette hausse du taux de traitement atteinte qu'améliorer le reste de la cascade de soins aurait un impact. De plus, restreindre la délivrance du traitement aux stades de fibroses modérés à sévères limiterait également l'impact du traitement sur la transmission, même en traitant l'ensemble des individus éligibles. Cependant, la perspective d'une élimination à 10 ans (c'est-à-dire d'une incidence des séroconversions nulle chez les UDI de Montréal) semble inenvisageable par l'utilisation du TasP uniquement. En analyse de sensibilité une diminution importante de l'incidence à 10 ans (-1.6/100 p.a) a été obtenue avec une faible variation du taux d'infection par partenaire infecté dans le scénario de référence (0.022, contre 0.025 dans l'analyse principale). Ce résultat suggère que dans l'optique d'une élimination du VHC, une stratégie de « TasP+ » incluant en plus des mesures précédentes une amélioration de la réduction des risques chez les UDI avec un accès élargie au matériel d'injection stérile et aux traitements de substitution (ou grâce à par de nouvelles mesures comme la mise en place de salles de consommation à moindre risque) serait nécessaire.

De la même manière que dans l'étude précédente sur la population d'UDI en Île-de-France, les résultats de cette étude font ressortir que le point faible de la cascade de soins se situe au niveau de l'initiation du traitement chez les individus déjà diagnostiqués et liés aux soins. Cette tendance dans les pays à haut revenus montre que, malgré les recommandations actuelles et l'arrivée des nouveaux AAD, dans la pratique actuelle c'est la perspective individuelle (l'impact sur la mortalité) qui prime sur la perspective collective (l'impact sur la transmission) dans le choix d'initier un traitement.

Les résultats de cette étude ont fait l'objet d'une présentation orale à la *8th IAS Conference on HIV Pathogenesis, Treatment & Prevention*, à San Francisco, Etat-Unis ; et ont été soumis pour publication.

4.2 Article 3 (soumis)

THE NECESSITY OF A TREATMENT SCALE-UP TO IMPACT HCV TRANSMISSION IN IN PEOPLE WHO INJECT DRUGS IN MONTRÉAL, CANADA: A MODELLING STUDY

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ABSTRACT

Background: HCV transmission remains high in people who inject drug (PWID). New direct-acting antivirals (DAAs), highly effective and more tolerable than previous regimens, make a "Treatment as Prevention" (TasP) strategy more feasible. This study assesses how improvements in the cascade of care could impact chronic hepatitis C burden among PWID in Montréal.

Methods: We used a dynamic model to simulate HCV incidence and prevalence after 10 years, and cirrhosis complications after 10 and 40 years, using eight scenarios of improved cascade of care.

Results: Using the current cascade of care and the new DAAs, the estimated HCV incidence and prevalence at 10 years were 9.4/100 p.y and 55.8%. Improved HCV testing, linkage to care or treatment adherence alone led to marginal improvements. Increases in the treatment initiation rate resulted in the largest decreases in incidence (6.4/100 p.y), prevalence (36.6%), and cirrhosis complications (-18% after 10 years, -37% after 40 years). When restricting treatment to fibrosis level ≥ F2, the decrease in HCV occurrence was smaller. Improving the whole cascade of care led to the greatest effect by halving the prevalence and incidence at 10 years and the number of cirrhosis complications after 40 years.

Interpretation: The current level of treatment access in Montréal is limiting a massive decrease in hepatitis C burden among PWID. A substantial treatment scale-up, regardless of fibrosis level, is necessary. Interventions to improve the other components of the cascade of care are necessary to optimize a TasP strategy and control the HCV epidemic, but only once the treatment scale-up is achieved.

INTRODUCTION

The number of people who inject drugs (PWID) in Montréal, defined as those who injected in the past six months, is estimated to be 4,000 (1). According to regional surveillance data (SurvUDI network) , approximately 70% of this population has been exposed (antibody positive) to the hepatitis C virus (HCV) (2) and the number of new infections remains high: 22.1/100 persons-years (p.y) for the 2010-2013 period (unpublished SurvUDI data) despite the implementation of risk reduction measures such as opioid substitution therapy and syringe and equipment distribution programs.

Access to HCV treatment remains limited in this population. Several components of the HCV cascade of care may explain poor treatment uptake. For example during 2003-2011, 23% of the infected PWID reported they were not aware of their infection; among those who were aware, 45% reported a physician consultation in the past 6 months, and 12% initiated HCV treatment (2). There may also be reluctance on the part of physicians to initiate antiviral treatment in PWID (3). Precarious living conditions and other co-morbidities (e.g., psychiatric disorders) may be identified as barriers to treatment initiation (4). Also, uncontrolled substance use often constitutes a treatment barrier for physicians as many are more likely to treat PWID participating in opiate substitution programs (3). In addition, until recently, the standard antiviral treatment regimen for HCV (dual therapy perginterferon plus ribavirin) was associated with numerous challenges. The regimen required a treatment duration of 24 to 48 weeks and the sustained virological response (SVR) rate was 80% for genotypes 2 and 3, but only 45% for genotype 1 (5, 6), the most common genotype in Montréal (7). Moreover, this treatment regimen required weekly injections of peginterferon, and was associated with severe adverse events such as rash, anemia and/or depression (5, 6).

However, direct-acting antiviral (DAA) regimens for HCV treatment are increasingly available. These new treatments are more effective (>90% SVR for all genotypes), shorter (12 weeks), less restrictive as oral regimens, and they cause few or no adverse events (8-13). This recent advances in the HCV therapeutic area provides an interesting opportunity to eliminate HCV infection in this population. The successful treatment of infected individuals could limit the transmission of the virus to current or future injecting partners and prevent the occurrence of serious health outcomes such as end-stage liver disease. However, if a “Treatment as Prevention” (TasP) strategy is to work, it will require to enhance HCV care, and thus addressing several elements, including increased HCV testing, linkage to HCV care, improved liver fibrosis assessment, enhanced HCV treatment uptake, improved adherence and cure of HCV, collectively termed the “HCV cascade of care” (14).

In this paper, we used a previously developed dynamic stochastic model for HCV transmission in PWID (15) to estimate the impact of a TasP strategy on HCV transmission and related morbidity when varying the components of the HCV cascade of care among PWID.

METHODS

In this section we briefly describe the model used to simulate HCV transmission and natural history, the scenarios simulated to estimate the impact of variation in the components of the cascade of care, and the sensitivity analyses we performed to assess the impact of the uncertainty on some parameter values. For more detailed about the model, the reader can refer to (15). A summary of the parameter values is given in Appendix A1.

Model

The starting population is Montréal's active (i.e., injection past 6 months) PWID population, with an estimated size of 4,000 individuals (1). The population size is assumed to be constant in time: each dead PWID is replaced in the model by another non-infected PWID. A previously described model of HCV transmission was used to estimate the impact of a treatment as prevention strategy (15). Briefly, it is a stochastic individual-based model taking into account the social network of PWID trough a random graph model, HCV transmission dynamics, the cascade of care, and chronic hepatitis C natural history. The social network of our population was defined as the network of injecting partners (i.e. people who inject together) to take into account the background risk of HCV infection between injecting partners (16). Due to a lack of data about the global topography of this network in Montréal, we used an Erdös-Rényi model (17), which can be calibrated using data on the individual-centered network. In this model, each dyad of PWID is linked with a constant probability p, which can be estimated from the size of the whole population N and the average number of injection partners expected $\bar{d}$ noting that . The transition chart of the model for HCV transmission and care is described in Figure 1. Briefly, it takes into account acute hepatitis C, testing, linkage to care, treatment and reinfection. The natural history of HCV infection is presented in Figure 2; it takes into account fibrosis progression through Metavir score (by grouping F0 and F1, and F2 and F3). Two complications are expected to occur in late-stage HCV infection (cirrhosis): decompensation and HCC, which can lead to death. Finally, the mathematical model takes into account injection cessation and general mortality (i.e. non-HCV-related mortality) which also depends on the injecting status (active or inactive PWID) which varies overtime.

Parameters

Key parameters are presented Table 1. Where possible we used regional data reflecting the local context. SurvUDI, which is a bio-behavioural surveillance network among PWID in Montréal, provided most of the estimates for model parameters (2). Other parameters were derived from the scientific literature.

Briefly, the infection rate was fitted using Approximate Bayesian Computation (18) to obtain an incidence of 22.1/100 person-years (p.y) during the first year of simulation in the reference scenario. This

value corresponds to the estimate found in SurvUDI for the 2010-2013 period. The mean time from the end of acute hepatitis C to detection was derived from the time of the last test in SurvUDI for the 2012-2014 period and estimated at 2 years.For the mean time to linkage to care, we assumed that after detection, the first consultation for an individual related to his/her HCV infection is measured by the occurrence of a HCV RNA-test. It occurs after a mean duration of 1.7 years according to Notifiable Disease Reporting System of the Montréal Public Health Department (unpublished data). According to SurvUDI data, 10.2% of the PWID detected have seen a physician for hepatitis C infection in the past year. Due to our definition of linkage to care (a consultation in the previous 6 months), we considered that these PWID were lost to follow-up during the year, and thus we estimated the annual loss to follow-up rate to 10.2%/y.

Details regarding the parameter values and underlying assumptions are given in Appendix A1.

Outcomes

The outcomes of interest were the occurrence of HCV infection and related morbidity and mortality. HCV occurrence was represented by the average incidence and prevalence of HCV infection after 10 years of simulations. The average number of cirrhosis complications (decompensated cirrhosis + HCC) avoided over 10 and 40 years, compared with the reference scenario, was used to report on changes in HCV-related morbidity and mortality. In addition, for each scenario, the mean numbers of treatments initiated (and completed unless the individual dies during the treatment) over 40 years were estimated (see Appendix A2).

Scenarios

We estimated the impact on HCV occurrence and morbidity/mortality in the Montréal PWID population of improvements in HCV testing, linkage to care, treatment rate, treatment initiation criteria and adherence to treatment using 8 scenarios. One thousand epidemic trajectories were simulated to derive the effects of each of the eight following scenarios:

S1 (reference): Represent the current HCV cascade of care but using the new DAAs (for all stages of liver fibrosis). Mean time to detection in chronic hepatitis C: 2y; mean time to linkage to care: 1.7y; annual loss to follow-up rate: 10.2%/y; treatment initiation rate (when linked to care): 5%/y; SVR rates: 81%; duration of the treatment: 12 weeks.

S2: S1 with an improvement in the mean time to detection of chronic HCV from 2y to 0.5y (1y after the infection, due to the 6 months of acute hepatitis C in the model), corresponding to annual testing, as supported by AASLD guidelines (19).

S3: S1 with an improvement in linkage to care, with a mean time to linkage to care from 1.7y to 0.5y and a loss to follow-up rate from 10.2%/y to 5%/y

S4: S1 with an improvement in adherence to treatment. In this scenario, we improved the SVR rate from 81% to the level demonstrated in clinical trials, i.e. 90%.

S5: S1 with an improvement in treatment initiation rate from 5%/y to 10%/y when linked to care.

S6: Improvement in treatment initiation rate from 5%/y to 20%/y when linked to care.
S7: Combined scenarios S2, S3, S4 and S6 to determine the impact of improvements in the entire cascade of care.
S8: S1 with an initiation of HCV treatment at fibrosis levels F2-F3-F4 only. Due to the high cost of the new DAAs (55,000$CAD (20)), there is currently some reluctance to treat people with minimal fibrosis (F0/F1 fibrosis scores) (19). Therefore, simulations were performed to limit treatment initiation to fibrosis scores between F2 and F4, i.e. 100% of the PWID with moderate or severe fibrosis were treated (vs. 5% of all PWID without cirrhosis complication in S1) while those with F0/F1 were excluded from treatment.

Sensitivity analysis

We performed a deterministic univariate sensitive analysis by varying the parameter values based on the uncertainty interval (95% confidence interval or interquartile range) if available, or by using values from other studies or other countries. The summary of the univariate sensitivity analysis is provided (see Appendix, Table A2). Tornado graphs were used to represent the results.
In addition, due to the uncertainty about the number of injecting partners, we also varied this parameter to cover the range of likely values in the literature (between 3 and 15) (15).
The details of theses analyses including ranges of parameter estimates used are provided in Appendix A3.

RESULTS

Boxplots representing the prevalence and incidence distributions after 10 years, and the proportion of cirrhosis complications avoided over 10 and 40 years are presented Figure 3 for the eight scenarios. The reference scenario for following comparisons is S1.

HCV transmission in the population

In the reference scenario S1, the mean incidence and prevalence estimates after 10 years were 9.4/100 p.y. [9.2; 9.7] and 55.8% [55.6; 55.9], respectively. Improved testing in S2, linkage to care in S3 or adherence to treatment in S4, each taken separately, led to similar incidence estimates of 9.3/100 p.y [9.1; 9.6], 9.1/100 p.y [8.8; 9.3] and 9.2/100 p.y [9.0; 9.5], respectively. S2, S3 and S4 also lead to similar prevalence estimates: 54.7% [54.6; 54.9], 53.2% [53.1; 53.4] and 54.5% [54.4; 54.7]. Improvements in the treatment initiation rate to 10%/y and 20%/y in S5 and S6 led to a decrease in HCV occurrence with incidence estimates of 8.1/100 p.y [7.9; 8.3] and 6.4/100 p.y [6.2; 6.6], respectively. Similarly, prevalence estimates decreased for S5 and S6: 47.5% [47.3; 47.6] and 36.6% [36.4; 36.7]. The combined scenario S7 (representing improvements in the whole cascade of care) was the most effective with the incidence dropping to 4.3/100 p.y [4.2; 4.4] after 10 years and prevalence to 24.0% [23.9; 24.2]. Finally, when restricting treatment to F2-F4 fibrosis scores in S8, the incidence and prevalence estimates were 7.3/100 p.y [7.1; 7.5] and 44.3% [44.1; 44.5], respectively.

Chronic hepatitis C complications

Compared with the reference scenario S1, improved testing in S2, had almost no impact with 0% [-1; 2] and 1% [0; 3] of cirrhosis complications avoided over 10 and 40 years, respectively. Improved linkage to care in S3, or adherence to treatment in S4, alone had a moderate impact in the long term, with 2% [1; 4] and 1% [-1; 3] of complications avoided after 10 years and 6% [5; 7] and 6% [5; 7] after 40 years. Improvements in the treatment initiation rate to 10%/y in S5 and 20%/y in S6, resulted in the avoidance of 7% [6; 9] and 18% [17; 20] of complications after 10 years, respectively while greater decreases were observed after 40 years: 21% [20; 22] and 37% [36; 38]. The combined scenario S7 demonstrated a decrease in the number of cirrhosis complications of 30% [29; 32] after 10 years and 54% [53; 54] after 40 years. Finally, treating only F2-F4 fibrosis levels in S8 led to a decrease in complications of 44% [43; 45] and 49% [48; 50] after 10 and 40 years.

Sensitivity analysis

The tornado graphs in Figure 4 present variations in outcomes under the conditions of S1 while considering parameter uncertainty levels. The parameters most sensitive (top 10) in outcome estimation are presented for each outcome. For the incidence after 10 years, the most sensitive parameters were the mean time to cessation of injection (with a variation in the reference scenario S1 of -6.0/100 p.y, +3.9/100 p.y.), the treatment initiation rate (-1.3/100 p.y., 1.7/100 p.y.) and the infection rate per infectious injecting partner (-1.6/100 p.y., 1.1/100 p.y.). The most sensitive parameters for the prevalence after 10 years were the treatment initiation rate (-8.3%, +8.7%) and the mean time to cessation of injection (-9.0%, +5.1%). Finally, for the number of cirrhosis complications within 10 years, estimates were most sensitive to the transition rate from F2/F3 to F4 (-18%, +22%), the fibrosis distribution in the population (-28%, +0%) and the decompensation rate (-10%, +15%). For cirrhosis complications after 40 years, estimates were most sensitive to the following parameters: the treatment initiation rate (-21%, +37%), the transition rate from F2/F3 to F4 (-29%, +26%) and the transition rate from F0/F1 to F2/F3 (-15%; +11%).

Results of the other sensitivity analyses are presented in Appendix A3. The trends of our results remained unchanged when we varied the number of injecting partners. In addition, we also simulated the 8 scenarios with the lower and upper bounds of the mean time to cessation of injection used in the univariate sensitivity analysis (4.7 years and 14 years), due to the large impact on prevalence and incidence. The trends observed for the various scenarios were relatively unchanged.

INTERPRETATION

We used an individual-based model to simulate the evolution of HCV infection among active PWID in Montréal while varying various steps in the cascade of care. Model parameters were primarily informed by local data. The results showed, compared with the current cascade of HCV care, that the

best approach to curtail ongoing HCV transmission and future cirrhosis complications in this population is to improve access to treatment. By increasing the treatment initiation rate from 5%/y to 10%/y and 20%, prevalence at 10 years decreased from 55.8% to 47.5% and 36.6%, respectively. Similarly, incidence rates at 10 years dropped from 9.4/100 p.y to 8.1/100 p.y and 6.4/100 p.y, respectively. In addition, the number of cirrhosis complications decreased by 21% and 37% over 40 years using 10%/y and 20%/y treatment initiation rates. On the other hand, improved testing, linkage to care or adherence to treatment alone, led only to minor decreases in the disease burden. However, combining these improvements with a higher treatment initiation rate permitted a decrease of almost 50% in the prevalence and incidence at 10 years and the number of cirrhosis complications over 40 years. Finally, by restricting treatment to patients with moderate and severe fibrosis (S8), the impact on HCV transmission was considerably lower compared to scenario S7 (no fibrosis restriction, treatment initiation of 20%/y), even in the optimistic case where 100% of the eligible individuals were treated. But there was a greater impact on the reduction in the number of cirrhosis complications in the short term: -44% (10 years). Nevertheless, both scenarios S7 and S8 would require a similar amount of treatment courses over 10 years; approximately 1,500 courses, see Appendix A2).

These results show that, even in the context of new DAAs, a large decrease in the disease burden through the use of a TasP strategy first requires greater access to treatment for PWID once they are diagnosed and linked to care. When this treatment scale-up is achieved, improvements in other parts of the cascade of care could result in additional benefits for both HCV transmission and morbidity/mortality. Without this treatment scale-up, a faster testing or linkage to care would be of limited benefit, as the patient would not be able to initiate antiviral treatment before several years, all while experiencing ongoing fibrosis progression. This approach would be inconsistent with recent statements from the European Association for the Study of the Liver (EASL) (21) where screening of PWID is promoted in part to improve access to treatment, but also to reduce transmission. For the same reason, while treatment initiation restricted to fibrosis scores $\geq$ F2 would reduce liver related morbidity, it would also delay treatment for many other infected PWID. This would effectively allow for several years of ongoing HCV transmission before individuals reach treatment eligibility. This restriction may be justified as it targets treatment to those most in need in whom liver disease is more imminent. However, from a public health perspective, the treatment of patients in the absence of liver disease (low fibrosis scores) is most important to reduce HCV occurrence, and consequently the disease burden over the long-term.

In other settings, previous modelling studies using different models showed that even a small increase in treatment availability for PWID can result in a large decrease in HCV transmission in the context of highly effective antivirals (22-24), particularly in a low prevalence context (24). However, these models didn't take into account the entire cascade of care, and thus did not identify the specific steps in the cascade having the largest impact on the course of the HCV epidemic. In Montréal, this appears to be treatment initiation once PWID are diagnosed and linked to care.

In our sensitivity analysis, the mean time to cessation of injection and the infection rate per infected injecting partner were sensitive parameters for estimating HCV incidence. These results suggest that improvements in primary and secondary prevention interventions, that is, public health interventions aimed at reducing the harms of substance use (e.g., delayed initiation of injection drug use, safe injection facilities) could round out a TasP strategy. In a previous modelling study in UK demonstrated the importance to combine risk reduction measures with a treatment scale-up to achieve a high decrease in HCV prevalence (25). In the present study, the current situation of the risk reduction measures in Montréal were implicitly included in the model and are reflected in the mean values of the infection rate per infected partner and the time to cessation of injection, and the heterogeneity with respect to harm reduction uptake was neglected. Estimating the impact of these preventive public health strategies in addition to variations in the HCV cascade of care would require a more complex model taking into consideration drug use initiation rates, injection equipment distribution programs and opioid substitution therapies/programs, as well as supervised injection facilities that will soon open in Montréal (26). Further investigation is needed to incorporate them in the model.

This study has several limitations. First, the network model is static and relatively simple compared with structures obtained for PWID in other countries through chain referral sampling (16). The paucity of data about the network dynamic and topology constrained us, and the development of a more realistic model would require field studies on PWID networks. Also, for simplicity, other comorbidities such as HIV infection were not explicitly included in the model. HIV-HCV coinfection is common in PWID and co-infected individuals (2) differ based on HCV disease prognosis and the HCV cascade of care (27). While current recommendations promote an individual-based treatment decision for PWID (19, 28), treatment is probably preferentially initiated in PWID in moderate to advanced levels of fibrosis. However, in our reference scenario, the treatment initiation is independent of the fibrosis score. Finally, due to the high cost of the new DAAs (around 55,000$ Canadian for a 12-week course (20)), extended access to these antivirals for the PWID population would mean increased costs for the health system (see Appendix A2 for the number of completed treatments needed for each scenario). Under the current situation, the cost of the introduction of the new DAAs for the public health insurance in Québec was estimated to 45 million Canadian dollars for the 3 first years after this introduction (29). Future work of this type could consider including health care costs in the model permitting an assessment of the costs of a TasP strategy.

There are also several strengths to our study. The large amount of local data available through ongoing regional surveillance work (SurvUDI and the Notifiable Disease Reporting System of the Montréal Public Health Department) and numerous past and current epidemiological studies (7, 30-32) ensures the model reflects the current situation of HCV infection and care for PWID in Montréal. Also, the model took into account the entire cascade of care for chronic hepatitis C, including testing, linkage to care and treatment. This is, to our knowledge, the first model to do so (33).

To conclude, a large decrease in chronic hepatitis C burden in Montréal could be reached through the use of a TasP strategy for PWID. However, the success of this strategy rests on first expanding access to antiviral treatment to PWID already engaged in HCV care. From a public health perspective, this represents a priority focus in improving the HCV cascade of care. Limiting treatment to moderate to severe fibrosis, while effective in circumventing cirrhosis complication in the short-term, would do little to curtail ongoing HCV transmission in this population. Coupling greater and more open treatment access as well as ongoing improvements in the HCV cascade of care would ultimately result in less HCV occurrence and disease burden. Regardless, elimination of HCV infection in this population would not be expected to occur in the short to mid-term. Such an ambitious objective would require a "TasP+" strategy, which would foster a commitment to greater treatment access as well as harm reduction services. In future work, a more sophisticated model could help evaluate the impact of a "TasP+" strategy in the context of ongoing improvements in the HCV cascade of care while also determining the health care investment needed to eliminate HCV infection among PWID.

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Table 1 Key parameters of the model

Parameter	Value	References
Population size	4,000	(1)
Average number of injecting partners during the injecting career	12	Derived from (32)
Initial distribution (HCV infection and cascade of care)		
Susceptible with high risk	10.10%	SurvUDI, 2012-2014, unpublished data
Susceptible with low risk	36.80%	
Acute hepatitis C	0%*	
Non-detected chronic hepatitis C	8.40%	SurvUDI, 2012-2014, unpublished data
Detected, non-linked to care chronic hepatitis C	24.40%	
Detected and linked to care chronic hepatitis C	15.30%	
Under treatment	0.40%	
Non-responders after treatment	4.60%	
Initial distribution in the natural history model		
F0/F1	61.1%	(Private communication, J. Bruneau)
F2/F3	23.3%	
F4	15.6%	
Decompensated cirrhosis	0%*	
HCC	0%*	
Infection rate by injecting partner in Susceptible (low risk)	0.025 $y^{-1}partner^{-1}$	Fitted by ABC to have a 22.1/100 p-y baseline incidence (SurvUDI, 2010-2013)
Mean time from the end of acute hepatitis C to detection	2.0y	Derived from SurvUDI, 2012-2014, unpublished data
Mean time before linkage to care	1.7y	Derived from Notifiable Disease Reporting System of the Montréal Public Health Department
Loss to follow-up rate	10.3%/y	Derived from SurvUDI, 2012-2014, unpublished data
Treatment initiation rate when linked to care	5%/y	Approximate value derived from SurvUDI, 2012-2014, based on current number of people under treatment (0.4%)
Treatment: incoming DAAs regimens		
Duration	12 weeks	(8-13)
SVR rate – treatment naive - all genotypes- clinical trials	90%	

*Hypothesis
PWID: people who inject drugs; SVR: sustained virological response

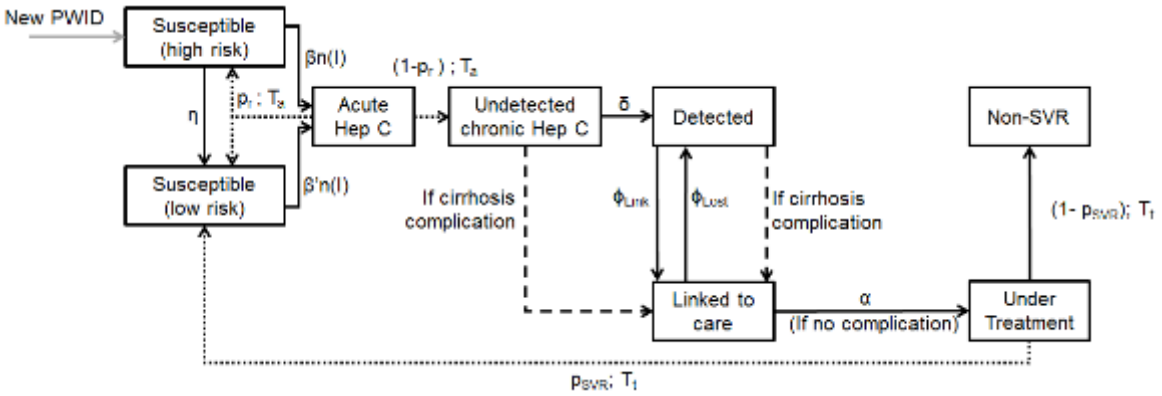

Figure 1 Transition chart of the model for HCV infection and care. New PWID enters the population as "Susceptible (high risk)" during all the simulation period to keep a constant population size (i.e each death in the population implies the arrival of a new PWID). Plain arrows correspond to transitions occurring according to exponential probability distributions. Dashed lines correspond to transitions occurring after a fixed time with a given probability. Dotted lines correspond to transitions related to the natural history model. An individual is considered as Detected if he/she has an HCV antibody positive test. An individual is considered as Linked to care if he/she had one or more consultation related to his/her HCV infection in the past 6 months (with the first link to care corresponding to the first positive RNA test, see Appendix A1).

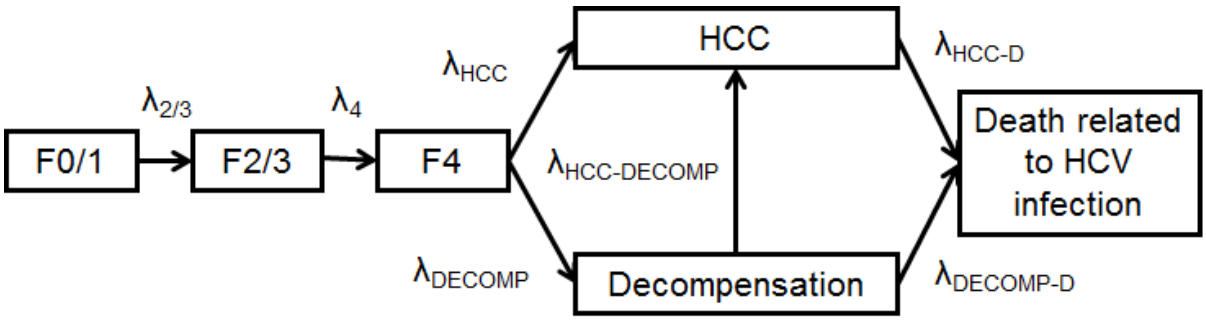

Figure 2 Transition chart for the natural history of chronic hepatitis C. All transitions occur according to exponential probability distributions. Metavir fibrosis scores F0 and F1 (respectively F2 and F3) were gathered in a F0/1 (respectively F2/3) state.

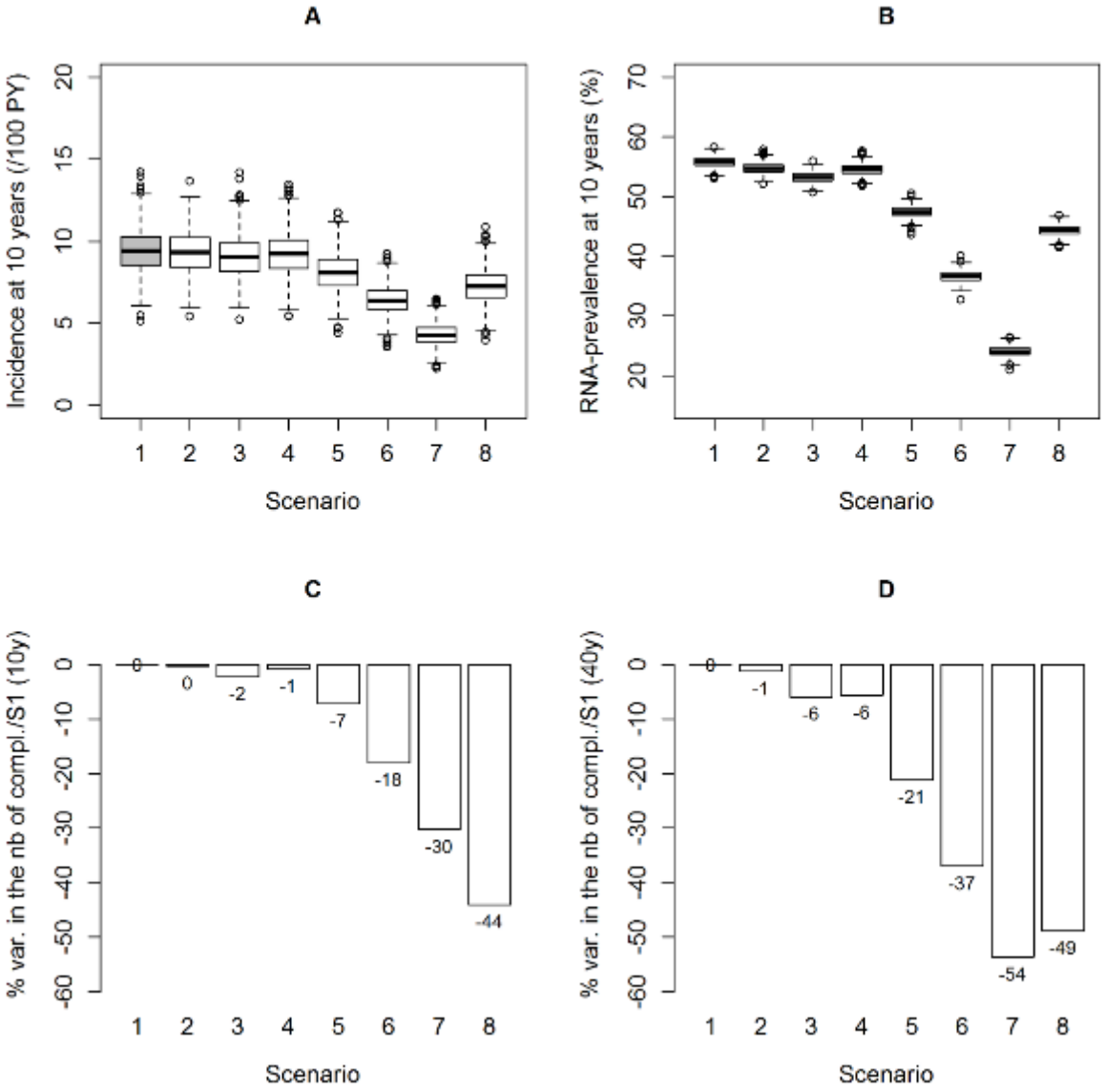

Figure 3 Results according to various HCV cascade of care scenarios; 1,000 simulations. A. Boxplots of the incidence at 10 years; B. Boxplots of the prevalence at 10 years; C. Proportion of cirrhosis complications avoided after 10 years (mean percentage of new cirrhosis complications avoided, compared with the reference scenario (S1)); D. Proportion of cirrhosis complications avoided after 40 years (mean percentage of new cirrhosis complications avoided, compared with the reference scenario (S1)). S1 (reference): current cascade of care with the new antivirals; S2: improvement in testing; S3: improvement in linkage to care; S4: improvement in adherence to treatment; S5: moderate improvement in the treatment initiation rate; S6: high improvement in the treatment initiation rate; S7: combined S2, S3, S4 and S6; S8: systematic treatment initiation when linked to care, but only for F2-F3-F4 fibrosis scores.

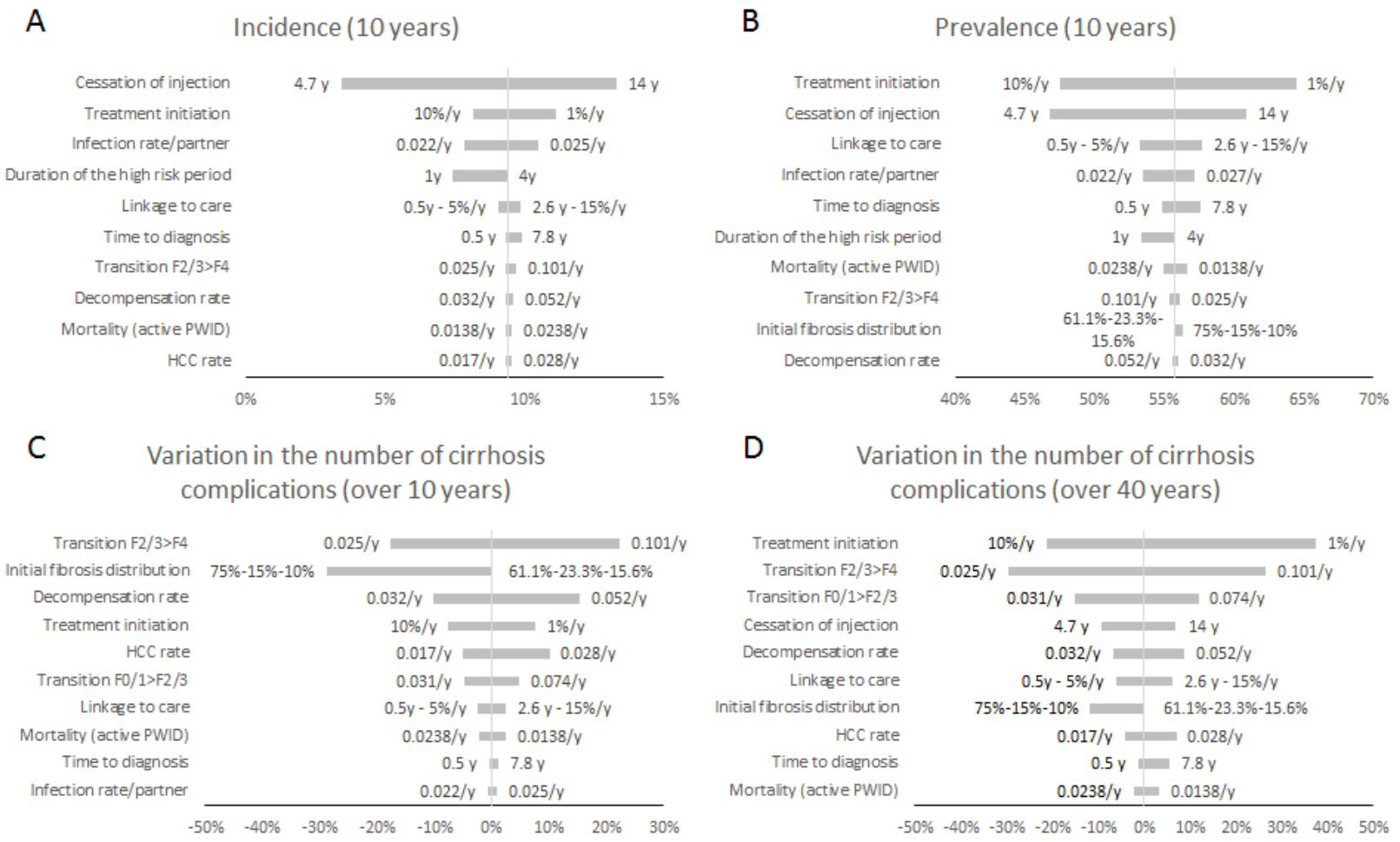

Figure 4 Tornado graphs representing variations in outcomes while considering parameter uncertainty demonstrating the top 10 most sensitive parameters in the model (using the reference scenario (S1)). The corresponding parameters values are given on the charts. A. Incidence at 10 years; B. Prevalence at 10 years; C. Variation in the proportion of new cirrhosis complications over 10 years, compared with the reference scenario (S1); D. Variation in the proportion of new cirrhosis complications over 40 years, compared with the reference scenario (S1).

4.3 Annexes

SUPPLEMENTARY MATERIAL

A1: MODEL PARAMETERS

The parameters necessary for running the model were mainly provided by SurvUDI data, or by the literature. They are presented in Table A1. We preferentially used data from regional studies when available. Hypotheses underlying some parameter values are detailed below. To assess the impact of these hypotheses on our simulations, we performed several sensitivity analyses (see the main text and supplementary material S2).

Mean number of injecting partners: in his PhD thesis (1), De, P. detailed a study about the social network of people who inject drugs (PWID) in Montréal. We estimated the average number of injecting partners as the product of the average number of PWID in the individual-centered network, the average proportion of PWID with whom the individual reported having injected, the turnover rate (by month) of the network and the average length (in months) of the injecting career from (Fazito *et al.* (2)) providing an estimate of 12 injecting partners per PWID.

Chronic HCV prevalence and initial distribution of susceptible PWID: according to SurvUDI data, 72% of active (in the last 6 months) PWID in Montréal are HCV antibody positive, and based on the proportion of antibody positive individuals among whom RNA can be detected (3), the initial prevalence of chronic hepatitis C is 53%.

Initial number of acute hepatitis C infections in the PWID population: due to short duration of acute hepatitis (6 months), we assumed that the baseline proportion of active PWID with an acute hepatitis C infection was negligible.

Initial distribution in the natural history model: due to the lack of data about this parameter, we used the distribution of patients followed at the Centre hopitalier de l'université de Montréal (CHUM) for their chronic hepatitis C infection and reporting inject drug use (private communication, J. Bruneau).

Infection rate by injecting partner : this rate was fitted to obtain an incidence of 22.1/100 person-years (p.y) during the first year of simulation in the reference scenario. This value corresponds to the estimate found in SurvUDI for the 2010-2013 period. The method used was Approximate Bayesian Computation (4). This parameter was also fitted to correspond to changes in the initial set of parameters (mean number of injecting partners and the mean duration before the cessation of injection) in the sensitivity analyses (Appendix A3).

Mean duration of the high risk period after injection initiation, relative risk of infection during this period and mortality rates of active PWID: we used estimates based on PWID in studies among street youth of Montréal (5).

Mean time from the end of acute hepatitis C infection to detection: this time was derived from the time of the last test in SurvUDI for the 2012-2014 period. The details of the method are given in (6).
Mean time to linkage to care: we assumed that after detection, the first consultation for an individual related to his/her HCV infection is measured by the occurrence of a HCV RNA-test. It occurs after a mean duration of 1.7 years according to Notifiable Disease Reporting System of the Montréal Public Health Department.
Loss to follow-up rate: according to SurvUDI data, 10.2% of the PWID detected have seen a physician for hepatitis C infection in the past year. Due to our definition of linkage to care (a consultation in the previous 6 months), we considered that these PWID were lost to follow-up during the year, and thus we estimated the annual loss to follow-up rate to 10.2%/y.
Treatment initiation rate when linked to care: using SurvUDI data, the current proportion of PWID under treatment at the time of the study was estimated to be 0.4% during the 2012-2014 period. If we assume that this proportion remains stable over the short term, knowing that the standard of care during this time period was the peg-interferon + ribavirin with treatment durations of between 24 and 48 weeks (7), and knowing that the initial distribution in the "Detected and linked to care chronic hepatitis C" state is 15.3%, approximately 5% of the compartment (i.e. 0.8%) will be treated during the year.
Mortality of inactive PWID: due to the lack of data, we used mortality of the general population in Québec (8).
Ratio of the effectiveness in the real-world situation to the efficacy in clinical trials: in absence of data about the effectiveness of new DAAs after approval and market availability, we estimated this ratio based on dual-therapy peg-interferon + ribavirin. We used the following sustained virological response (SVR) rates as clinical trials values: 50% for genotypes 1/4 and 80% for genotypes 2/3 (7); and as real-world values for PWID: 42.9% for genotypes 1/4 and 73.1% for genotypes 2/3 (9). Using the genotype distribution of (10), we estimated this ratio to be 0.90.
Mean duration before the cessation of injection: due to the absence of data about PWID in Montréal, we used estimates from Fazito *et al.* for North America (2).

Table A1 parameters of the model

Parameter	Value	References
Population size	4,000	(11)
Average number of injecting partners during the injecting career	12	Derived from (1)
Initial distribution (HCV infection and cascade of care)		
Susceptible with high risk	10.10%	SurvUDI, 2012-2014, unpublished data
Susceptible with low risk	36.80%	
Acute hepatitis C	0%*	
Non-detected chronic hepatitis C	8.40%	

Detected, non-linked to care chronic hepatitis C	24.40%	SurvUDI, 2012-2014, unpublished data
Detected and linked to care chronic hepatitis C	15.30%	
Under treatment	0.40%	
Non-responders after treatment	4.60%	
Initial distribution in the natural history model		
F0/F1	61.1%	(Private communication, J. Bruneau)
F2/F3	23.3%	
F4	15.6%	
Decompensated cirrhosis	0%*	
HCC	0%*	
Infection rate by injecting partner in Susceptible (low risk)	0.025 $y^{-1}partner^{-1}$	Fitted by ABC to have a 22.1/100 p-y baseline incidence (SurvUDI, 2010-2013)
Relative risk of infection in Susceptibles (high risk)	3	(5)
Mean duration of the high-risk period, i.e. Susceptibles (high risk)	4 y	
Mean duration of acute hepatitis C	0.5 y	(12)
Probability of spontaneous recovery	26%	
Mean time from the end of acute hepatitis C to detection	2.0y	Derived from SurvUDI, 2012-2014, unpublished data
Mean time before linkage to care	1.7y	Derived from Notifiable Disease Reporting System of the Montréal Public Health Department
Loss to follow-up rate	10.3%/y	Derived from SurvUDI, 2012-2014, unpublished data
Treatment initiation rate when linked to care	5%/y	Approximate value derived from SurvUDI, 2012-2014, based on current number of people under treatment (0.4%)
Treatment: incoming DAAs regimens		
Duration	12 weeks	(13-18)
SVR rate – treatment naive - all genotypes- clinical trials	90%	
Annual mortality among active PWID	18.4/1000	(19)
Annual mortality among inactive PWID	7.5/1000	(8)
Ratio of the effectiveness in real life to the efficacy in clinical trials	0.90	Derived from (7, 9, 10)
Mean duration before the cessation of injection	9.5y	(2)
Transition rate from F0/F1to F2/F3	0.052/y	(20)
Transition rate from F2/F3 to F4	0.054/y	
Transition rate from F4 to Decompensated cirrhosis	0.04/y	
Transition rate from F4 to HCC	0.021/y	(21, 22)
Transition rate from Decompensated cirrhosis to Death related to HCV	0.306/y	

Transition rate from HCC to Death related to HCV	0.433/y	
Transition rate from Decompensated cirrhosis to HCC	0.21/y	
Relative risk after a SVR		
Decompensated cirrhosis	0.08	
HCC	0.27	(23)
Death related to HCV	0.13	

*Hypothesis
PWID: people who inject drugs; SVR: sustained virological response; HCC: hepatocellular carcinoma

A2: NUMBER OF TREATMENTS PER SCENARIO

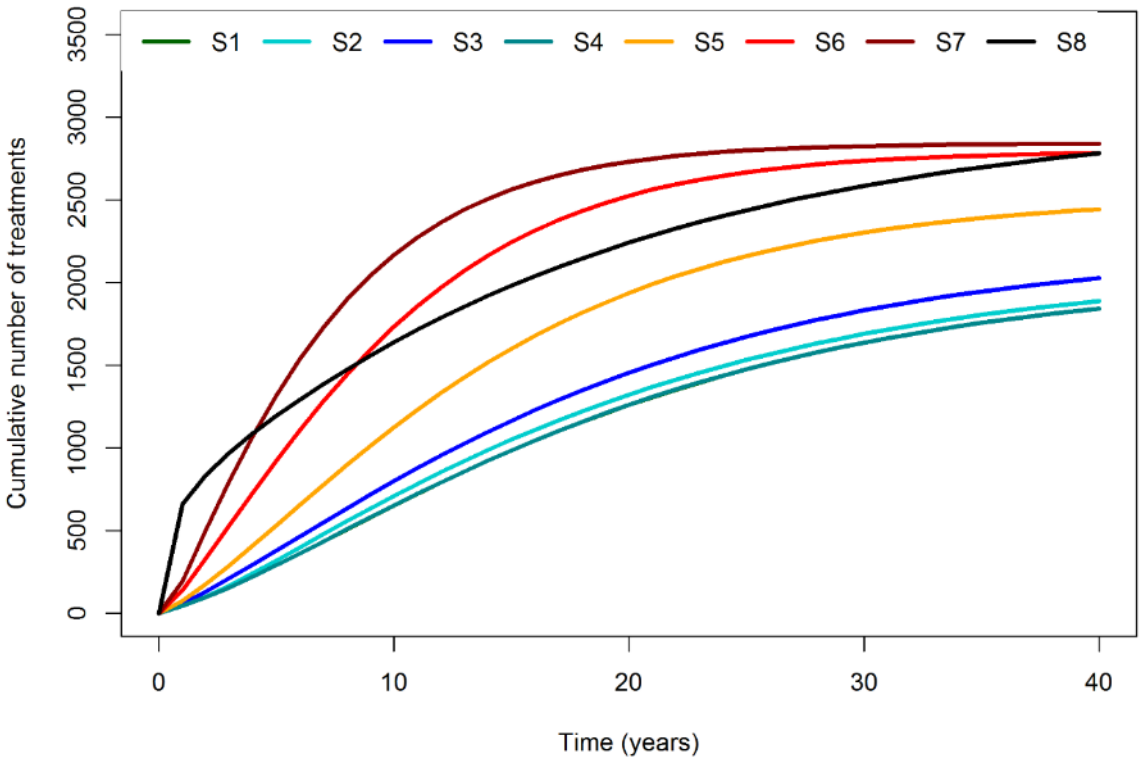

Figure S1 Cumulative number of treatments initiated in each scenario over 40 years of simulation

A3: SENSITIVITY ANALYSES

Univariate sensitivity analysis – parameters ranges

In the univariate sensitivity analysis, the values of selected parameters were varied based on their uncertainty intervals (see Table A2). When unavailable, we used values from other settings or assumptions. Explanations for some of these assumptions are given below.

Initial fibrosis distribution in infected PWID was estimated for people infected by drug injection, but not necessarily for those who were active injectors. It also assumes a first evaluation has been done and thus a population that may be more advanced relative to HCV care access. We made this initial distribution vary using less severe fibrosis scores.

In our main analysis, the risk of infection per infectious partner was assumed to remain the same after a SVR. Due to the possible cessation of drug injection and the possible treatment of infectious partners during the time elapsed before being treated, the reinfection rate is actually lower than the primary infection rate in our model: over the first 10 years of simulations, the incidence of primary infection in the reference scenario is 16.0/100 p.y. meanwhile the incidence of reinfection after a SVR is 4.9/100 p.y. However, in the literature, the annual reinfection rate ranges between 2% and 4% (9). Despite the conservative nature of our estimate, we used a relative risk of 0.5 after a SVR in the sensitivity analysis.

Table A2 Values of the parameters used in the univariate sensitivity analysis

Parameters	Base case value	Range in sensitivity analysis	References
Initial distribution in the natural history model			
F0/F1	61.1%	75*	
F2/F3	23.3%	15*	
F4	15.6%	10*	
Infection rate (per infectious injecting partner) among Susceptibles (low risk)	0.025/y	0.022 – 0.027	From ABC estimation
Mean duration of the high-risk period, i.e. Susceptibles (high risk)	4.0 y	1.0 -4.0	(24)
Relative risk of reinfection after SVR	1	0.5-1*	
Time between chronic infection and detection	2.0 years	0.5 – 7.8	(25)
Average time before linkage to carev / Loss to follow-up rate	1.7 y / 14%/y	0.5 – 4 / 2.6 – 15	(6)
Annual mortality among active PWID mortality	18.4/1000	13.8 – 23.8	(26, 27)
Annual mortality among inactive PWID mortality	7.5/1000	7.0 - 8.0*	
Average duration of injecting career	9.5 years	4.7 - 14	(2)
Transition rate from F0/F1 to F2/F3	0.052/y	0.031 - 0.074	(20)

Transition rate from F2/F3 to F4	0.054/y	0.025 – 0.101	
Transition rate from F4 to Decompensated cirrhosis	0.04/y	0.032 – 0.052	(21, 22)
Transition rate from F4 to HCC	0.021/y	0.017 – 0.028	
Transition rate from Decompensated cirrhosis to Death related to HCV	0.306/y	0.129 – 0.395	
Transition rate from HCC to Death related to HCV	0.433/y	0.319 – 0.499	
Transition rate from Decompensated cirrhosis to HCC	0.021/y	0.017 – 0.028	

*Hypothesis

PWID: people who inject drugs; SVR: sustained virological response; HCC: hepatocellular carcinoma

Mean number of 3 injecting partner

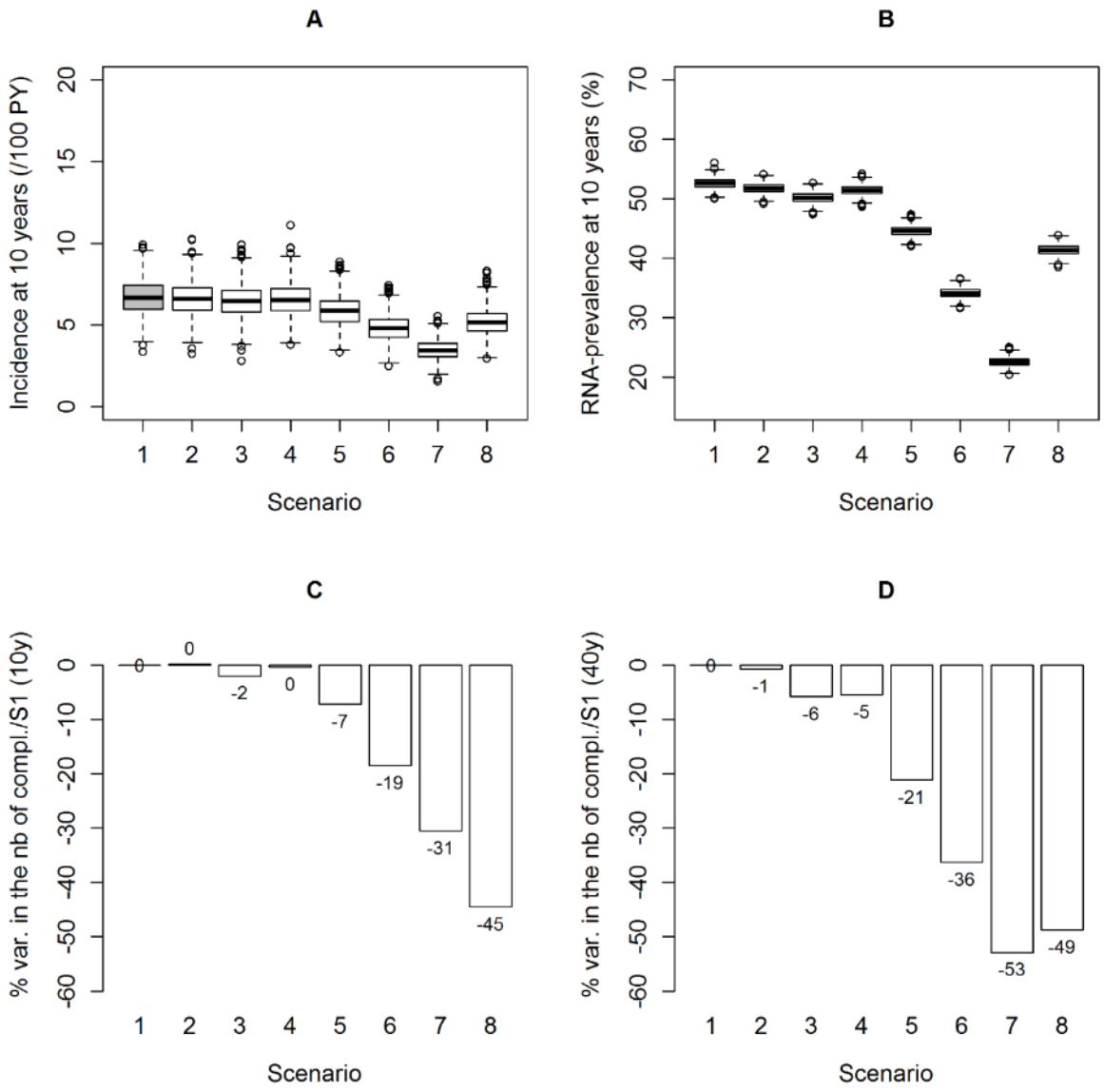

Figure S1 Results according to scenario based on 1,000 simulations, with a mean number of 3 injecting partners. A. Boxplots of the incidence at 10 years; B. Boxplots of the prevalence at 10 years; C. Proportion of cirrhosis complications avoided after 10 years (mean percentage of new cirrhosis complications avoided, compared with the reference scenario (S1)); D. Proportion of cirrhosis complications avoided after 40 years (mean percentage of new cirrhosis complications avoided, compared with the reference scenario (S1)). The infection rate per infectious partner with this set of parameters was estimated to be 0.098/y using Approximate Bayesian Computation to have an initial incidence of 22.1/100 p.y. S1 (reference): current cascade of care with the new antivirals; S2: improvement in testing; S3: improvement in linkage to care; S4: improvement in adherence to treatment; S5: moderate improvement in the treatment initiation rate; S6: high improvement in the treatment initiation rate; S7: combined S2, S3, S4 and S6; S8: systematic treatment initiation when linked to care, but only for F2-F3-F4 fibrosis scores.

Mean number of 15 injecting partner

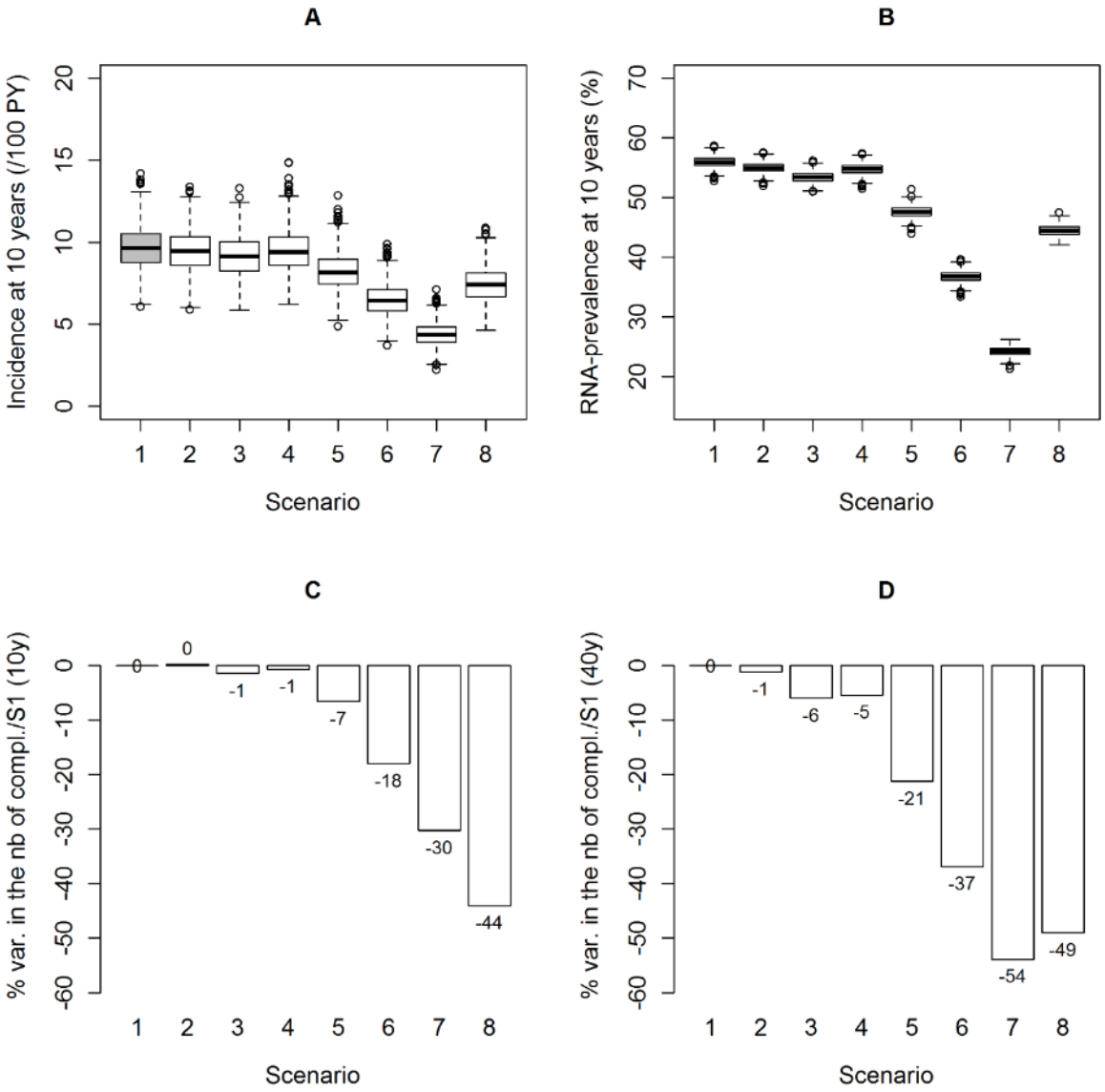

Figure S2 Results according to scenario based on 1,000 simulations, with a mean number of 15 injecting partners. A. Boxplots of the incidence at 10 years; B. Boxplots of the prevalence at 10 years; C. Proportion of cirrhosis complications avoided after 10 years (mean percentage of new cirrhosis complications avoided, compared with the reference scenario (S1)); D. Proportion of cirrhosis complications avoided after 40 years (mean percentage of new cirrhosis complications avoided, compared with the reference scenario (S1)). The infection rate per infectious partner with this set of parameters was estimated to be 0.020/y using Approximate Bayesian Computation to have an initial incidence of 22.1/100 p.y. S1 (reference): current cascade of care with the new antivirals; S2: improvement in testing; S3: improvement in linkage to care; S4: improvement in adherence to treatment; S5: moderate improvement in the treatment initiation rate; S6: high improvement in the treatment initiation rate; S7: combined S2, S3, S4 and S6; S8: systematic treatment initiation when linked to care, but only for F2-F3-F4 fibrosis scores.

Mean duration before cessation of injection 4.7 years

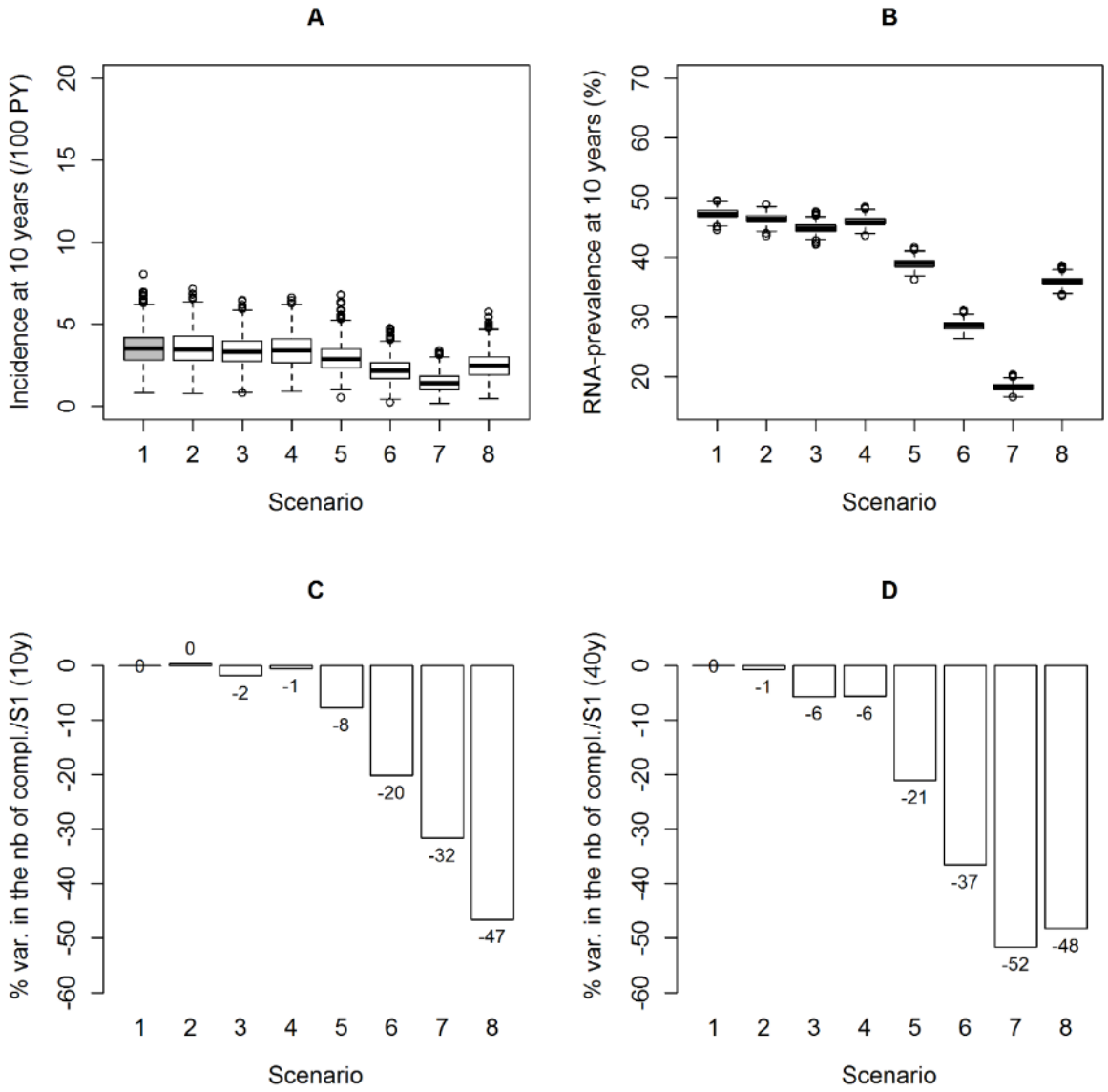

Figure S3 Results according to scenario based on 1,000 simulations, with a mean duration of the injecting career of 4.7 years. A. Boxplots of the incidence at 10 years; B. Boxplots of the prevalence at 10 years; C. Proportion of cirrhosis complications avoided after 10 years (mean percentage of new cirrhosis complications avoided, compared with the reference scenario (S1)); D. Proportion of cirrhosis complications avoided after 40 years (mean percentage of new cirrhosis complications avoided, compared with the reference scenario (S1)). The infection rate per infectious partner with this set of parameters was estimated to be 0.026/y using Approximate Bayesian Computation to have an initial incidence of 22.1/100 p.y. S1 (reference): current cascade of care with the new antivirals; S2: improvement in testing; S3: improvement in linkage to care; S4: improvement in adherence to treatment; S5: moderate improvement in the treatment initiation rate; S6: high improvement in the treatment initiation rate; S7: combined S2, S3, S4 and S6; S8: systematic treatment initiation when linked to care, but only for F2-F3-F4 fibrosis scores.

Mean duration before cessation of injection 14 years

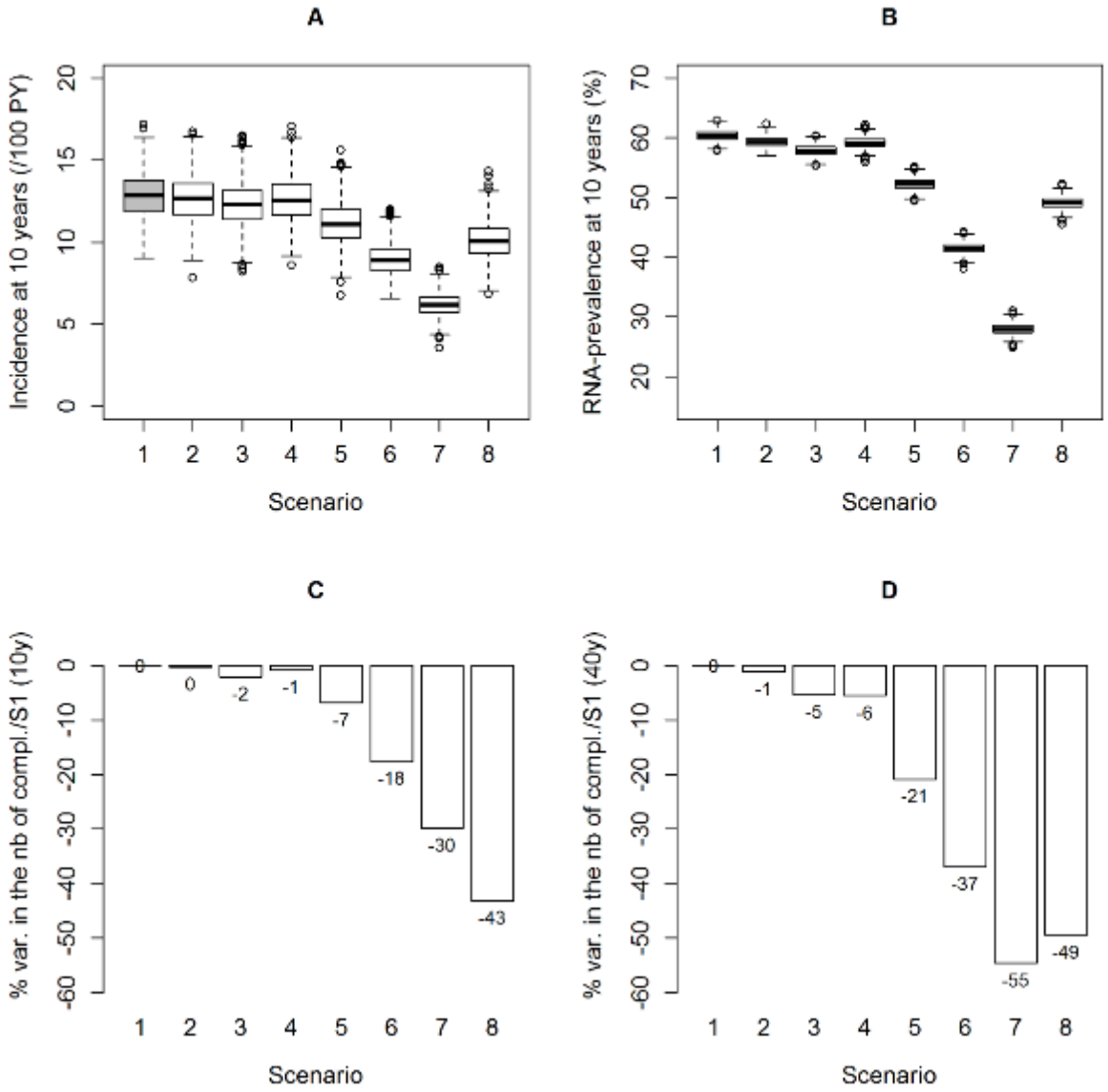

Figure S4 Results according to scenario based on 1,000 simulations, with a mean duration of the injecting career of 14 years. A. Boxplots of the incidence at 10 years; B. Boxplots of the prevalence at 10 years; C. Proportion of cirrhosis complications avoided after 10 years (mean percentage of new cirrhosis complications avoided, compared with the reference scenario (S1)); D. Proportion of cirrhosis complications avoided after 40 years (mean percentage of new cirrhosis complications avoided, compared with the reference scenario (S1)). The infection rate per infectious partner with this set of parameters was estimated to be 0.024/y using Approximate Bayesian Computation to have an initial incidence of 22.1/100 p.y. S1 (reference): current cascade of care with the new antivirals; S2: improvement in testing; S3: improvement in linkage to care; S4: improvement in adherence to treatment; S5: moderate improvement in the treatment initiation rate; S6: high improvement in the treatment initiation rate; S7: combined S2, S3, S4 and S6; S8: systematic treatment initiation when linked to care, but only for F2-F3-F4 fibrosis scores.

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5 Estimation de la probabilité de survenue d'un évènement rare : application à la probabilité d'élimination du VHC chez les UDI par une stratégie de « Treatment as Prevention »

5.1 Résumé

Estimer la probabilité de survenue d'un évènement rare en s'appuyant sur un modèle probabiliste plutôt que sur des données statistiques est nécessaire dans de nombreux domaines, par exemple pour évaluer un risque financier, le risque de défaillance d'un avion de ligne ou le risque de survenue d'une catastrophe naturelle ou industrielle (Rubino et al. 2009). Dans le domaine de la santé publique, estimer la probabilité de survenue de certains évènements peut également représenter un enjeu important. Dans le cas de maladies infectieuses, la probabilité qu'une épidémie persiste pendant un certain laps de temps, ou qu'elle dépasse un certain seuil (au niveau du nombre d'individus infectés) sont des exemples d'évènements d'intérêt relatif à la pérennisation de l'épidémie. C'est par exemple le cas de l'infection par le virus Ebola, pour laquelle de nombreuses épidémies de taille modérée ont eu lieu en Afrique au cours des 50 dernières années, avant qu'une épidémie majeure ne se déclenche en Afrique de l'Ouest dans le courant de l'année 2014. La probabilité d'extension de l'épidémie à l'ensemble du monde est devenue une question centrale (Gomes et al. 2014). Dans le domaine de l'hépatite C, à l'inverse, l'utilisation du TasP pose la question de la probabilité d'élimination du VHC, c'est-à-dire la possibilité d'atteindre localement une incidence nulle (Dowdle 1998).

Lorsque la probabilité de survenue de l'évènement est faible, l'estimation de la probabilité de survenue de cet évènement par des méthodes de Monte-Carlo classiques pose problème. En effet, cette technique repose sur l'estimation d'une moyenne empirique $\frac{1}{n}\sum_{i=1}^{n} X_i$ où n représente le nombre de simulations effectuées et X_i est la variable aléatoire indicatrice de la survenue de l'évènement d'intérêt dans la simulation i. Si la loi des grands nombres assure la convergence presque-sûrement de cet estimateur, une estimation précise de la probabilité de survenue d'un évènement rare va nécessiter un grand nombre de simulations, afin de s'assurer que l'évènement d'intérêt a été observé un nombre raisonnable de fois.

L'objectif de cet article était de passer en revue différentes méthodes d'estimation de probabilités de survenue d'évènements rares afin de comparer les performances de ces différentes méthodes sur des exemples simples, et d'estimer la probabilité d'élimination du VHC dans une population d'UDI en France par une stratégie de TasP.

Les trois méthodes comparées sont : l'estimation par méthode de Monte-Carlo, l'échantillonnage préférentielle (ou *importance sampling)*, et l'algorithme IBPS (pour *interacting branching particle system*).

L'estimateur de Monte-Carlo, telle que défini ci-dessus consiste simplement à simuler le modèle un grand nombre de fois pour estimer dans quelle proportion de simulations l'évènement se produit.

La méthode par échantillonnage préférentielle consiste à sélectionner, pour les simulations, un jeu de paramètres favorisant la survenue de l'évènement rare dans la distribution des trajectoires épidémiques (Asmussen et al. 2007; Bucklew 2013). L'estimateur final est alors une moyenne empirique pondérée par la *fonction d'importance* ϕ, le rapport entre la vraisemblance de la trajectoire considérée sous le jeu de paramètres initial et la vraisemblance sous le jeu de paramètres sélectionné pour favoriser l'apparition de l'évènement rare. Notons $\mathbb{P}$ la mesure de probabilité sous le jeu de paramètres initial et $\mathbb{P}_{new}$ la mesure sous le jeu de paramètres sélectionné. On a alors :

$$\mathbb{P}(\mathcal{E}) = \int \phi \mathbb{I}(\mathcal{E}) d\mathbb{P}_{new}$$

Avec $\mathcal{E}$ l'évènement d'intérêt. Cette intégrale peut elle-même être estimée par des méthodes de Monte-Carlo. Le problème réside alors dans le choix de ce jeu de paramètres. Nous avons pour cela considéré un algorithme adaptatif par *cross-entropy*, un algorithme itératif où, à chaque étape, le nouveau jeu de paramètre sélectionné est celui minimisant l'entropie par rapport à la distribution originale des trajectoires (Rubinstein 1997).

Enfin, la méthode IPBS est également une méthode itérative (Villén-Altamirano et al. 1991; Dean et al. 2011). Elle repose sur la décomposition de la probabilité de l'évènement rare en un produit de probabilités conditionnelles correspondant à des évènements plus susceptible de se produire lors des simulations. Par exemple, considérons un évènement d'intérêt de la forme

$$\mathcal{E} = \{\tau_A \leq \mathcal{T}\}$$

avec A un ensemble, $\tau_A = \inf\{t \geq 0 : Z(t) \in A\}$, Z la trajectoire de l'épidémie (par exemple, dans le cas d'un modèle SIR, $Z = (S(t), I(t), R(t))$ la répartition dans chaque compartiment à l'instant t) et $\mathcal{T}$ un temps d'arrêt presque sûrement fini. Les évènements décrits plus haut (extinction d'épidémie, dépassement d'un seuil, etc.) peuvent la plupart du temps s'écrire sous cette forme. L'idée de la méthode IPBS consiste à subdiviser l'ensemble A en une suite croissante de sous-ensembles $A_0 \supset A_1 \supset \cdots \supset A_{K+1} = A$, dont la survenue est de plus en plus difficile dans les simulations. On a donc :

$$\mathbb{P}(Z \in A) = \mathbb{P}(Z \in A_0) \prod_{k=0}^{K} \mathbb{P}(Z \in A_{k+1} \mid Z \in A_k)$$

Si cette suite de sous-ensembles est bien choisie, aucune des probabilités conditionnelles mentionnées ne correspond à un évènement rare, et ces probabilités peuvent être estimées par des méthodes de Monte-Carlo. L'algorithme consiste alors à simuler un jeu de trajectoires et à sélectionner, à chaque itération k, les trajectoires ayant atteint l'ensemble A_k. Les autres trajectoires sont rejetées et remplacées par une des trajectoires sélectionnées, par un tirage aléatoire. Chaque trajectoire est ensuite prolongée par simulation. Encore une fois, pour s'affranchir du problème de la sélection des différents seuils, nous avons utilisé un algorithme adaptatif en sélectionnant une proportion des trajectoires à chaque étape (par exemple, les 20% de trajectoires ayant atteint l'incidence la plus faible). La difficulté restante consiste à choisir ce pourcentage.

Chacune de ces méthodes a ensuite était appliquée à trois modèles afin d'estimer la probabilité pour une épidémie de dépasser un seuil d'infectés N_c :

1) Dans une épidémie modélisée par un modèle de Reed-Frost, un modèle à temps discret et deux compartiments (Susceptible et Infectieux) (Abbey 1952). Les paramètres utilisés étaient fictifs.
2) Dans une épidémie modélisée par un modèle SIR sans démographie (Kermack et al. 1927), stochastique et à temps continu. Les deux ensembles de paramètres utilisés provenaient d'un article d'O'Neill and Roberts (O'Neill et al. 1999), le premier correspondant à une épidémie fictive et le second à une épidémie de variole en 1975 au Nigeria.
3) Dans une épidémie décrite par un modèle SIR structuré par âge avec démographie et *contact tracing* (c'est-à-dire avec détection plus rapide des individus infectieux grâce aux individus déjà détectés) modélisant l'épidémie de VIH à Cuba (Clemencon et al. 2008; Blum et al. 2010). Pour cet exemple, la méthode par échantillonnage préférentielle n'a pas été appliquée, à cause de temps de calcul engendrés.

Pour chacun de ces tests, 1 000 estimations ont été effectuées, et la valeur de la probabilité estimée, son écart-type et le temps de simulations ont été calculés. L'estimation moyenne par Monte-Carlo a servi de référence, la quantité de simulations effectuées (1 000 fois 1 000 trajectoires) garantissant une estimation correcte de la probabilité.

Les résultats montrent que, premièrement, avec les méthodes de Monte-Carlo, une large proportion des estimations donnent une probabilité nulle de survenue de l'évènement, ce qui peut conduire à sous-estimer son risque de survenue, et donne un écart-type relativement élevé dans les estimations. Deuxièmement, les méthodes par échantillonnage préférentiel, bien que fournissant une estimation moyenne proche de la référence et un écart-type plus faible que la méthode de Monte-Carlo, nécessite des temps de calcul beaucoup plus élevés que les autres méthodes (jusqu'à 45 fois plus élevés), ce qui peut poser problème pour les modèles nécessitant des temps de calcul élevés. Enfin, les méthodes IPBS, bien que prometteuses par certains aspects (temps de calcul modéré par rapport à la méthode par échantillonnage préférentiel, écart-type parfois plus faible que la méthode de Monte-Carlo) pose problème au niveau de choix du seuils de trajectoires à retenir, l'écart avec l'estimation de référence pouvant, dans certains cas, devenir très important.

Finalement, la méthode IPBS a été appliquée au modèle de transmission du VHC chez les UDI en France utilisée pour l'analyse coût-efficacité du chapitre 6 afin d'estimer une probabilité d'élimination (c'est-à-dire d'obtenir une incidence nulle) à 10 ans dans une communauté de 524 UDI. Les paramètres du modèle correspondent au scénario « améliorations combinées de la cascade de soins » (scénario 7) de l'analyse du chapitre 3 : le diagnostic d'hépatite C chronique se fait en moyenne 0.5 an après le passage à la chronicité ; le lien aux soins 0.5 an en moyenne après le diagnostic ; le taux de perte de vue est de 5%/an ; le traitement est initié chez les individus liés aux soins et dont le stade de fibrose se situe entre F0 et F4 ; et le taux de réussite du traitement est de 90%. Malgré toutes ces améliorations de la cascade de soins, la probabilité d'élimination du VHC a été estimée à 1.8%. Ce résultat confirme que

l'élimination du VHC par une approche basée sur le traitement est hautement improbable, et que, pour atteindre cet objectif, la recherche de stratégies alternatives de réduction des risques est une nécessité.

Des extensions de ce travail sont envisageables, particulièrement pour la méthode d'échantillonnage préférentielle. En effet, le principal problème de cette méthode est la recherche d'un jeu de paramètres favorisant la survenue de l'évènement d'intérêt. Notons $\overline{X^{(n)}} = \frac{1}{n}\sum_{i=1}^{n} X_i$ la proportion de simulation (parmi un total de n) où l'évènement s'est produit. Dans la méthode par échantillonnage préférentielle, on cherche un jeu de paramètres favorisant la survenue de l'évènement, donc à augmenter une probabilité de la forme $P(\overline{X^{(n)}} > x)$, avec $0 < x < 1$. L'étude des grandes déviations pour les modèles considérés, c'est-à-dire du comportement asymptotique de cette probabilité, pourrait permettre d'améliorer la performance de cette méthode.

Ma contribution à cet article à consister à programmer en C++ les différents modèles ainsi que le calcul des estimateurs par échantillonnage préférentielle et par IBPS. J'ai également participé à la rédaction des méthodes, des résultats et des conclusions.

Cette étude a fait l'objet d'une publication parue dans *Statistics in Medicine* (Clemencon et al. 2015).

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On computer-intensive simulation and estimation methods for rare-event analysis in epidemic models

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This article focuses, in the context of epidemic models, on *rare events* that may possibly correspond to crisis situations from the perspective of public health. In general, no close analytic form for their occurrence probabilities is available, and crude Monte Carlo procedures fail. We show how recent intensive computer simulation techniques, such as *interacting branching particle methods*, can be used for estimation purposes, as well as for generating model paths that correspond to realizations of such events. Applications of these simulation-based methods to several epidemic models fitted from real datasets are also considered and discussed thoroughly. **Copyright © 2015 John Wiley & Sons, Ltd.**

Keywords: stochastic epidemic model; rare-event analysis; Monte Carlo simulation; importance sampling; interacting branching particle system; genetic models; multilevel splitting

1. Introduction

Since the seminal contribution of [1, 2], the mathematical issues raised by the modeling and statistical analysis of the spread of communicable infectious diseases have never ceased to receive attention in the applied probability and statistics communities. Given the great diversity of situations encountered in practice (impact of demographic phenomena, presence of control strategies, endemicity, population heterogeneity, time-varying infectivity, etc.), a wide variety of stochastic epidemic models have been introduced in the literature, striving to incorporate more and more relevant features in order to account for real-life situations, while remaining analytically tractable. The study of the properties of the related stochastic processes (branching approximations, long-term behavior, large population asymptotics, etc.) and the design of efficient inference methods tailored for (generally partially observed) epidemic data are still stimulating research on mathematical epidemiology. Beyond considerations of purely academic nature, many notions and techniques developed in this field are important for practitioners. Epidemic models are used to understand and control infectious diseases, and their theoretical analysis sheds some light on how to come up with figures such as the reproduction number R_0 of the epidemics (when well defined). From a public health guidance perspective, they can be deployed in order to simulate the likeliest scenarios or compute the probabilities of certain events of interest and plan control measures to staunch a disease outbreak in real time. However, in most situations, these probabilities cannot be directly inferred from historical data, no closed analytical form depending on the model parameters is available for such quantities, and the latter are related to events that occur very rarely, for which crude Monte Carlo (CMC) estimation completely fails.

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It is the main purpose of this paper to review possible techniques for rare-event simulation and inference in the context of epidemic models. Motivated by practical issues in public health, we are concerned here with critical events such as an exceedingly long duration for an epidemic, an extremely large total number of positive diagnoses (i.e., large final size of the epidemic) in nonendemic cases, and the occurrence of a severe outbreak at a short horizon. Here, we list a number of events that may correspond to crisis situations and express the latter as excesses of a (very large) threshold by a random variable or a (randomly stopped) stochastic process for a general class of susceptible–infected–removed (SIR) epidemic models. *Importance sampling* (IS) and *particle filtering* methods are next adapted to tackle the problem of estimating the occurrence probabilities of these events, as well as that of simulating realizations of the latter. Beyond the description of the methodological aspects, application of these techniques for analyzing a collection of rare events related to several numerical epidemic models, some of them being fitted from real data, is also discussed. One may indeed reasonably expect that, following the example of the various fields where the analysis of rare events (e.g., natural disasters, component failures, and network intrusions) is now currently used to perform worst-case analyses in risk management, ranging from hydrology to operations research through finance or security (see the references listed in [3] for instance), public health may also take advantage of methods such as those promoted in the present article.

This article is structured as follows. Section 2 introduces a general class of epidemic models, to which the simulation/estimation techniques subsequently described apply and next review events related to these models, that may correspond to health crisis situations and generally occur very rarely. Simulation-based procedures for estimating the probability of occurrence of these events are described in Section 3, while practical applications of these techniques, based on real datasets in some cases, are considered in Section 4 for illustration purposes. In the first example, an HIV-AIDS epidemic model with contact tracing fitted to real data related to the HIV spread in Cuba is considered with the aim to estimate the probability that the incidence rate over a certain period of time exceeds a critical threshold. The second example is related to an hepatitis C virus (HCV) epidemic model for people who inject drugs, fitted to French data: by means of the methodology we promote in this paper, we tackle the issue of determining whether one may reasonably expect that new treatments may lead to a short-term elimination of HCV in the population considered or not. Some concluding remarks are finally collected in Section 5. In this work, it is shown that the CMC method often fail to provide good estimates of rare events. IS methods are a well-known alternative to estimate the occurrence probabilities of rare events. However, their efficiency relies on the choice of proper instrumental distributions, which is very complicated for most probabilistic models encountered in practice. Particle systems with genealogical selection offer an efficient computationally based tool for estimating the targeted small probabilities.

2. Background

It is the goal of this section to introduce a general class of epidemic models to which the computer-intensive estimation techniques described in the subsequent section apply. The (rare) events that shall be next statistically analyzed are formulated in terms of path properties of stochastic processes.

2.1. Epidemic models

The vast majority of (stochastic) epidemic models considered in the literature are of the *compartmental* type. They assume that the population of interest is divided into several strata or compartments, corresponding in particular to the various possible serological statuses, and stipulate a probabilistic framework that describes the transitions from one compartment to another.

2.1.1. The Reed–Frost model. One of the simplest epidemic models is the discrete-time chain-binomial model, generally referred to as the Reed–Frost model, which describes the spread of an infectious disease in a homogeneous and homogeneously mixing population. New infections are assumed to occur in generations, $t = 0,\ 1,\ \ldots$, and immunity is gained by the infectives of generation t at generation $t + 1$. Denoting by S_t and I_t the numbers of individuals at the t-th generation who are *susceptible* and *infective*, respectively, and by $1-q$ the probability that an infective transmits the disease to a given susceptible at any

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generation (infections being assumed to occur independently from each other), the sequence $\{(S_t, I_t)\}_{t\in\mathbb{N}}$ with initial state $(s_0, i_0) \in \mathbb{N}^{*2}$ is a Markov chain with transitions as follows: for all $t \in \mathbb{N}$, (s_t, i_t) in $\mathbb{N}^2$ and i_{t+1} in $\{0,\ 1,\ \ldots,\ s_t\}$,

$$\mathbb{P}\left\{I_{t+1} = i_{t+1} \mid (S_t, I_t) = (s_t, i_t)\right\} = \binom{s_t}{i_{t+1}} \left(1 - q^{i_t}\right)^{i_{t+1}} \left(q^{i_t}\right)^{s_t - i_{t+1}} \tag{1}$$

and

$$S_{t+1} = S_t - I_{t+1}. \tag{2}$$

The set $\mathbb{N} \times \{0\}$ is *absorbing* for the Markov chain (S_t, I_t), meaning that the epidemics ceases as soon as the chain reaches this set (and then stays there forever); one may refer to [4] for an account of the Markov chain theory.

2.1.2. The standard stochastic susceptible–infected–removed model. The most basic continuous-time stochastic epidemic model, generally referred to as the standard (Markovian) SIR model in a closed population of size n (see the seminal contribution of [2] for instance), counts three compartments: the *susceptible class S*, the *infective class I*, and the *removed/recovered class R*. This corresponds to the situation where the epidemic is of short duration, making acceptable the assumption of a closed population, and the disease provides immunity against a possible reinfection. Figure 1 depicts the diagram flow of this simple epidemic model (taking $\mu = \rho \equiv 0$). For clarity, we index the events E through which the sizes $S(t)$, $I(t)$, and $R(t)$ of the three compartments that form the population evolve temporarily: we write $E = 1$ when the event that occurs is an infection and $E = 2$ when it corresponds to the removal of an infective. Taking by convention $T_0 = 0$ as time origin, the (continuous-time) dynamics of the model stipulates that all durations in competition are independent; infections and removals occur at time $t \geqslant 0$ with the rates $\lambda(S(t), I(t)) = \lambda S(t) I(t)/n$ and $\gamma(I(t)) = \gamma I(t)$, where $(\lambda, \gamma) \in \mathbb{R}_+^*$, respectively. Hence, the process $Z = \{(S(t), I(t), R(t))\}_{t\geqslant 0}$ evolves in a Markovian fashion, by jumps at random times $0 < T_1 < T_2 < \ldots$, when events $E_1,\ E_2,\ \ldots$ in $\{1,\ 2\}$ successively occur. The dynamics can be described by stochastic differential equations driven by Poisson point measures.

2.1.3. Variants of the standard susceptible–infected–removed model. When the epidemic under study acts on a large temporal scale, it may be necessary to incorporate additional features in the model (cf. rates μ and ρ featured in Figure 1) accounting for the demography of the population over which the disease spreads in an endemic manner. The number and the nature of the compartments involved in the epidemic models may also vary, depending on the infectious disease considered. For instance, the SIRS model corresponds to the situation, where immunity is lost after some time, while some AIDS epidemic models count numerous compartments, in order to account for the (nonexponentially distributed) AIDS incubation period (this approach is usually referred to as *stage modeling* [5]). Additionally, the possible heterogeneity of the population may lead to removal of the assumption of *uniform mixingness* and consider instead *multitype epidemic models* (refer for instance to Chapter 6 in [6] for a review of SIR models where the population is segmented into a finite number of subcommunities) or a population *structured by continuous variables* (see [7] for such a measure-valued stochastic process and the references therein) or the spread on random graphs that represent the underlying social network structure of the population (e.g., [8, 9]). Indeed, there are many variants of the model described earlier, much too numerous to be listed here exhaustively. For clarity, the problem of estimating the probability of rare events related to the spread of a transmittable disease shall be addressed in the context of simple or even simplistic models, where the epidemics is described by a discrete-time Markov chain or a jump Markov process, extensions to more general situations being straightforward in most cases.

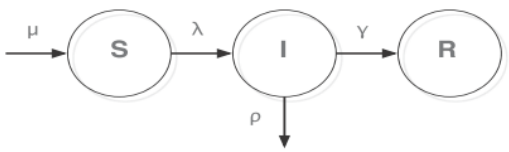

Figure 1. Diagram flow of a basic susceptible (S)–infected (I)–removed (R) stochastic model with demography.

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2.2. Rare/dramatic events in infectious disease epidemics

In the management of epidemics of communicable infectious diseases, the following events and quantities are of particular interest to public health decision makers. Here and throughout, we set $\inf \emptyset = +\infty$ by convention. The event of interest is denoted by $\mathcal{E}$. We will see that pertinent events often take the form $\mathcal{E} = \{\tau_A \leqslant \mathcal{T}\}$, where A is a subset of the space $\mathbb{N}^3$ where the epidemics process Z takes its values and where $\tau_A = \inf\{t \geqslant 0 : \ Z(t) \in A\}$ and $\mathcal{T}$ are almost surely finite stopping times. Hence, we are interested in level-crossing probabilities of the form

$$\mathbb{P}\left\{\tau_A \leqslant \mathcal{T}\right\}. \tag{3}$$

- *Duration of the epidemics.* In nonendemic situations, the epidemic starts at a time arbitrarily set to $t = 0$ and ends at a short-term horizon, described by the (almost surely finite) stopping time

$$\tau = \inf\{t \geqslant 0 : \ \ I(t) = 0\}.$$

  Sharply estimating the probability $p_d(T) = \mathbb{P}\{\tau > T\}$ that the epidemics lasts more than a (very long) period of time $[0, T]$, with $0 < T < +\infty$, is an essential concern from the public health perspective. The computation of $1 - p_d(T)$ corresponds to (3) in the case where $\mathcal{T} = T$ and $A = \mathbb{N} \times \{0\} \times \mathbb{N}$.
- *The final size of the epidemics.* The final size of the epidemics corresponds to the total number of infected individuals between times 0 and τ; it is thus defined as the random variable $R(\tau)$. The probability $p_f(N_c) = \mathbb{P}\{R(\tau) \geqslant N_c\}$ that the size $R(\tau)$ exceeds a (critical) threshold value $N_c \geqslant 1$ (smaller than n in the case of a closed population of total size $n \geqslant 1$) is of vital interest to quantify the means to be put in place (quarantine measures, supply of medications, number of hospital beds, etc.). Considering the stopping time $\tau_{R,N_c} = \inf\{t \geqslant 0 : \ \ R(t) \geqslant N_c\}$, notice that one may write

$$p_f\left(N_c\right) = \mathbb{P}\left\{\tau_{R,N_c} \leqslant \tau\right\}. \tag{4}$$

  $p_f(N_c)$ reduces to (3) with $\mathcal{T} = \tau$ and $A = \mathbb{N} \times \mathbb{N} \times \{N_c, \ N_c + 1, \ \ldots\}$.
- *The incidence of the epidemics.* In order to handle in real time a crisis situation, it is relevant to consider *time-dependent* quantities such that the probability that the (noncumulative) number of infectious individuals reaches a critical value N_I at a certain time horizon $T < \infty$. Let $\tau_{I,N_I} = \inf\{t \geqslant 0 : \ \ I(t) \geqslant N_I\}$ be the corresponding stopping time; the probability one seeks to estimate is then given by

$$p_I\left(T, N_I\right) = \mathbb{P}\left\{\tau_{I,N_I} \leqslant T\right\}. \tag{5}$$

  The quantity $p_I(T, N_I)$ corresponds to (3) when $\mathcal{T} = T$ and $A = \mathbb{N} \times \{N_I, N_I + 1, \ldots\} \times \mathbb{N}$.

Along these lines, because public health decision makers often adjust their policies, depending on the number of recently diagnosed cases, one may also be interested in the following quantity, related to removed individuals (assuming by convention that, once detected, an infected individual is removed from the subpopulation of infectives): the probability that the number of cases diagnosed between times t and $t + u$ increases by more than a threshold value $N_R \geqslant 1$, which is given by $\mathbb{P}\left\{R(t + u) - R(t) \geqslant N_R\right\}$. Although many other rare events of this type, related to an excessive duration or an exceedance of a large threshold, are of potential interest, given the wide variety of epidemic models (echoing the great diversity of real situations), methods for simulating rare events and estimating their probability of occurrence shall be investigated here through the examples listed earlier in the context of basic SIR models for the sake of simplicity.

3. Simulation methods for rare-event analysis

The use of Monte Carlo simulation techniques is widespread in mathematical epidemiology (e.g., [10]). However, CMC completely fails when applied to rare events such as those listed in Section 2.2. We first provide in Section 3.1 two illustrations showing the limits of CMC. An alternative in rare-event simulation is known as IS, presented in Section 3.2. Roughly speaking, it consists of simulating under a different probability distribution (referred to as the *instrumental distribution*, equivalent to the original probability measure along a certain filtration) under which the event of interest $\mathcal{E}$ is more frequent. However, in the absence of large-deviation results for the vast majority of stochastic SIR models in the literature, proper instrumental distributions are difficult to obtain. In Section 3.3, we present the interacting and branching particle system (IBPS) methods method. We describe the method and perform numeric experiments in Section 4.

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3.1. Illustrations of the numerical inadequacy of crude Monte Carlo for simulating rare events

We study numerically two examples to illustrate the low quality of CMC for estimating the probabilities of rare events.

First, let us consider the basic Markovian SIR model without demography (Section 2.1). For this simple model, the distribution of the final size $R(\tau)$ is proved to be the unique solution of a triangular linear system (see Theorem 2.2 in [6] for instance or [11] for exact results of the same type in a more general framework), making the exact computation of the quantity $p_f(N_c)$ feasible (neglecting numerical stability issues, occurring even for moderate values of the population size n), whatever the threshold $N_c \geqslant 1$. As shown by Figure 2, for this particular example, the accuracy of CMC estimates of the probability $p_f(N_c)$ rapidly deteriorates when N_c takes very large values (close to the total size of the population), with very few (or even no) realizations of the stochastic process achieving the event $\{R(\tau) \geqslant N_c\}$, leading to a significant underestimation of $p_f(N_c)$, in spite of a large number of Monte Carlo replications.

Additional comments can be found in Section 4, when discussing the results.

3.2. Importance sampling

A standard approach to rare-event simulation is known as *IS* [12, 13]. The (unbiased) estimate of the probability of occurrence of the rare event is obtained by multiplying the empirical frequency of the simulations under the instrumental distribution by the likelihood ratio ϕ, referred to as the *importance function*. For instance, when considering the standard Markovian SIR model described in the preceding section, a natural way of accelerating the occurrences of the events listed in Section 2.2 is to speed up the infection process, while slowing down the removals (i.e., increasing the value of the parameter λ and decreasing that of the parameter γ). More precisely, let $\mathbb{P}$ be the probability measure under which the process $\{(S(t), I(t), R(t))\}_{t\geqslant 0}$ is a standard Markovian SIR model with parameters $(\lambda,\ \gamma) \in \mathbb{R}_+^{*2}$ and such that $(S(0), I(0)) = (s_0, i_0) \in \mathbb{N}^{*2}$. Let $\mathbb{P}_{\text{new}}$ correspond to the pair $(\lambda_{\text{new}},\ \gamma_{\text{new}}) \in \mathbb{R}_+^{*2}$, such that $\lambda_{\text{new}} \geqslant \lambda$ and $\gamma_{\text{new}} \leqslant \gamma$. Clearly, these probability measures are absolutely continuous with respect to each other along the canonical filtration $\mathcal{F} = \{\mathcal{F}_t\}_{t\geqslant 0}$ (i.e., $\mathcal{F}_t$ is the σ-algebra generated by the collection of random variables $\{(S(u), I(u))\}_{u\in[0,t]}$ for all $t \geqslant 0$): on $\mathcal{F}_t$, the importance function (i.e., the likelihood ratio $d\mathbb{P}/d\mathbb{P}_{\text{new}}\,|_{\mathcal{F}_t}$) is given by

$$\phi_t = \exp\left(-\int_0^t \left(\lambda - \lambda_{\text{new}}\right) S(s)I(s)/n + \left(\gamma - \gamma_{\text{new}}\right) I(s)ds\right) \left(\lambda/\lambda_{\text{new}}\right)^{N(t)-R(t)} \left(\gamma/\gamma_{\text{new}}\right)^{R(t)},$$

where $N(t)$ denotes the number of events $E \in \{1,\ 2\}$ occurring between times 0 and t and $T_{N(t)}$ is the last time when an event of this type occurs before time t. This extends to the situation where t is

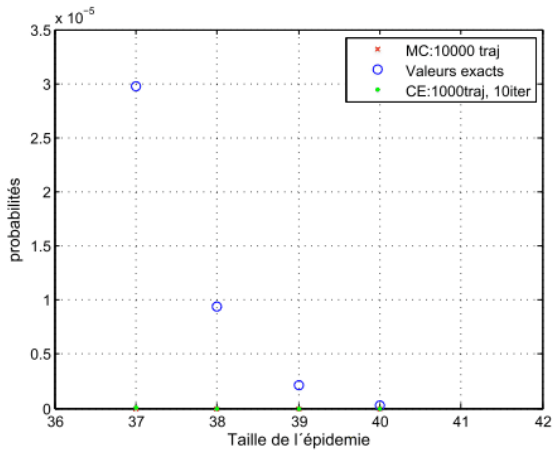

Figure 2. In a Markovian SIR model with $(s_0, i_0) = (40, 1)$ and parameters $\lambda = 1$ and $\gamma = 1$, crude Monte Carlo estimate ('MC') of the probability $p_f(N_c)$ that the size of the epidemics takes a given value is plotted as a function of N_c ('Taille de l'épidémie') based on 10,000 Monte Carlo replicates of the trajectory of the epidemic process. True values ('Valeurs exactes') and cross-entropy estimates ('CE') with $K = 10$ iterations and $N = 1000$ sample paths are also computed.

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an $\mathcal{F}$-stopping time, such as the times of exceedance considered in Section 2.2. Hence, if $\mathcal{E} \in \mathcal{F}_t$, we have $\mathbb{P}\{\mathcal{E}\} = \int \phi_t \cdot \mathbb{1}\{\mathcal{E}\}\, d\mathbb{P}^{\text{new}}$, denoting by $\mathbb{1}\{\mathcal{E}\}$ the indicator function of the event $\mathcal{E}$. The success of IS crucially depends on the choice of the instrumental distribution (the specification of the instrumental parameters $(\lambda_{\text{new}},\ \gamma_{\text{new}})$ in the example previously mentioned). Ideally, it should be selected so as to reduce drastically the variance of the random variable $\phi_t \cdot \mathbb{1}\{\mathcal{E}\}$; otherwise, the IS approach may completely fail. Optimal choice of probability changes can be based on large-deviation techniques, when the latter are tractable for the stochastic model considered (refer to Chapter 5 in [12] for further details). However, in the absence of large-deviation-type results for the vast majority of the stochastic SIR models considered in the literature (see [14] however), one faces significant difficulties for selecting IS estimators with small variance in practice. Recently, a number of refinements of the IS strategy have been proposed (*sequential Monte Carlo methods* in particular), involving an iterative search of a nearly optimal instrumental distribution [15]. All these methods are said to be *intrusive*, insofar as their implementation requires a call for simulation routines related to modified versions of the distribution of interest.

3.2.1. Cross-entropy method for importance sampling.. In the framework of estimating rare events, the *cross-entropy method* (CE) introduced in [16] can be used to modify iteratively the instrumental distribution for estimating the occurrence probability of $\mathcal{E}$ [17–19]. In the cases that are considered here, the laws of the Markov processes depend on parameters: for instance, q in the Reed–Frost model or (λ, μ) in the continuous-time SIR model. Let us denote by ϕ the set of parameters and by $\mathcal{L}(Z, \phi)$ the likelihood of the path $Z = (S_t, I_t)_{t\in\mathbb{N}}$ in the Reed–Frost case or $Z = (S(t), I(t), R(t))$ in the continuous-time SIR model. The idea is to choose as instrumental distribution the law $\mathcal{L}(Z, v)$ with the parameter value v that minimizes the entropy with respect to the original distribution (with parameter ϕ) conditioned on the rare event $\mathcal{E}$. We describe the algorithm in the discrete case. The methodology also applies to the standard continuous-time Markovian SIR model when it comes to estimating the quantity (4). Indeed, considering the embedded Markov chain $Z = (S(T_k), I(T_k))_{k\in\mathbb{N}}$, where the T_k's denote the successive times when the epidemic process jumps, one may write the probability that the size of the epidemics exceeds some critical threshold value N_c as $p_f(N_c) = \mathbb{P}\{Z_{\tau_\Lambda} \in A\}$, where $\tau_\Lambda = \inf\{k \in \mathbb{N} :\ Z_k \in \mathbb{N}\times\{0\}\}$ and $A = \{N_c,\ N_c + 1,\ \ldots\} \times \{0\}$.

For clarity, we recall below the general principle of the CE method for the purpose of estimating the quantity $\theta = \mathbb{P}\{Z_{\tau_\Lambda} \in A\}$, the latter serving as a benchmark case in the experimental section (Section 4.1). Here, Z is a Markov chain started at z_0 and whose distribution is parameterized by ϕ, and we denote by $\mathcal{L}(Z, \phi)$ its likelihood. As alternative adaptive IS methods has led to very similar results in our experiments; they are not considered here (refer to [15]).

ADAPTIVE IMPORTANCE SAMPLING THROUGH THE CE METHOD

1. **INITIALIZATION.** SET $v^{(0)} = \phi$.
2. **ITERATIONS.** FOR $k = 1,\ \ldots,\ K$,

   (A). DRAW N SAMPLE PATHS STARTING FROM x_0 WITH THE PARAMETER $v^{(k-1)}$:

$$Z^{(i)} = \left(z_0,\ Z_1^{(i)},\ \ldots,\ Z_{\tau_\Lambda^{(i)}}^{(i)}\right),\ \text{FOR } 1 \leqslant i \leqslant N.$$

   (B). COMPUTE THE IS ESTIMATE

$$\widehat{\theta}_{k,N} = \frac{1}{N}\sum_{i=1}^{N} \frac{\mathcal{L}\left(Z^{(i)}, \phi\right)}{\mathcal{L}\left(Z^{(i)}, v^{(k-1)}\right)} \cdot \mathbb{1}\left\{Z_{\tau_\Lambda^{(i)}}^{(i)} \in A\right\}.$$

   (C). DEFINE THE NEW PARAMETER $v^{(k)}$ AS THE MAXIMUM IN v OF

$$L(v) = \frac{1}{N}\sum_{i=1}^{N} \mathbb{1}\left\{Z_{\tau_\Lambda^{(i)}}^{(i)} \in A\right\} \frac{\mathcal{L}\left(Z^{(i)}, \phi\right)}{\mathcal{L}\left(Z^{(i)}, v^{(k-1)}\right)} \ln \mathcal{L}\left(Z^{(i)}, v\right).$$

3. **OUTPUT.** PRODUCE THE ESTIMATE $\widehat{\theta}_{K,N}$ OF THE TARGET PROBABILITY.

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3.3. Interacting and branching particle system methods

In contrast to the IS strategy and its variants, IBPS methods for rare-event simulation are *nonintrusive* in the sense that no modification of the code to run for simulating paths $Z = \{(S(t), I(t), R(t))\}_{t\geqslant 0}$ of the (epidemic) model under study is required. Roughly speaking, the IBPS principle is as follows. We start with a population of N trajectories $Z^{(1)}, \ldots, Z^{(N)}$ (which we call *particles*) and modify the latter in an iterative manner: paths for which the event of interest $\mathcal{E}$ 'almost occurs' (in a sense that shall be specified, depending on the nature of the event $\mathcal{E}$) are 'multiplied', while the others are 'killed', following in the footsteps of the celebrated Repetitive Simulated Trials after Reaching Thresholds algorithm originally introduced in the context of teletraffic data models [20, 21].

So-termed *splitting techniques* (refer to [22]), thoroughly investigated in [23] (see also [24] and [25]), are fully tailored for estimating the rare-event probability (3), as well as the conditional law of the epidemic process Z given the rare event of interest $\{\tau_A \leqslant \mathcal{T}\}$ is realized. The idea is to consider a sequence of increasing subsets of the state space, $A_0 \supset A_1 \supset A_{K+1} = A$, describing more and more difficult obstacles that the process Z must pass over, before reaching the target set A. Consider the related hitting times, defined by the recurrence relation:

$$T_0 = \inf\left\{t \geqslant 0 \,:\, Z(t) \in A_0\right\} \text{ and } T_k = \inf\left\{t \geqslant T_{k-1} \,:\, Z(t) \in A_k\right\} \text{ for } k \geqslant 1.$$

We assume that $Z(0) \in A_0$ with probability 1, so that $T_0 = 0$ almost surely. Clearly, the rare-event probability (3) factorizes the following manner:

$$\mathbb{P}\left\{T_{K+1} \leqslant \mathcal{T}\right\} = \mathbb{P}\left\{T_{K+1} \leqslant \mathcal{T} \mid T_K \leqslant \mathcal{T}\right\} \times \cdots \times \mathbb{P}\left\{T_1 \leqslant \mathcal{T} \mid T_0 \leqslant \mathcal{T}\right\}, \tag{6}$$

in a product of conditional probabilities of events (hopefully) much less rare and whose realizations can be more easily simulated. The technique described subsequently precisely permits us to estimate each factor in (6) and build progressively epidemic paths realizing the rare event $\{\tau_A \leqslant \mathcal{T}\}$ as well.

In many situations, the A_k's are determined by a collection of increasing levels (the choice of the number K of intermediate levels and that of the levels themselves will be discussed later; Remark 2). For instance, when it comes to estimating the probability $p_I(T, N_I)$ that the number of infectives exceeds a critical threshold value N_I before a certain time $T < \infty$, one may consider a sequence of sublevels $0 = N_I^{(0)} < \cdots < N_I^{(K+1)} = N_I$ that defines subsets $A_k = \mathbb{N}\times\{N_I^{(k)}, N_I^{(k)}+1, \ldots\}\times\mathbb{N}$ for $k = 0, \ldots, K+1$.

More precisely, the particle population model evolves according to the following genealogical structure [26]. At generation $k \in \{1, \ldots, K\}$, a particle Z having reached the k-th level before time $\mathcal{T}$ (i.e., such that $T_k \leqslant \mathcal{T}$) is kept while the others are deleted (*selection* stage) and replaced by new particles (*mutation* stage) (Figure 3). A new particle is a novel epidemic path Z^{new} whose path segment on $[0, T_k]$ coincides with that of a particle Z chosen randomly among the particles such that $T_k \leqslant \mathcal{T}$ and whose trajectory

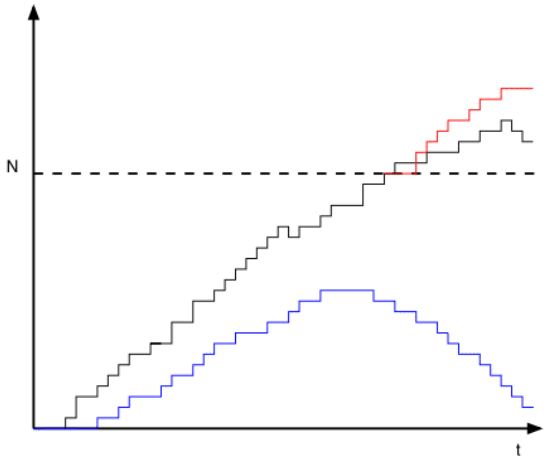

Figure 3. Multilevel splitting: the path in blue does not reach the current level N and is thus killed, while that in black does and can be selected in order to produce an *offspring*, generated by sampling from the time of exceedance (in red).

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on $[T_k, \mathcal{T}]$ (or on $[T_k, T_{k+1}^{\text{new}}]$ from a practical perspective) is simply sampled from the distribution of the epidemic process when the initial condition is $Z(T_k)$. Of course, the algorithm stops (and is restarted) if no particle survives. Adaptive variants are described in the following. The *selection* stage is implemented by means of *weight functions* ω_k defined on the path space by $\omega_k(Z) = 1$ when $T_k \leqslant \mathcal{T}$ and by $\omega_k(Z) = 0$ otherwise. The method is then performed in k steps as follows.

A quite similar approach can be considered for the estimation of the probability $p_f(N_c)$ that the total size of the epidemics rises above a large threshold $N_c \geqslant 1$.

THE IBPS ALGORITHM

1. **Initialization.** Start with a collection of $N \geqslant 1$ simulated trajectories $Z_0^{(1)}, \ldots, Z_0^{(N)}$ of the epidemic process indexed by $i \in \{1, \ldots, N\}$, with the same initial condition $Z(0) = (s_0, i_0, 0)$, to which the weights $\omega_0^{(i)} = 1$, $1 \leqslant i \leqslant N$, are assigned. Denote by $T_0^{(i)} = 0 < T_1^{(i)} < \cdots < T_{K+1}^{(i)}$ and $\mathcal{T}^{(i)}$ the related stopping times.
2. **Iterations.** For $k = 1, \ldots, K$,
3. Let $\mathcal{I}_{1,k}$ be the subset of indices $i \in \{1, \ldots, N\}$ corresponding to the epidemic paths $Z_{k-1}^{(i)}$ having reached the subset A_k before time $\mathcal{T}^{(i)}$ and denote by $\#\mathcal{I}_{1,k}$ its cardinality (the algorithm is stopped and restarted if it is equal to 0). Set $\mathcal{I}_{0,k} = \{1, \ldots, N\} \setminus \mathcal{I}_{1,k}$. For each path indexed by $i \in \mathcal{I}_{1,k}$, set $Z_k^{(i)} = Z_{k-1}^{(i)}$. We also define P_k as the proportion of particles Z that have reached the subset A_k before time $\mathcal{T}$ among those that have previously reached A_{k-1}.

   (a). For each path indexed by $i \in \mathcal{I}_{0,k}$:

   - (SELECTION STEP) independently draw a particle $Z_k^{(j)}$ from distribution $\sum_{j=1}^N \omega_k^{(j)} \cdot \delta_{Z_k^{(j)}}$, with $\omega_k^{(j)} = \omega_k(Z_k^{(j)})/(\sum_{l=1}^N \omega_k(Z_k^{(l)}))$,
   - (MUTATION STEP) Define $Z_k^{(i)}$ as the path confounded with $Z_k^{(j)}$ until time $T_k^{(j)}$ and prolongate by (nonintrusive) simulation of the epidemic process from the state $Z_k^{(j)}(T_k^{(j)})$.

   (b). Compute $P_k = \#\mathcal{I}_{1,k}/N$ and pass onto stage $k+1$.
4. **Output.** Compute the estimate of the target probability $\pi = \mathbb{P}\{\tau_A \leqslant \mathcal{T}\}$:

$$\widehat{\pi}_N = P_1 \times \cdots \times P_{K+1}.$$

Compute also the empirical distribution

$$\mathcal{L}_N = \frac{1}{N} \sum_{i=1}^{N} \delta_{Z_{K+1}^{(i)}},$$

which may serve as an estimate of the conditional law $\mathcal{L}$ of the epidemic process given the occurrence of $\{\tau_A \leqslant \mathcal{T}\}$.

Before showing how the IBPS performs on a variety of examples, a few remarks are in order.

Remark 1 (*A more deterministic genetic evolution scheme*)
It should be first underlined that alternative choices for the genealogical dynamics, different from that consisting of drawing uniformly among the surviving particles, could be possibly pertinent. As proposed in [24] (Section 3.2 therein), one may also consider an N-particle approximation model based on the following selection/mutation scheme: in a deterministic fashion, one keeps at each stage k all paths that have reached the k-th level, that is, N_k particles say. Then the other $N - N_k$ particles are killed and replaced by a particle whose path segment on $[0, T_k]$ is chosen uniformly at random among the N_k 'successful' particles and completed by (independent) sampling on $[T_k, \mathcal{T}]$.

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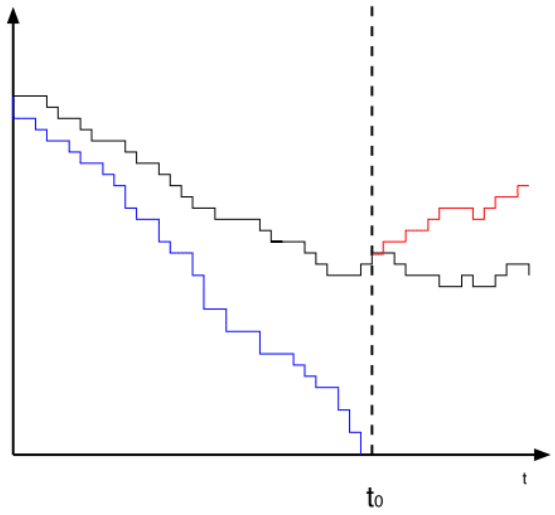

Figure 4. Time multilevel splitting: the path in blue becomes extinct before time t_0 and is thus killed, while that in black does not and can be selected in order to produce an *offspring*, generated by sampling from time t_0 (in red).

Remark 2 (*Tuning parameters*)
Accuracy (consistency and asymptotic normality in particular) of the estimator $\widehat{\pi}_N$ produced by the IBPS algorithm has been established as the number of particles N increases to infinity in [24,27]. However, the practical implementation requires us to pick several parameters: the number of intermediate levels and the levels themselves. As explained in [28], they should be chosen, so that all factors in the product (6) are approximately of the same order of magnitude and possibly in an adaptive way during the simulations. When applied to the problem of estimating $p_I(T, N_I)$ for instance, the adaptive variant of the multilevel splitting proposed in [27] would consist, at each step, in sorting all the simulated paths $Z^{(i)}$ by decreasing order of the quantity $\sup_{t\in[0,T]} I^{(i)}(t)$ and take the k-th term as current intermediate level with fixed $k \in \{1, \ldots, N\}$ (hence killing at each step $N-k$ trajectories).

Remark 3 (*Persistence of the epidemics*)
Observe also that the approach described earlier can be extended in order to estimate the probability that the epidemic lasts more than a (long) time $T > 0$, $p_d(T)$. Instead of stratifying the state space of the epidemic process Z (along the I or R axis), the idea is to write $p_D(T) = \mathbb{P}\{I(T) \geqslant 1\}$ and split the time axis by introducing successive durations $t_0 = 0 < t_1 < \cdots < t_{K+1} = T$ (Figure 4). The sequence of decreasing events is then defined by $\{I(t_k) \geqslant 1\}$ for $k = 0, \ldots, K+1$, and we have

$$p_D(T) = \mathbb{P}\left\{I\left(t_{K+1}\right) \geqslant 1 \mid I\left(t_K\right) \geqslant 1\right\} \times \cdots \times \mathbb{P}\left\{I\left(t_1\right) \geqslant 1 \mid I\left(t_0\right) \geqslant 1\right\}.$$

In this case, any particle Z produces an offspring, by simulating on $[t_k, T]$ (or on $[t_k, t_{k+1}]$ in practice) a novel path segment starting from $Z(t_k)$, when it corresponds to an epidemic path that does not become extinct before t_k and is killed otherwise (Figure 4). A detailed description is provided in the Appendix.

Remark 4 (*Discrete-time models*)
We point out finally that the IBPS approach can be naturally applied in a discrete-time context, so as to estimate tail probabilities $\mathbb{P}\{\sum_{k=0}^{t-1} I_k \geqslant N_c\}$, with $N_c \in \mathbb{N}$, at a given horizon $t \geqslant 1$ in a Reed–Frost model for instance. Selection/mutation steps are then performed at each intermediate time $k \in \{1, \ldots, t-1\}$: at stage k, $N \geqslant 1$ discrete paths are selected by means of a weight function ω_k defined on the path space and next mutate, through sampling of N independent chains from time k to time t. The crucial point naturally consists of a good choice for the weight functions used in the selection stage (which should be ideally based on an analysis of the variance of the corresponding estimates, when tractable). Typical choices are of the form $\omega_k(Z) = \exp(\alpha V(I_k))$ or $\omega_k(Z) = \exp(\alpha(V(I_k) - V(I_{k-1})))$, where $V : \mathbb{R} \to \mathbb{R}$ is a certain *potential function* and $\alpha \geqslant 0$; see Section 4 for some examples.

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4. Numerical experiments

Now that a comprehensive description of the IBPS approach has been given, it is the purpose of this section to provide strong empirical evidence that it is relevant in practice for rare-event estimation in the context of (strongly Markovian) epidemic processes. Its robustness regarding the number of particles considered is illustrated by the supplementary tables displayed in Appendix B.

4.1. Toy examples

As a first go, we start with experiments based on simplistic epidemic models (Section 3), in order to check the accuracy of the estimates produced by IBPS methods. For comparison purposes, CMC and (adaptive) IS estimates are also displayed. Monte Carlo replications have been generated, so as to estimate the variability of the estimators considered as well. In addition, the computation time for each method is reported (observe however that there is room for improving the routines used in these experimental studies).

Table I. Estimates of the tail probability $\theta = \mathbb{P}\{\sum_{k=0}^{t-1} I_k \geqslant N_c\}$ in a Reed–Frost model, with $N_c = 90$.

Method	$\widehat{\theta}$	SE	Time (s)
CMC	1.4e−2	(3.7e−3)	21
CE	1.5e−2	(1.8e−3)	633
IBPS(1) $\alpha = 0.1$, 50%	9.1e−4	(2.8e−4)	72
IBPS(1) $\alpha = 0.01$, 50%	1.0e−3	(2.6e−4)	75
IBPS(1) $\alpha = 0.1$, 80%	1.5e−2	(2.3e−3)	54
IBPS(1) $\alpha = 0.01$, 80%	9.7e−3	(1.2e−3)	56
IBPS(1) $\alpha = 0.1$, 95%	1.4e−2	(3.1e−3)	40
IBPS(1) $\alpha = 0.01$, 95%	1.4e−2	(3.1e−3)	41
IBPS(2) $\alpha = 0.1$, 50%	1.0e−3	(2.8e−4)	74
IBPS(2) $\alpha = 0.01$, 50%	9.9e−4	(2.4e−4)	75
IBPS(2) $\alpha = 0.1$, 80%	1.0e−3	(2.8e−4)	55
IBPS(2) $\alpha = 0.01$, 80%	9.4e−3	(1.7e−3)	36
IBPS(2) $\alpha = 0.1$, 95%	1.4e−2	(3.0e−3)	40
IBPS(2) $\alpha = 0.01$, 95%	1.4e−2	(3.0e−3)	43

SE, standard error; CMC, crude Monte Carlo; CE, cross-entropy; IBPS, interacting and branching particle system.

Table II. Estimates of the tail probability $\theta = \mathbb{P}\{\sum_{k=0}^{t-1} I_k \geqslant N_c\}$ in a Reed–Frost model, with $N_c = 95$.

Method	$\widehat{\theta}$	SE	Time (s)
CMC	3.0e−4	(5.5e−4)	21
CE	3.0e−4	(1.3e−4)	364
IBPS(1) $\alpha = 0.1$, 50%	2.0e−4	(8.8e−5)	73
IBPS(1) $\alpha = 0.01$, 50%	6.7e−5	(4.2e−5)	77
IBPS(1) $\alpha = 0.1$, 80%	4.1e−4	(3.4e−4)	54
IBPS(1) $\alpha = 0.01$, 80%	2.2e−4	(2.4e−4)	55
IBPS(1) $\alpha = 0.1$, 95%	3.2e−4	(4.2e−4)	38
IBPS(1) $\alpha = 0.01$, 95%	3.2e−4	(4.2e−4)	39
IBPS(2) $\alpha = 0.1$, 50%	1.0e−3	(5.6e−5)	74
IBPS(2) $\alpha = 0.01$, 50%	6.6e−5	(4.5e−5)	76
IBPS(2) $\alpha = 0.1$, 80%	2.5e−5	(2.4e−4)	56
IBPS(2) $\alpha = 0.01$, 80%	2.1e−4	(2.3e−4)	55
IBPS(2) $\alpha = 0.1$, 95%	3.1e−4	(4.3e−4)	39
IBPS(2) $\alpha = 0.01$, 95%	3.1e−4	(4.3e−4)	39

SE, standard error; CMC, crude Monte Carlo; CE, cross-entropy; IBPS, interacting and branching particle system.

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4.1.1. Reed–Frost model. In this discrete-time model, we consider the probability $\mathbb{P}(\sum_{k=0}^{t-1} I_k > N_c)$ for $t = 10$ and $N_c = 90$ or $N_c = 95$. Tables I and II display estimates of this probability, together with their empirical standard deviations based on $N = 1000$ Monte Carlo replications. The IBPS approach is here implemented with two different potential functions (cf. Remark 4): the method referred to as *IBPS*(1) is based on the weight function $\omega_k(Z) = \exp(\alpha V(I_k))$ with $V(I) = I$, while that referred to as *IBPS*(2) involves $\omega_k(Z) = \exp(\alpha(V(I_k) - V(I_{k-1})))$ with $V(I) = I$. For both IBPS methods, we test $\alpha = 0.1$ and $\alpha = 0.01$. The levels A_k appearing in the algorithms are set according to Remark 2: we define these levels such that, at each step, a certain proportion of paths is kept (50%, 80%, or 95%) in our numerical example.

Two cases are considered, for $N_c = 90$ (Table I) and $N_c = 95$ (Table II). In the case $N_c = 90$, the rare event has a probability estimated by CMC of 1.4e−2, while this probability is 3.0e−4 for $N_c = 95$.

For both examples, we see that the estimation of CMC matches with the estimation obtained by the CE or IBPS methods when the levels are chosen such that at each step 95% of the paths are kept. When $N_c = 95$, the standard deviation of the estimates is high, and the obtained values are not always accurate.

4.1.2. Standard Markovian susceptible–infected–removed model. We now consider a simple continuous-time Markovian epidemic model with no demography, as described in Section 2.1, in the case where the target is again the tail probability related to the epidemic size, namely, $p_f(N_c)$. We use the parameters proposed in the two examples presented by O'Neill and Roberts [29]. The first set of parameters corresponds to a toy model: $s_0 = 9$, $i_0 = 1$, $\mu \equiv 0$, $\lambda(S, I) = \lambda SI$ with $\lambda = 0.12$, and $\gamma(I, R) = \gamma I$ with $\gamma = 1$. We compared the results obtained by means of the CMC, CE, and IBPS methods, with $N = 1000$. Here, the method referred to as *IBPS*(1) implements the algorithm described in the previous section, while that referred to as *IBPS*(2) corresponds to the variant explained in Remark 1. The results are displayed in Table III.

The second example in [29] comes from Bailey [30, p. 125]. It is a smallpox outbreak in a closed community of 120 individuals in Abakaliki, Nigeria. Here, the model is as before with the parameters $s_0 = 119$, $i_0 = 1$, $\lambda = 0.0008254$, and $\gamma = 0.087613$. The results are displayed in Table IV.

In both examples, CMC provides a good estimator of the rare probability (with 90.4% of nonzero estimates, in the second example, i.e., where the rare event has been observed). We take its results as a benchmark.

In Table III, in a population of 10 individuals, we can see that every method provides a good estimate. Switching to a population of 120 individuals, one observes that CE faces difficult numerical problems related to the computation of the likelihood ratios. This method is avoided in the sequel.

The IBPS method that turns out to be more robust is the IBPS method 1, where the levels are defined so that 1% of the paths are kept. In contrast to the Reed–Frost example, where the IBPS methods that work best correspond to a high proportion of kept trajectories (95%), here, the methods that give the results that match the best CMC correspond to those where only 1% of the paths at each iteration are kept. This may be explained by the number of iterations needed. IBPS for the Reed–Frost model is implemented with a constant number of iterations, which is the number of time steps until t. Being too restrictive, we

Table III. Estimates of the tail probability $\theta = p_f(N_c)$ of the size of the epidemics in a standard Markovian susceptible–infected–removed model without demography. Toy example for a population of size 10 provided in [29].

Method	$\widehat{\theta}$	SE	Time (s)
CMC	2.0e−2	(4.5e−3)	4,020
CE	2.0e−2	(2.5e−3)	176,382
IBPS(1), 1%	2.1e−2	(4.5e−3)	7,677
IBPS(1), 5%	2.1e−2	(4.0e−3)	8,153
IBPS(1), 20%	2.5e−2	(3.5e−3)	8,896
IBPS(2), 1%	2.0e−2	(4.5e−3)	7,882
IBPS(2), 5%	2.1e−2	(8.0e−3)	8,167
IBPS(2), 20%	2.4e−2	(2.2e−2)	8,996

SE, standard error; CMC, crude Monte Carlo; CE, cross-entropy; IBPS, interacting and branching particle system.

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Table IV. Estimates of the tail probability $\theta = p_f(N_c)$ of the size of the epidemics in a standard Markovian susceptible–infected–removed model without demography. Example of the smallpox outbreak in Nigeria.

Method	$\widehat{\theta}$	SE	Time (s)
CMC	2.5e−3	(1.6e−3)	4,334
CE	1.6e−3	(2.3e−4)	36,325
IBPS(1), 1%	2.7e−3	(1.3e−3)	9,911
IBPS(1), 5%	2.9e−3	(9.0e−4)	10,561
IBPS(1), 20%	3.6e−3	(6.7e−4)	11,878
IBPS(2), 1%	2.8e−3	(2.9e−3)	10,093
IBPS(2), 5%	3.1e−3	(5.3e−3)	11.255
IBPS(2), 20%	3.6e−3	(5.8e−3)	12.240

SE, standard error; CMC, crude Monte Carlo; CE, cross-entropy; IBPS, interacting and branching particle system.

obtain only zero as conditional probability estimates. For the continuous-time SIR model, the number of iterations is directly linked to the proportion of kept paths, which should be viewed as a tuning parameter. The algorithm stops when the fixed proportion of best paths reaches the level N_c. When too many paths are kept, the iteration becomes lengthy. In contrast, keeping an insufficient number of trajectories could jeopardize the numerical results obtained.

4.2. An age-structured HIV epidemic model with contact-tracing

We now consider a numerical individual-centered epidemic model, proposed and studied in the context of an asymptotically large population in [7], which is effectively used for anticipating the spread of HIV in Cuba and has been statistically fitted by the means of *approximate Bayesian computation* techniques (see [31] for further details) based from the HIV data repository described at length in [32]. Experiments are naturally (and fortunately) impossible in the context of epidemics. The capacity to simulate events of interest and estimate their probability of occurrence is thus of prime importance, in order to compare the effects of different control strategies for instance. Here, we investigate the impact of the contact-tracing mechanism on the probability of having a large final size for the epidemics by means of the IBPS method described in the previous.

As most realistic epidemic models really used by practitioners, it is more complex than the standard Markovian SIR model with demography recalled in Section 2.1, although based on the same general concepts. Precisely, this model accounts for the effect of the contact-tracing detection system set up since 1986 in order to control the HIV epidemics across the island by stipulating a *structure by age* on the class R (corresponding to the individuals diagnosed as HIV positive). The R subpopulation is hence described by a *point measure* R_t indicating the time points since each individual in the R compartment has been identified by the public health system as infected; that is, $R_t([a_1, a_2])$ represents the number of positive diagnoses between times $t - a_2$ and $t - a_1$ for all $0 \leqslant a_1 < a_2 < +\infty$. Apart from this, the (Markovian) dynamics of the epidemic process $\{(S(t), I(t), R_t(da))\}$ is described by the flow diagram in Figure 1 with $\mu \equiv 0$, $\lambda(S, I) = \lambda SI$ and $\gamma(I, R) = \gamma_1 I + \gamma_2 I \int_{a=0}^{+\infty} \exp(-ca) R(da)$ with $\lambda = 5.4\ 10^{-8}$, $\rho \equiv 0\ 10^{-6}$, $\gamma_1 = 0.13$, $\gamma_3 = 0.19$, and $c = 1$. The second term involved in the rate $\gamma(I, R)$ models the way detected individuals contribute to contact-tracing detection (notice incidentally that the smaller the parameter c, the more difficult are the early stages of search for contact; refer to Section 2.1 in [7]).

Our purpose is to estimate $p_f(N_c)$ for various values of N_c: 8500, 8800, and 9000. As previously discussed, IBPS is obtained with 1000 particles. For the CMC, 10e6 simulations have been performed. This permits us to obtain a good estimate of the small probability $p_f(N_c)$ and also to compare CMC with IBPS. Indeed, if we separate the 10e6 simulations into 1000 runs of 1000 simulations, this allows us to count how many times the run provides an estimate equal to zero (the rare event has not been observed). As shown in Table V, the CMC fails for the last two cases: whereas for $N_c = 8500$, only 2.4% of the simulations lead to an empirical probability equal to 0; this proportion is 84.4% and 98.6% for

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Table V. Estimates of the tail probability $\theta = p_f(N_c)$ of the size of the age-structured epidemic model with contact tracing for Cuban HIV epidemic.

Method	$\widehat{\theta}$	(SE)	Time (s)
	$N_c = 8500$		
CMC	3.4e−3	(1.8e−3)	4,794
IBPS1, 1%	3.5e−3	(1.7e−3)	6,566
IBPS2, 1%	3.5e−3	(3.8e−3)	8,530
	$N_c = 8800$		
CMC	1.7e−4	(4.0e−4)	4,409
IBPS1, 1%	1.5e−4	(3.0e−4)	8,332
IBPS2, 1%	1.7e−4	(9.7e−4)	12,519
	$N_c = 9000$		
CMC	1.4e−5	(1.2e−4)	4,988
IBPS1, 1%	4.3e−6	(4.4e−5)	14,323
IBPS2, 1%	8.4e−6	(2.1e−4)	17,053

SE, standard error; CMC, crude Monte Carlo; IBPS, interacting and branching particle system.

$N_c = 8800$ and $N_c = 9000$, respectively. This emphasizes the importance of the IBPS methods. CE methods do not give good results on such large populations, the computation of likelihood ratios being very sensitive numerically.

4.3. An individual-based model for hepatitis C virus infection among people who inject drugs

Chronic hepatitis C is a viral infectious disease leading to severe hepatic complications in the long term, responsible for 350,000–500,000 deaths in the world each year [33]. Hepatitis C is a blood-borne disease; thus, the incidence of the infections is particularly high in people who inject drugs (PWID) because of the sharing of injecting equipment [34]. New treatments are becoming available. With these new treatments, a sustained virological response (SVR), that is, an undetectable viral load 6 months after the end of the

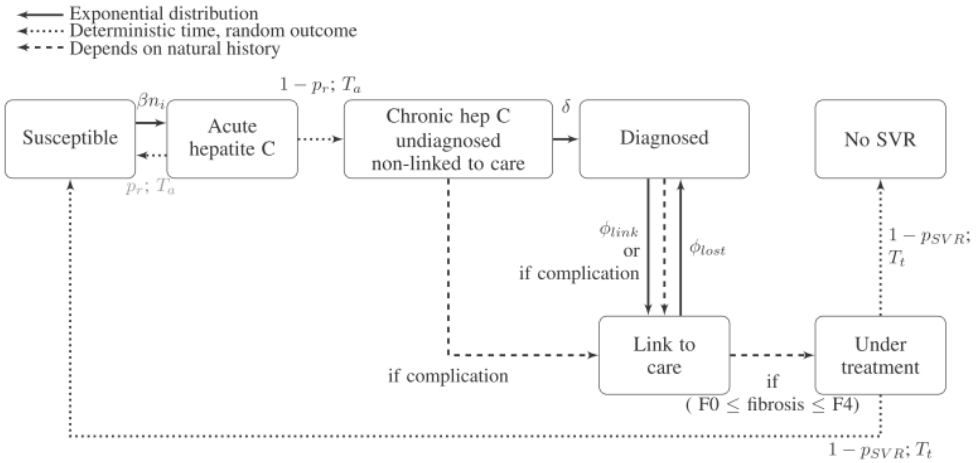

Figure 5. Diagram flow of infection and cascade of care modeling for hepatitis C virus infection among PWID. Greek letters refer to rates, p_r and p_{SVR} to probabilities and T_a and T_t to (deterministic) time before leaving the compartment. β depends on the status of the PWID with respect to the risk reduction measures (access to sterile injecting equipment and access to substitution therapies). n_i denotes the number of infected injecting partners of the PWID. δ depends on the status of the PWID with respect to injection: active or inactive injector (i.e., before or after the cessation of injection). SVR, sustained virological response.

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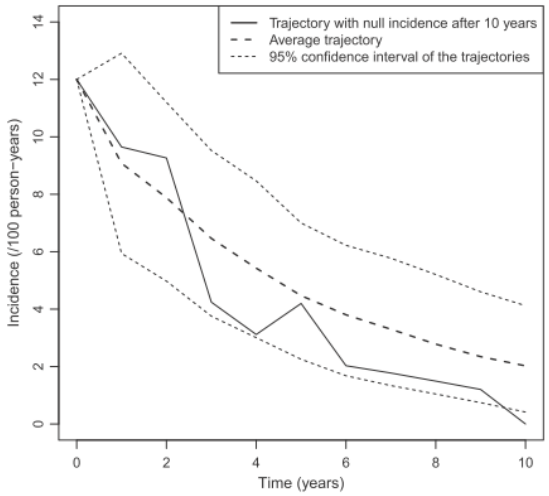

Figure 6. Example of trajectory with elimination of hepatitis C virus infections after 10 years. In dotted lines, the mean and 95%-confidence interval for the paths simulated without the constraint of touching 0 after 10 years are shown.

treatment, can be reached in more than 90% of patients in phase 3 clinical trials [35–40]. The patients are considered to be cured after an SVR, and they are no longer able to transmit the virus [41]. This situation leads the medical community to consider a possible elimination of hepatitis C among PWID [42], defined as the 'reduction to zero of the incidence of infection caused by a specific agent in a defined geographical area as a result of deliberate efforts; continued measures to prevent re-establishment of transmission are required' [43], by treating infected people before they transmit the infection. However, this strategy called *treatment as prevention* needs an early initiation of the treatment in the population in order to avoid the transmission of the disease.

In [44], an individual-based continuous-time stochastic model is used to assess the impact of improvements in the cascade of care on HCV transmission in a PWID population in France. A household graph is used to model the social network of injecting partners in the population. This model also includes the progression of the natural history of chronic hepatitis C in PWID with fibrosis progression (quantified by the Metavir scores from F0 to F4, which correspond to liver cirrhosis), two complications of cirrhosis (decompensation and hepatocellular carcinoma), and hepatic transplant.

This model is used to estimate the probability to obtain a null incidence at 10 years (i.e., $p'_I(10,0) = \mathbb{P}(\inf\{t \geqslant 0 \ : \ I(t) = 0\} \leqslant 10)$) after the implementation of improvements in the cascade of care aiming at an early initiation of HCV treatment in a community of 524 PWID in France. An overview of the infection and cascade of care model is available in Figure 5. The measures include an improvement of testing, linkage to care, access to treatment, and treatment adherence. The corresponding parameter values are set to $\delta = 2$, $\phi_{\text{Link}} = 2$, $\phi_{\text{Lost}} = 0.05$, and $p_{\text{SVR}} = 90\%$ and a treatment initiation for PWID diagnosed, linked to care and with a fibrosis score between F0 and F4. The incidence is estimated at the end of each year of the simulation, and we use the discrete-time variant of the IBPS algorithm with the weights $\omega_k(Z) = \exp(\alpha(I_{k-1} - I_k))$, with I_k as the incidence at the end of year k and $\alpha = 0.1$. The algorithm is implemented with 1000 simulated epidemic trajectories and an adaptive threshold corresponding to 95% of the trajectories that have reached the lowest incidences at each time.

We estimated $p'_I(10,0)$ to 0.018 in the model (see Figure 6 for the simulation of a path leading to a null incidence at 10 years). This result shows that despite the introduction of highly effective treatments in a scenario where massive improvements in the HCV cascade of care are achieved, an elimination of HCV would be unlikely in PWID in the short term by using a treatment-as-prevention strategy alone. Reaching this goal would probably require additional preventive interventions such as improvements of current risk reduction measures (access to sterile injecting equipments and access to opioid substitution therapies for instance) or introduction of new ones (such as supervised consumption rooms).

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5. Conclusion

Although (fortunately) rare, crisis situations related to the spread of a communicable infectious disease, are of great concern to public health managers. However, proper use of simulation-based statistical methods tailored for the estimation of such rare events is not well documented in the mathematical epidemiology literature. Indeed, the vast majority of analyses focus on the likeliest scenarios, on events occurring with large or even overwhelming probability (e.g., a large outbreak when the basic reproduction number is larger than 1). In contrast, the present article provides an overview of recent techniques for rare-event probability estimation and simulation in the context epidemic models and shows how they can be used practically in order to provide efficient risk assessment tools for public health management. The numerical results displayed in this paper provide strong empirical evidence that simulation methods based on IBPS are quite promising for this specific purpose.

Appendix A: Temporal multilevel splitting

Here, we show that the branching particle model sketched in Remark 3 can be used for estimating the probability $p_d(T)$ introduced in Section 2.2. More generally, we consider a continuous-time strong Markov process $Z = \{Z(t)\}_{t\geqslant 0}$, taking its values in a measurable space E with initial state $z_0 \in E$ and a Harris recurrent set $B \subset E$. Let $\tau_B = \inf\{t > 0 : Z(t) \in B\}$ denote the hitting time to set B. Our goal here is to estimate the tail probability $\pi = \mathbb{P}\{\tau_B > t\}$, that is, the probability that the hitting time τ_B exceeds the (large) threshold value $t > 0$, by the means of time sublevels $t_0 = 0 < t_1 < \cdots < t_K < t_{K+1} = t$. At each stage k, the selection step simply consists of drawing with replacement among the paths Z that have not reached B before time t_k: we set $\omega_k(Z) = 1$ in this case and $\omega_k(Z) = 0$ otherwise.

TEMPORAL MULTILEVEL SPLITTING

(1) **Initialization.** Start with a collection of $N \geqslant 1$ simulated trajectories $Z_0^{(1)}, \ldots, Z_0^{(N)}$ of the Markov process indexed by $i \in \{1, \ldots, N\}$, with the same initial condition z_0 and the same weights $\omega_0^{(i)} = 1$, $1 \leqslant i \leqslant N$. Denote by $\tau_B^{(i)}$ the corresponding hitting times.

(2) **Iterations.** For $k = 1, \ldots, K$,

(a) Let $\mathcal{I}_{1,k}$ be the subset of indices $i \in \{1, \ldots, N\}$ corresponding to the paths $Z_{k-1}^{(i)}$ that have not reached the subset B before time t_k, that is, such that $\tau_B^{(i)} > t_k$, and denote by $\#\mathcal{I}_{1,k}$ its cardinality (when it is equal to 0, the algorithm is stopped and restarted). Set $\mathcal{I}_{0,k} = \{1, \ldots, N\} \setminus \mathcal{I}_{1,k}$. For each path indexed by $i \in \mathcal{I}_{1,k}$, set $Z_k^{(i)} = Z_{k-1}^{(i)}$.

(b) For each path indexed by $i \in \mathcal{I}_{0,k}$:

* (SELECTION STEP) independently draw a particle $Z_k^{(j)}$ from distribution $\sum_{j\in\mathcal{I}_{1,k}} \omega_k^{(j)} \cdot \delta_{Z_k^{(j)}}$, with $\omega_k^{(j)} = 1/\#\mathcal{I}_{1,k}$.
* (MUTATION STEP) Define $Z_k^{(i)}$ as the concatenation of the path $Z_k^{(j)}$ on $[0, t_k]$ with a path simulated from the state $Z_k^{(j)}(t_k)$ for times larger than t_k.

(c) Compute $P_k = \#\mathcal{I}_{1,k}/N$ and pass onto stage $k + 1$.

(3) **Output.** Compute the estimate of the target probability $\pi = \mathbb{P}\{\tau_B > t\}$:

$$\widehat{\pi}_N = P_1 \times \cdots \times P_{K+1},$$

where P_{K+1} is defined as the proportion of particles Z that have not reached the subset B before time t among those that had not reached A before time t_K. Compute also the empirical distribution

$$\mathcal{L}_N = \frac{1}{N}\sum_{i=1}^{N} \delta_{Z_{K+1}^{(i)}},$$

which may serve as an estimate of the conditional law $\mathcal{L}$ of the epidemic process given that event $\{\tau_B > t\}$ occurs.

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We highlight the fact that the probability $\mathbb{P}\{\tau_B > t\}$ is actually of the same form as (3). Indeed, this corresponds to the situation of the bivariate Markov process $\{(Z(t), t)\}_{t\geqslant 0}$ with the (rare) set $A = \mathbb{N}^* \times [T, +\infty[$ and $\mathcal{T}$ as the extinction time τ. Therefore, works by [27] may be adapted to prove consistence and asymptotic normality when the number of particles N tends to infinity. In particular, an adaptive variant of the temporal multilevel splitting is as follows.

A.1. Adaptive variant

The method described earlier requires us to fix in advance the number of time points and the time points themselves, whereas, ideally, they should be determined in an adaptive fashion. We start by running N independent paths of the epidemics and rank them by decreasing durations $\mathcal{T}^{(i)}$, $1 \leqslant i \leqslant N$. The first threshold t_1 can be chosen as the duration of the $k-1$-th longest epidemics, so that k paths are kept and $N-k$ are killed. For each killed path, we resample from the k paths that have been kept and resimulate the part of the path after t_1. This allows us to define recursively a system of longer and longer epidemic paths.

Appendix B: Additional tables

The supplementary tables displayed in the following illustrate the robustness of the IBPS approach regarding the choice of the number N of particles chosen to implement it.

Table B1. Estimates of the tail probability $\theta = \mathbb{P}\{\sum_{k=0}^{t-1} I_k \geqslant N_c\}$ in a Reed–Frost model, with $N_c = 90$ and 100, 1000, or 10,000 epidemic paths.

	Number of trajectories					
	$N = 100$		$N = 1000$		$N = 10{,}000$	
Method	$\widehat{\theta}$	SE	$\widehat{\theta}$	SE	$\widehat{\theta}$	SE
CMC	1.5e−2	(1.2e−2)	1.4e−2	(3.7e−3)	1.5 e−2	(1.2e−3)
IBPS(1), $\alpha = 0.01$, 95%	1.5e−2	(1.0e−2)	1.4e−2	(3.1e−3)	1.5 e−2	(1.0e−3)
IBPS(2), $\alpha = 0.01$, 95%	1.4e−2	(9.9e−3)	1.4e−2	(3.0e−3)	1.4 e−2	(9.5e−4)

SE, standard error; CMC, crude Monte Carlo; IBPS, interacting and branching particle system.

Table B2. Estimates of the tail probability $\theta = \mathbb{P}\{\sum_{k=0}^{t-1} I_k \geqslant N_c\}$ in a Reed–Frost model, with $N_c = 95$ and 100, 1000, or 10,000 epidemic paths.

	Number of trajectories					
	$N = 100$		$N = 1000$		$N = 10{,}000$	
Method	$\widehat{\theta}$	SE	$\widehat{\theta}$	SE	$\widehat{\theta}$	SE
CMC	2.5e−4	(1.6e−3)	3.0e−4	(5.5e−4)	3.0e−4	(1.7e−4)
IBPS(1), $\alpha = 0.01$, 95%	3.7e−4	(1.6e−3)	3.2e−4	(4.2e−4)	3.1e−4	(1.4e−4)
IBPS(2), $\alpha = 0.01$, 95%	2.1e−4	(1.3e−3)	3.1e−4	(4.3e−4)	3.0e−4	(1.4e−4)

SE, standard error; CMC, crude Monte Carlo; IBPS, interacting and branching particle system.

Table B3. Estimates of the tail probability $\theta = p_f(N_c)$ of the size of the epidemics in a standard Markovian SIR model without demography and 100, 1000, or 10,000 epidemic paths. Example of [29] with a population of 10 individuals.

	Number of trajectories					
	$N = 100$		$N = 1000$		$N = 10{,}000$	
Method	$\widehat{\theta}$	SE	$\widehat{\theta}$	SE	$\widehat{\theta}$	SE
CMC	2.0e−2	(1.4e−2)	2.0e−2	(4.5e−3)	2.0e−2	(1.4e−3)
IBPS(1), 1%	2.0e−2	(1.4e−2)	2.1e−2	(4.5e−3)	2.0e−2	(1.4e−3)
IBPS(2), 1%	2.0e−2	(1.4e−2)	2.0e−2	(4.5e−3)	2.0e−2	(1.4e−3)

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Table B4. Estimates of the tail probability $\theta = p_f(N_c)$ of the size of the epidemics in a standard Markovian susceptible–infected–removed model without demography and 100, 1000, or 10,000 epidemic paths. Example of the smallpox outbreak in Nigeria.

	Number of trajectories					
	$N = 100$		$N = 1000$		$N = 10{,}000$	
Method	$\widehat{\theta}$	SE	$\widehat{\theta}$	SE	$\widehat{\theta}$	SE
CMC	2.6e-3	(5.1e-3)	2.5e-3	(1.6e-3)	2.4e-3	(5.0e-4)
IBPS(1), 1%	2.1e-3	(4.6e-3)	2.7e-3	(1.3e-3)	2.8e-3	(4.2e-4)
IBPS(2), 1%	2.4e-3	(5.0e-3)	2.8e-3	(2.9e-3)	2.8e-3	(2.9e-3)

SE, standard error; CMC, crude Monte Carlo; IBPS, interacting and branching particle system.

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6 Efficacité et coût-efficacité d'améliorations des interventions de réduction des risques et d'améliorations de la cascade de soins de l'hépatite C chronique chez les UDI de la région parisienne

6.1 Résumé

Les chapitres précédents ont permis de démontrer, aussi bien dans le contexte français que dans le contexte québécois, l'intérêt d'un accès élargi au traitement, indépendamment de la sévérité de la fibrose hépatique, pour réduire à la fois l'incidence du VHC dans la population, sa prévalence ainsi que le nombre de complications associées à l'hépatite C chronique. Améliorer le dépistage, les liens avec le système de soins ou l'adhérence au traitement n'avait qu'un très faible impact sur l'incidence et la prévalence de la maladie, mais un impact important sur le nombre de cirrhoses décompensées et de CHC. Cependant, le nombre de traitements nécessaires différait selon les scénarios. Particulièrement, pour l'étude sur les UDI en Île-de-France, le scénario le plus efficace (combinaison d'une amélioration du dépistage, des liens aux soins et de l'adhérence avec un traitement initié indépendamment de la sévérité de la maladie) nécessitait un grand nombre de traitements durant les premières années de simulations : environ 4 000 durant les 5 premières années, contre 1 500 dans le scénario de référence. Le coût élevé des nouveaux traitements antiviraux (environ 46 000€ pour 12 semaines de traitement par sofosbuvir + ledipasvir par exemple (Legifrance 2015)) pose la question de l'efficience de ce type de stratégie.

De plus, les scénarios évalués dans ces deux études se limitaient aux approches médicales, c'est-à-dire à l'utilisation du traitement antiviral uniquement. Pourtant, en amont de la transmission, d'autres interventions sont possibles. La réduction des risques chez les UDI a débuté en France en 1987, par l'autorisation de la vente libre de seringues en pharmacies (Expertise collective INSERM 2010) . D'autres mesures ont suivis, comme la vente de kits d'injection complets en pharmacies, les distributeurs automatiques de seringues ou la création des Centres d'Accueil et d'Accompagnement à la Réduction des risques pour Usagers de Drogues (CAARUD), des structures créées à destination des usagers de drogues où ceux-ci peuvent – entre autres – accéder à des matériel d'injection stérile. Les traitements de substitution aux opiacés, comme la méthadone ou la buprénorphine, font aussi partie du dispositif de réduction des risques. En France, ces traitements sont extrêmement répandus dans la population UDI : d'après l'enquête ANRS-Coquelicot, 85% des injecteurs actifs (dans le dernier mois) ont reçu un traitement de substitution aux opiacés au cours des 6 mois précédents l'enquête (données non-publiées). Ces mesures permettent de diminuer le risque infectieux chez les UDI, dont le risque d'infection par le VHC (Turner et al. 2011). Toutefois, le risque d'infection étant très élevé durant la première année d'injection (Sutton et al. 2006; Hagan et al. 2008; Sutton et al. 2008), il est nécessaire que les UDI y accèdent le plus rapidement possible.

L'objectif de cette étude était donc d'évaluer le coût-efficacité d'améliorations de l'accès au matériel d'injection stérile, aux traitements de substitution aux opiacées et d'améliorations de la cascade de soins

de l'hépatite C chronique (dépistage, lien aux soins, critère d'initiation du traitement et adhérence au traitement) dans une population d'UDI en Île-de-France.

Pour cela, le modèle utilisé précédemment a été modifié afin d'y intégrer la réduction des risques (accès au matériel d'injection et traitement de substitution). A chaque statut dans ce modèle de réduction était associé un risque relatif de transmission d'infection par le VHC (Turner et al. 2011). L'âge des individus a également été intégré au modèle, ce qui a permis de prendre en compte le vieillissement de la population, et donc une mortalité selon l'âge des individus (INED 2012). De plus, le modèle de graphe aléatoire utilisé pour représenter le réseau des partenaires d'injection a été modifié. Le modèle utilisé ici était un modèle « de ménage » : chaque UDI appartient à un petit groupe (ménage) au sein duquel les liens sont forts. A l'inverse, deux individus appartenant à des groupes différents ont une probabilité faible d'être liés entre eux. Concrètement, l'algorithme de construction du modèle est le suivant :

1) Chaque individu de la population est aléatoirement assigné à une catégorie de ménage : individu seul, binôme ou groupe de 5 ; avec probabilité π_1, $\pi_2$ou π_5. Les groupes sont ensuite constitués aléatoirement pour chaque catégorie.
2) Les individus appartement au même groupe sont automatiquement liés entre eux.
3) Chaque couple d'individus de la population appartenant à des ménages différents est rélié avec une probabilité $p_{ij}, (i,j) \in \{1,2,5\}^2$, dépendant de la catégorie de ménage auquels ces individus appartiennent.

Le choix de ce type de structure à la place du modèle d'Erdős–Rényi utilisé précédemment, plus mélangeant, était motivé par la recherche d'un modèle intégrant ces ménages. En effet, de telles structures étaient observées dans les résultats d'une enquête sur les réseaux d'UDI à Melbourne (Rolls et al. 2011). En l'absence de données sur les réseaux d'UDI en France, ce sont ces données australiennes qui ont été utilisées pour estimer les paramètres du modèle (π_1, π_2 ou π_5 et $p_{ij}, (i,j) \in \{1,2,5\}^2$) par calcul bayésien approché (voir chapitre 3), l'ensemble de statistiques cibles étant constitué de décomptes d'apparition de motifs dans le réseau australien (le nombre d'individus isolés, de couples isolés, d'arêtes et de triangles dans le graphe), ainsi que le diamètre du graphe, i.e. la plus grand distance possible entre deux individus. La taille de la population dans l'étude de Melbourne était estimée à 524 UDI, mais nous avons regroupé 20 populations de 524 UDI pour chaque simulation afin de se ramener à une taille de population similaire à celle de l'étude précédente (10 000 UDI).

Les coûts directs associés aux interventions de réduction des risques ; au dépistage, au suivi et au traitement de l'hépatite C ; ainsi que les consommations de soins ont été intégrés au modèle.

Comme dans les études précédentes, les paramètres du modèle provenaient principalement de l'enquête ANRS-Coquelicot ou de la littérature scientifique. Les coûts et utilités ont été estimés à partir de la littérature.

Les principaux critères de jugement étaient l'espérance de vie moyenne, l'espérance de vie ajustée sur la qualité (i.e. en années de vie ajustées sur la qualité ou QALY), le coût moyen par usager sur l'ensemble de la durée de vie en euros de 2015. Un taux d'actualisation annuel de 4% a été appliqué sur

ces sorties jusqu'à 30 ans et de 2% après 50 ans, avec une décroissance linéaire entre 30 et 50 ans (Haute Autorité de Santé 2011). Les simulations ont été effectuées jusqu'au décès du dernier individu de la population peuplant initialement le modèle, et les quantités mentionnées précédemment ont été estimées pour cette population. Nous avons également estimé le nombre d'infections et le nombre de réinfections post-traitement (i.e. après une RVS) dans la population.

Les scénarios évalués étaient les suivants :

Scénario 1 (S1) : la pratique actuelle. Durée moyenne entre le début de l'injection et la participation à un programme d'accès au matériel d'injection : 1 an ; durée moyenne entre le début de la participation à un programme d'accès au matériel d'injection et l'accès aux traitements de substitution : 0.5 ans ; durée moyenne entre le passage à la chronicité et le diagnostic : 1.25/1.45 ans ; durée moyenne avant lien aux soins après le diagnostic : 2.6 ans ; taux annuel de perte de vue : 14%/an ; taux de RVS : 86% (95% de RVS dans les essais cliniques, auxquels on applique une diminution de 10% pour prendre en compte la différence entre la vraie vie et les essais cliniques) ; initiation du traitement si le score de fibrose est supérieur ou égal à F2.

Scénario 2 (S2) : Amélioration de la réduction des risques. Dans ce scénario, nous avons favorisé un accès plus rapide au matériel d'injection et aux traitements de substitution. Durée moyenne entre le début de l'injection et la participation à un programme d'accès au matériel d'injection : 0.25 an (vs. 1 an pour S1) ; durée moyenne entre le début de la participation à un programme d'accès au matériel d'injection et l'accès aux traitements de substitution : 0.25 ans (vs. 0.5 dans S1). Les autres paramètres sont identiques à S1.

Scénario 3 (S3) : Initiation du traitement à partir de F0. Les individus liés aux soins initiaient le traitement antiviral à partir de F0 (vs. F2 dans S1). Les autres paramètres étaient identiques à S1.

Scénario 4 (S4) : Amélioration de la cascade de soins. Il s'agissait ici d'une amélioration du dépistage, du lien aux soins et de l'adhérence aux traitements antiviraux. Durée moyenne entre le passage à la chronicité et le diagnostic : 0.5 ans (vs. 1.25/1.45 ans pour les injecteurs actifs/inactifs dans S1) ; durée moyenne avant lien aux soins après le diagnostic : 0.5 ans (vs. 2.6 ans dans S1) ; taux annuel de perte de vue : 5%/an (vs. 14%/an dans S1), taux de RVS : 95% (vs. 86% dans S1). Les autres paramètres sont identiques à S1.

Scénario 5 (S5) : Combinaison des scénarios S3 et S4.

Scénario 6 (S6) : Combinaison des scénarios S2, S3 et S4.

Une analyse de sensibilité univariée a également été effectuée sur les paramètres clés du modèle. Les 6 scénarios de l'analyse principale ont été simulés en faisant varier les paramètres du modèle de réduction des risques, l'incidence initiale, la durée entre le passage à la chronicité et le diagnostic, la durée entre le diagnostic et le lien aux soins, le risque de réinfection.

Par ailleurs, l'impact d'une diminution du coût du traitement de 25%, 50% et 75% a été évalué.

Dans l'analyse principale, le coût moyen par UDI de 25 598€ dans le scénario de la pratique actuelle (S1), pour une durée de vie ajustée sur la qualité de 16.57 QALY en moyenne. L'espérance de vie

augmentait légèrement lorsque l'accès aux interventions de réduction des risques était amélioré (S2) : +0.01 QALY, mais cette intervention était dominée par le scenario S4. Avec S4, améliorer la cascade de soins permettait d'obtenir une espérance de vie ajustée sur la qualité de 16.81 QALY pour un coût moyen de 31 437€ (+, en étant également très coût-efficace (ICER=4 715€/QALY). Le scénario combinant cette amélioration de la cascade de soins avec une initiation du traitement à F0 (S5) était le plus efficace tout en demeurant très coût-efficace, avec une espérance de vie ajustée sur la qualité de 17.02 QALY pour un ICER de 22 859€/QALY. C'était également le scénario ayant le plus d'impact sur le nombre d'infections (avec S6, qui combine ce scénario avec une amélioration de la réduction des risques) : 2 008 en moyenne, contre 3 271 avec S1. Les autres scénarios étaient dominés par S5 (ils étaient moins chers et plus efficaces).

Les résultats notables de l'analyse de sensibilité concernent la réduction des risques et l'incidence initiale. En l'absence de réduction des risques dans le modèle, l'espérance de vie sous les conditions du scénario 1 est plus faible (-0.09 QALY) et le nombre d'infections est 50% plus élevé. Par contre,

Avec l'incidence initiale de Montréal et de Londres (22.1/100 personne-années (p.a) (Leclerc et al. 2011) et 42/100 p.a (Judd et al. 2005) contre 12/100 p.a dans l'analyse principale), au coût actuel, le scénario combinant une amélioration des interventions de réduction des risques, de la cascade de soins avec un traitement dès F0 (S6) devient le plus efficace, mais n'est plus coût-efficace avec l'incidence londonienne (ICER=132 529€/QALY).

Ces résultats font ressortir deux points importants. Premièrement, améliorer les dispositifs de réduction des risques dans l'analyse principale n'apportait qu'un gain très faible sur l'espérance de vie des UDI. L'analyse de sensibilité a cependant démontré que ces dispositifs étaient nécessaires afin de maintenir le nombre d'infections le plus bas possible. De plus, dans cette étude, nous n'avons considéré qu'une amélioration des dispositifs existants en France : l'accès au matériel stérile et les traitements de substitution aux opiacés. D'autres mesures sont envisageables, comme les salles de consommation à moindres risques (Milloy et al. 2009). Nous ne prenons pas en compte les bénéfices apportés par la réduction des risques sur d'autres comorbidités liés à l'usage de drogues injectables, comme le VIH ou la mortalité liée à l'usage de drogue lui-même (overdoses). En effet, l'accès au matériel stérile ou à la substitution permet de diminuer les occurrences de l'infection par le VIH (MacArthur et al. 2014) ou de la mortalité liée à l'usage de drogues en lui-même (Cornish et al. 2010). Enfin, en utilisant en analyse de sensibilité une incidence initiale plus élevée que dans l'analyse principale, correspondant à des estimations à Montréal et Londres, introduire une amélioration des interventions de réduction des risques en plus d'une amélioration de la cascade de soins et du traitement dès le stade F0 devenait modérément efficace, avec une amélioration de l'espérance de vie de l'ordre de 0.01 QALY.

Deuxièmement, une stratégie combinant une amélioration de l'ensemble de la cascade de soins de l'hépatite C chronique (dépistage, lien aux soins, adhérence au traitement) avec une initiation du traitement indépendamment de la sévérité de la maladie apparait comme efficace et coût-efficace, tout en étant optimale pour diminuer le nombre de nouvelles infections dans la population, et ceci malgré le

risque de réinfection, qui était pourtant considéré comme identique au risque d'infection primaire dans l'analyse principale. Ce résultat prouve qu'une approche de type TasP, en plus d'être efficace sur la transmission de la maladie (dans une perspective d'élimination du VHC), est aussi extrêmement efficace pour réduire le fardeau de l'hépatite C chez les UDI en France. Cette stratégie serait toutefois chère au coût actuel du traitement.

Les résultats de cette étude ont été présentés sous forme de poster au *Liver Congress* de l'*American Association for the Study of Liver Diseases* (AASLD) en novembre 2015 à San Francisco, Etats-Unis. Ils feront également l'objet d'un article. La version présentée dans ce chapitre est un document de travail, qui n'est pas encore finalisé.

6.2 Article 5

Cost-effectiveness of risk reduction measures and improvements in the cascade of care of chronic hepatitis C in people who inject drugs in France

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ABSTRACT

Background: Chronic hepatitis C, with a seroprevalence of 70%, is a major health issue for people who inject drugs (PWID) in France. Despite risk reduction interventions like needle and syringe provision (NSP) or opioid substitution therapies (OST), hepatitis C virus (HCV) infection incidence remains around 12/100 person-years. The availability of new direct-acting highly effective antivirals represents an opportunity to decrease HCV transmission and morbidity/mortality, but these new treatment regimens are associated with high costs. The objective of this study is to estimate the effectiveness and cost-effectiveness of improvements in risk reduction interventions, chronic hepatitis C cascade of care, and treatment access in a population of PWID in France.

Methods: We used a dynamic model of HCV transmission including chronic hepatitis C natural history and the social network to estimate individual trajectories in a fictive population of PWID in France. The model included the hepatitis C transmission, cascade of care and natural history. Scenarios evaluated were: S1: reference scenario=current practice. Time to access to needle and syringe programs (NSP) after injection initiation=1y, time to access to opioid substitution therapy (OST) when in NSP=0.5y, time to diagnosis after infection=1.25/1.45y, time to linkage to care after diagnosis=2.6y, loss to follow-up rate=14%/y, sustained virological response rate=95%, treatment initiation: fibrosis ≥F2; S2: improved risk reduction interventions. Access to NSP (alone) after injection initiation=0.25y, time before access to OST when in NSP=0.25y; S3: treatment initiation: fibrosis ≥F0; S4: improved cascade of care. Time to diagnosis=0.5y, time to linkage to care=0.5y, LTFU rate=5%/y, SVR rate=95%; S5: combine S3 and S4; S6: combine S2, S3 and S4. For each scenario, the mean life expectancy in discounted quality adjusted life years (QALY) and direct lifetime discounted costs were estimated among PWID in Paris metropolitan area from 2015 until death. Costs.related to risk reduction interventions, testing, care and treatment (46,000€ per treatment course for the new antivirals) were included. The incremental cost-effectiveness ratio (ICER) and the mean number of infections and reinfections were also estimated.

Results: In the current practice (S1), the discounted adjusted life expectancy was 16.57 QALYs, for a mean lifetime cost of 25,598€. Compared with the current practice, improve risk reduction interventions in S2 was barely effective: +0.01 QALYs on average; and with a higher ICER than when we improve testing, linkage to care and adherence to treatment in S4. This scenario led to a life expectancy of 16.81 (+0.24) QALYs, and was very cost-effective (ICER=4,715€/QALY). S5, that combined these improvements with a treatment initiation at F0 was the most effective scenario, with a life expectancy of 17.02 QALYs (+0.45); remained cost-effective, with an ICER=22,859€/QALY; and avoided 39% of infections. Other scenarios were most expensive and less effective.

Conclusion: With the new DAAs regimens, combining improvements in testing, linkage to care and adherence to treatment with a treatment initiation without restrictions on the severity of the liver

disease in PWID would be highly effective, very cost-effective, and would avoid more than a third of the future infections.

INTRODUCTION

Chronic hepatitis C is a blood borne viral disease responsible of more than 500,000 deaths annually in the world (1). Among people who inject drugs (PWID), the risk of hepatitis C virus (HCV) transmission is high, due to injecting equipment sharing (2). This, combined with other health issues related to injection practices such as HIV infection or overdoses, have led to the introduction of risk reduction interventions in many countries. In France, these interventions are currently mainly based on opioid substitution therapies (OST) using methadone or buprenorphine, and access to sterile injection equipment through needles and syringes provision (NSP) programs (3). However, HCV seroprevalence in this population remains high: around 70% (4), despite the high coverage of these interventions in big cities. 85% of active PWID (i.e. injecting in the last month) report having been OST during the last 6 months (ANRS-Coquelicot study (5), unpublished data), and the access to injection equipment is diversified through low thresholds structures, pharmacies, dispensing machines (3) and even postal distribution (6). NSP and OST are however not immediately initiated after injections are started; time to their initiation may be decreased in PWID.

Recently, with the availability of new direct-acting antiviral (DAAs) regimens, a new approach has emerged to decrease the transmission of HCV. These new therapies are more effective than the previous standard of treatment using dual therapy peg-interferon + ribavirin, with around 95% of sustained virological response (SVR) rates in clinical trials (7-17). Moreover, they are better tolerated than the previous standard of treatment using dual therapy peg-interferon + ribavirin. Thus, the elimination of HCV using the "treatment as prevention" (TasP), i.e. by the early treatment of infected PWID to prevent HCV transmission, is now considered (18). A previous modelling study in a PWID population in France showed that low HCV prevalence rates (<10%) could be achieved by a TasP strategy implying improvements of testing, linkage to care and adherence to treatment, and a treatment initiation even in F0/F1 fibrosis scores (19). However, first in that analysis risk reduction strategies were not considered. Next, the cost of the new therapies (until 46,000€ for a 12-weeks treatment in France) raises the question of the economic impact and feasibility of this strategy.

In the present paper, we use a dynamic individual-based model of HCV transmission in PWID to assess the effectiveness and cost-effectiveness of interventions designed to improve risk reduction and cascade of care in PWID in France in the context of the incoming DAAs.

METHODS

Model

The HCV transmission, cascade of care and health outcomes in a population of initially active (i.e. injecting in the last month) PWID in France were simulated using an updated version of a previously developed dynamic model (20). Briefly, in this model each PWID has a status indicating his/her HCV infectious status: susceptible or infected, and each infected individual has a status in the cascade of

care according to the diagnosis, the linkage to care and the treatment, see Figure 1. The infection rate depends on the number of infectious injecting partners of the injectors, which is modelled through a random graph. We used in the present article a new random graph model, based on the assumption of the existence of households, i.e. small groups of strongly connected PWID in the population which can themselves be connected together, see Supplementary Material S1. In addition, the progression of the liver disease related to chronic hepatitis was modelled using a natural history model taking into account the fibrosis progression from F0 to F4, the cirrhosis complications (decompensation and hepatocellular carcinoma, HCC), and the death related to HCV infection, see Figure 2. Compared with the previous version of the model, we added hepatic transplants for HCV complications, which are associated with high costs (3).

Finally, we added a model describing the status of each PWID according to the following risk reduction interventions: access to sterile injecting equipment (referred as "NSP") and OST, see Figure 3. In this model, PWID start in "No risk reduction intervention" state, corresponding to the period before they enter a NSP program, and progress to the "NSP" state. After entering NPS, they can begin to be substituted and progress to the "NSP+OST" state. PWID can stop their OST and return in the "NSP" (alone) state in the model.

Input Parameters

The key parameters of the model are presented in Table 1. The initial incidence was supposed to be 12/100 person-years (p.y), the median value for western countries (21), and the infection rate per infected partner was adjusted to obtain this incidence during the first year using Approximate Bayesian Computation (22). The average duration between the first injection and the recruitment in NSP was not available in the medical literature. However, concerning HCV infection, PWID are known to be more at risk of infection during the first year of their injecting career (23). We assumed that the lack of access to risk reduction interventions could explain this situation, and thus we assumed an average duration of 1 year between the first injection and the entry in NSP. The high proportion of active PWID currently under OST, and experts' opinions suggesting that NSP and OST are initiated almost simultaneously led us to consider a very short duration before entering in the NSP+OST compartment (6 months). About 37% of PWID under OST remains under treatment 10 months of the year, giving according to the survival function of the exponential distribution 2.32 years in average before cessation of OST (18). In addition, this data and the high proportion of PWID under OST suggest that the cessation of OST occurs for short periods: we assumed OST re-initiation after 3 months. Relative risk of HCV infection in each compartment were estimated in a meta-analysis in (24). In this study NSP parameters were estimated considering a high-coverage needle program (i.e. where a sterile syringe is available for 100% of the injections of the user).

The transition parameters and the initial distribution in the HCV cascade of care were mainly derived from ANRS-Coquelicot study data, a HCV-seroprevalence cross-sectional survey conducted among drug users in France (5). Input parameters for the social network model were estimated by

Approximate Bayesian Computation by using data of a population of PWID in Melbourne (25) due to the absence of local data in France, see Supplementary Information. From these parameters, we simulated networks of the size of PWID in Paris area in the previous study (10,000 PWID) (19). The details on the parameters are provided in Supplementary Material S1.

Cost & utilities

We first included annual medical costs associated with risk reduction interventions. Structural costs associated with these interventions were derived from the budget of French structures in charge of risk reduction and care in PWID: reception and harm reduction support centers for drug users (CAARUD) and medical centers for drug and alcohol dependence (CSAPA). To these costs were added cost of opioid substitution therapies and needles (18, 20, 26). Costs associated with HCV testing were included for susceptible PWID given that interventions promoting HIV testing were among evaluated strategies. Cost associated with HCV follow-up (only for PWID diagnosed and linked to care in the model) were provided by a study on health care consumption in chronic hepatitis C in France (3), and are given Table 2. Finally, the cost of the new DAAs was set to 46,000€ (27). Due to the lack of data about the quality of life of PWID in France, we used data from a German study (28).

Due to the lack of data about French population and with new DAAs regimens, we used utilities estimated from an HCV-infected German population with dual therapy (28, 29), see Table 3. For PWID before injection cessation, we adjusted the number of life years gained by a factor 0.9 (49). The detailed costs and utilities included in the model are given in Supplementary Material.

Strategies

In the main analysis, we simulated eight intervention each representing a scenarios corresponding to different improvements in risk reduction interventions, cascade of care of chronic hepatitis C and treatment initiation criteria:

Scenario 1 (S1): reference scenario=current practice in the main analysis. Time before access to NSP after injection initiation=1y, time before access to OST when in NSP=0.5y, time to diagnosis after infection=1.25/1.45y, time to linkage to care after diagnosis=2.6y, loss to follow-up rate when linked to care=14%/y, SVR rate=86% (95% of SVR in the clinical trials (7-17) to which we applied a decrease of 10% to take into account the difference between real life and clinical trial, see Table S2 in supplementary material), treatment initiation: fibrosis ≥F2.

Scenario 2 (S2): S1 with improved risk reduction interventions. In this scenario, we improved access to NSP and OST in the population. Indeed, as the risk of HCV infection is particularly high during the first year of injection (23, 30), a faster access to NSP or OST could avoid infections. Access to NSP after injection initiation=0.25y, time before access to OST when in NSP=0.25y.

Scenario 3 (S3): S1 with treatment initiation from F0. All individual with a diagnosis and linked to care are treated in this scenario (excluding those with a cirrhosis complication).

Scenario 4 (S4): S1 with improved cascade of care. In this scenario, we improved testing, linkage to care, loss to follow-up rate and adherence to antiviral treatments. Time to diagnosis=0.5y, time to

linkage to care=0.5y, LTFU rate=5%/y, SVR rate=95% (we considered that a better adherence could allow to reach a SVR rate similar to that of clinical trials).

Scenario 5 (S5): combined scenario S3 and S4. In this scenario, we improved the cascade of care of chronic hepatitis C and the treatment was initiated from F0.

Scenario 6 (S6): combined scenario S2, S3 and S4. Here, we improved risk reduction interventions, the cascade of care of chronic hepatitis C and the treatment was initiated from F0.

Outcomes

We simulated populations of 524 PWID which is the estimated size of the PWID community where the study was conducted in Melbourne (6). Twenty simulated networks were used per simulation to have a population size similar to that used previously (10,000 PWID) (19). The outcomes were estimated on the initial cohort of PWID (prevalent PWIDs); PWID entering the population during simulations (incident PWID) were not taken into account. We performed 250 simulations for each scenario on which the average lifetime cost, life expectancy in life years (LYs) and life expectancy in quality-adjusted life years (QALYs) were estimated in each simulation. We applied on these outcomes an annual discount rate of 4% before 30 years, which was linearly decreased until 2% between 30 and 50 year, and set at 2% after 50 years, consistently with the French guidelines (31). The incremental cost-effectiveness ration (ICER) was estimated in euros/QALY. According to World Health Organization guidelines (32), a scenario was considered as very cost-effective if the ICER was below French GPD per capita (around 30,000€ (33)) and as cost-effective if the ICER was below 3 times the French GPD per capita. For each scenario, we also estimated the mean number of infections in the population, and the mean number of reinfections after a SVR. Costs were in 2015 euros.

Sensitivity analysis

First, we performed a univariate sensitivity analyses for some key parameters, using values from other settings. We changed the initial HCV incidence from 12/100 p.y in the main analysis to 22/100 p.y (Montréal, Canada, unpublished data from SurvUDI network (34) on the 2010-2013 period) and 42/100 p.y (London, United-Kingdom (35)); the mean time to diagnosis from 1.25/1.45y to 2.0y (Montréal, Canada, unpublished data from SurvUDI network (34) on the 2012-2014 period) and 7.8y (London, United-Kingdom (36)); and the loss to follow-up rate from 14%/y to 20%/y and 30%/y (assumptions). Due to the uncertainty about risk reduction parameters, we also performed several sensitivity analyses by varying the relative risk of seroconversion on NSP and OST+NSP, and the initial distribution of the population reached by these risk reduction interventions. The following set of parameters were in particular varied: relative risk of seroconversion in NSP=0.9 vs. 0.5 in the main analysis (assumption); relative risk of seroconversion in NSP+OST=0.48 vs. 0.21 in the main analysis (from (24), when NSP coverage <100%, i.e not a high-coverage needle program); initial distribution in NSP=15% vs. 8.9% in the main analysis and in NSP+OST=50% vs. 85.7% in the main analysis. We used this distribution because this was the stable distribution when we multiplied by 2 the time before access to NSP and before access to OST in the model, and we changed the transitions rates

accordingly to ensure the distribution do not return mechanically to the previous one. We also simulated the reference scenario in absence of risk reduction interventions in the population. We estimated the impact of a decreased risk of reinfection after a SVR, by dividing by 3 the risk of infection for PWID after a SVR (37, 38); the risk of reinfection was equal to infection in the main analysis. Finally, we estimated the impact of a 25%, 50% and 75% decrease in the treatment cost.

RESULTS

Main analysis

The complete results of the main analysis are given in Table 1. We sorted results by increasing costs. S1 (the current practice) was the less expensive scenario, with an average lifetime cost of €25,598 (standard deviation=224). In this scenario, the adjusted average life expectancy was 16.57 (0.05) QALYs, the total number of infections was 3,271 (81), among which 872 (40) reinfections following a previous SVR. Improve risk reductions interventions in S2 led to a moderate increase in the adjusted life expectancy estimated at 16.58 (0.06) QALYs but had a higher incremental cost-effectiveness ratio than the strategy improving testing, linkage to care and adherence to treatment which is a more effective strategy (extended dominance). This strategy, S4, increased the adjusted average life expectancy to 16.81 (0.05) QALYs, and was also very cost-effective, with an ICER of 4,715€/QALY. In S5, when we combined improvements in strategy S4 with a treatment initiation from F0 instead of F2 in the current practice led to an adjusted life expectancy of 17.02 (0.05) QALYs and decreased the number of new infections in the population to 2,008 (86)(vs. 3,271 in the current practice) for a lifetime cost of €31,437 (270). This scenario was also very cost-effective, with an ICER of 22,859€/QALY. In S6, combine improvements in risk reduction interventions; testing, linkage to care, and adherence to treatment; with a treatment initiation from F0 led to similar efficacy outcomes but with a higher lifetime cost: €31,523 (259). Finally, when the only intervention was a treatment initiation from F0 in S3 vs. from F2 in the current practice, the adjusted life expectancy was lower: 16.72 (0.05) QALYs, which corresponds to -0.30 QALY compared with S4. This scenario is thus dominated. This was also the most expensive scenario, with a lifetime cost of €31,885 (387), and the scenario with the highest number of reinfections: 1,430 (66).

Sensitivity analysis

The complete results of the sensitivity analysis are given in Supplementary Material S2. We only mention here the most notable results.

Briefly, from a 50% decrease in the treatment cost (23,000€ instead of 46,000€), the scenario S3, were we improved testing, linkage to care and adherence to treatment, became the less expensive scenario with a lifetime cost of €24,409 (181) vs €24,810 (218) in the reference scenario S5. The scenario S5, which is S3 combined with a treatment from F0, remained cost-effective, with an ICER of 15,380€ for an increase +0.21 QALYs in the adjusted life expectancy.

When we increased the initial incidence from 12/100 p.y. to the values estimate for Montréal (22/100 p.y.) and London (42/100 p.y.), the gap between the lifetime cost in the strategies where treatment is initiated from F2 (S1, S2 and S4) and that in the strategies where the treatment is initiated from F0 (S3, S5 and S6) increased. The scenario S6 combining improvement in risk reduction interventions, in the cascade of care and with treatment initiated from F0 became the most effective, but not cost-effective when we considered London's incidence estimates (ICER=146,226€/QALY). The scenario S5, which did not considered improvement in risk reduction measure, was dominated the scenario 6. Using testing rates from another setting (i.e. London) with a mean time to diagnosis of 7.8 years vs. 1.25/1.45 years for active/inactive PWID in the current practice, treating from F0 (S3) became less expensive than the combined strategies S5 and S6, but this scenario remains dominated by S4 (improved testing, linkage to care and adherence to treatment). Similar results were obtained when we varied the mean time to linkage to care (4.0 years vs. 2.6 years in the current practice). This results was not observed with the mean time to diagnosis of Montréal, which is 2.0 years.
When we changed the initial distribution of the population is risk reduction measures for less favorable conditions: initial distribution in NSP=15% and in NSP+OST=50% vs. 8.9% and 85.7% respectively: combined with lower transitions to NSP and OST: transition from "No risk reduction interventions" to NSP in 2 years (vs. 1 year in the sensitivity analysis) and from NSP alone to NSP+OST in 1 year (vs. 0.5 years in the sensitivity analysis), S4 (improve cascade of care) became less expensive than S2 (improved risk reduction intervention), with €25,682 (214) vs. €26,745 (194).
If we also changed the relative risk of seroconversion to lower values: relative risk of seroconversion in NSP=0.9 vs. 0.5 in the main analysis (hypothetic values); relative risk of seroconversion in NSP+OST=0.48 vs. 0.21 in the main analysis; we obtained similar results.
Finally, when we simulated an absence of risk reduction interventions in the population in S1, the man adjusted life expectancy was lower than in the main analysis (-0.09 QALY) and the number of infections higher (4,747 vs. 3,271).

DISCUSSION

In this study, we used a dynamic, individual-based model including the social network and the natural history of chronic hepatitis C to assess the cost-effectiveness of scenarios including improvements in risk reduction measures and improvements in the cascade of care of hepatitis C in the population of PWID of Paris area. Several important points emerged from this analysis.
Firstly, improve existing risk reduction interventions with faster access to NSP and OST (S2) only slightly increased the adjusted average life expectancy (0.1 QALYs) compared with the current practice and had a higher incremental cost-effectiveness ratio than the strategy improving testing, linkage to care and adherence to treatment which is a more effective strategy. Secondly, improve testing, linkage to care and adherence to treatment (S4) allowed to increase the adjusted average life expectancy to 16.81 QALYs (vs. 16.57 in the current practice) and was very cost-effective, despite a

high number of reinfections (1,140 vs. 872 in the current practice). Thirdly, improvement in testing, linkage to care and adherence to treatment with treatment initiation from F0 vs. F2 in the current practice considerably increased the lifetime cost, which reached 33,437€, but was also the most effective strategy. The adjusted average life expectancy with this strategy reached 17.02 QALYs, because it dramatically decreased the number of new infections in the population: around 2,000 over the simulation period vs. 3,300 in the current practice. This strategy was also very cost-effective, with an ICER of 22,859€/QALY. Improving in addition to this strategy NSP and OST (S6) resulted in similar outcomes but for higher costs. Finally, a strategy relying in initiating treatment at F0 instead of F2 (S3) alone was the most expensive strategy with a lifetime cost of 31,885€), and was dominated by S5.

In this study, the impact of an improvement in risk reductions interventions was relatively weak in the main analysis. This result can be explained by the current high coverage of these measures in the baseline population: 85% of the active PWID population on OST during the past 6 months (Coquelicot study (5), unpublished data). However, there remains uncertainties around parameters we used for risk reduction interventions. Most of the published studies about HCV in IDU populations recruited in harm reduction support centers, healthcare centers and accommodation facilities for drug users. Thus, the hidden part of the population constituted of people who do not attend such structures, more marginalized, were not included. Effectiveness and coverage rate of such interventions are maybe optimistic. In addition, in the absence of data regarding the proportion of injections covered by NSP in France, we used the relative risk associated with a high-coverage needle program (i.e. where a sterile syringe is available for 100% of the injections of the user) in the main analysis (24). However, when we used less favorable initial conditions in sensitivity analysis, using a relative risk of seroconversion in NSP=0.9 vs. 0.5 in the main analysis; relative risk of seroconversion in NSP+OST=0.48 vs. 0.21 in the main analysis initial distribution in NSP=15% and in NSP+OST=50% vs. 8.9% and 85.7% respectively in the main analysis, the results remains similar. In addition, in sensitivity analysis, when we used higher incidence of 22/100 p.y and 42/100 p.y corresponding to estimates from Montréal and London, the scenario S6, with improvements in risk reduction, HCV cascade of care and treatment from F0 became the most effective, instead of S4, which is the same scenario without improvement in testing. This result shows that there is an initial incidence threshold in the interval of realistic values above which an improvement in risk reduction interventions would increase life expectancy, even if the baseline coverage is already high. Moreover, we did not take in consideration health benefits obtained through improvement in reduction intervention on other common health issues in PWID, such as HIV infection prevention (39, 40), drug related morbidities (41) or drug related crimes (42). Finally, we only assessed the impact of a scale-up in currently implemented measures namely NSP and OST. To highly improve the impact of risk reduction interventions, original measures are possible. In some countries other interventions have been taken, like supervised injection facilities (SIF). In a meta-analysis, SIF have been proven to significantly decrease the frequency of needle/syringe sharing,

lending or borrowing (43). Moreover, data bout SIF in Vancouver shown the potentially favorable effect of such structure on OST initiation and drug injection cessation (44).

Improve testing, linkage to care and adherence to treatment together was highly cost-effective. In a previous modelling study about HCV cascade of care in PWID (19), we have shown that such interventions would have a limited impact on HCV transmission but a visible impact on complications occurrence (between 11% and 13% of cirrhosis complications avoided after 40 years when implemented separately). This decrease in the number of complications explains the increase in life expectancy compared with the current practice, despite a similar number of new infections. Combining these improvements with a treatment initiation from F0 instead of F2 was the most effective scenario and was very cost-effective, despite the high increase in cost due to the change in treatment initiation criteria. This was also the most effective scenario to avoid new infections in the population. This decrease in the number of new infection could only be reached through a combination of improvement in the cascade of care and treatment initiation criteria: when the only intervention is a change in treatment initiation criteria to treat from F0 (S5), the number of new infections remains almost equal to that of the current practice, due to the high number of reinfections. S5 was also the most expensive of the 6 we estimated at the current treatment cost. This is consistent with our previous results showing that treating from F0 alone would have few impact on the number of HCV complications (and thus on the cost associated with the latter) (19), because from this point of view, being treated in F0 instead of most severe fibrosis scores is neutral.

Thus, with the current treatment cost, a treatment as prevention strategy, combining improvements in all the cascade of care with a treatment initiation from F0 was highly effective and cost effective. However, the cost would be high: compared with the current practice, the additional cost would be 5,839€ per PWID, after applying discount rate. This corresponds to an additional cost of €61 million for the whole population, compared with the current practice. In addition, our initial incidence estimate was 12/100 p.y in the main analysis which correspond to a median estimate in high income countries (21). Using a upper, but realistic value for the initial incidence (42/100 p.y (35)) in the sensitivity analysis, we showed that this strategy became not cost-effective with the current treatment cost. In another sensitivity analysis, we showed that this scenario would be the least expensive under a 50% decrease in treatment cost (23,000 vs. 46,000 in the main analysis), even less expensive than the current practice. A decrease in HCV treatment cost is therefore important to be able to implement a treatment as prevention strategy.

The literature is scarce about the impact of combined measures including risk reduction interventions and antiviral treatment in PWID. Martin *et al.* have studied the impact of combined interventions including NSP, OST and treatment delivery among PWID in London (45). They found that combining NSP and high coverage needle and syringe program is a necessity to halved HCV prevalence over 10 years. In our model, we found similar results: when we changed the risk reduction intervention coverage and the associated relative risks in sensitivity analysis, the number of infections was nearly

25% more important than in the main analysis, under the condition of the reference scenario. In absence of risk reduction interventions, there were 50% more infections in this scenario compared with the main analysis, and the adjusted life expectancy was 0.09 QALY lower in the population. This point confirms the necessity to maintain a high level of risk reduction intervention. In our study, we also studied costs and strategies impacting the entire cascade of care, and we can add that despite the necessity of such interventions, improve testing, linkage to care and adherence to treatment is critical and would be more cost-effective than improving risk reduction interventions.

This study presents several limitations. First, we did not consider that hepatitis C diagnosis would lead to change in risk practices in the model. However, some published studies show that awareness of HCV infection is not associated with a decrease in risk practices (46, 47). Secondly, as mentioned above, the impact of risk reduction interventions on other health issues like HIV infection and drug related morbidity, and the impact on drug related crime were not included in the model. Third, in the absence of data about PWID social networks in France, we used data from a study in Melbourne (25). However, despite the possibility of different network structures in France, the use of these data allow us to build a realistic network model, with a restriction of HCV transmission possibilities to a small subgroup of injecting partners.

This study also present several strengths. This is, to our knowledge, the first to study the cost-effectiveness of interventions including risk reduction interventions, hepatitis C cascade of care and hepatitis C treatment initiation criteria, with the evaluation of combined strategies. The model also included the social network of PWID.

In conclusion, in the era of the new DAAs, the combination of an improvement in testing and linkage to care, together with an unconditional access to treatment (i.e. from F0) could maximize the impact of the antiviral treatment on the life expectancy of PWID in France. This strategy would be cost-effective, but it would also be expensive. In high prevalence settings, it would not be even cost-effective at the current treatment cost. In the absence of more accurate data about the access to sterile injecting material in the population, and particularly on the number of injections covered, it is difficult to conclude on the effectiveness of improved risk reductions interventions. Given it current coverage, this strategy seems however to not bring an additional benefit when combined with TasP in the main analysis. However, maintaining the current level of access to sterile equipment seems to be a necessity.

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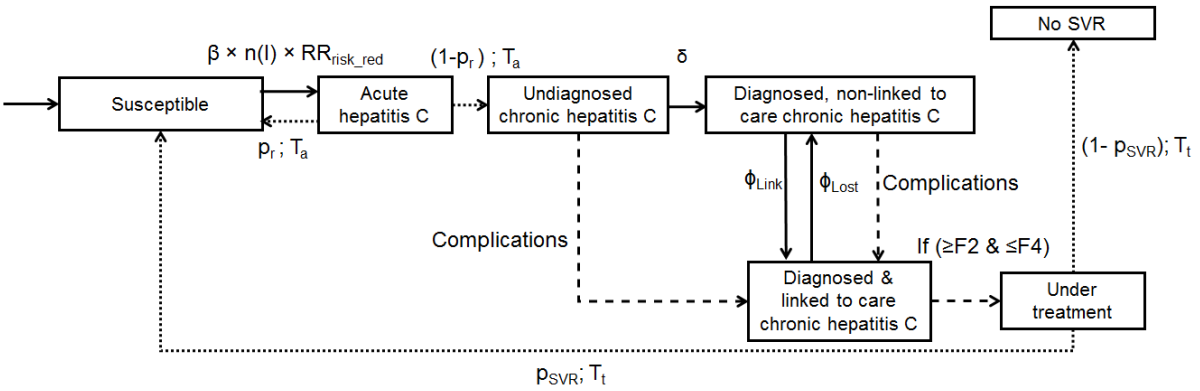

Figure 1 model for HCV infection and care. A new PWID enters the model as susceptible. Plain arrows correspond to transitions occurring according to exponential probability distributions. Dashed lines correspond to transition occurring after a fixed time with a given probability. Dotted lines correspond to transitions related to a transition in the natural history model. n(i) refers to the number of infectious injecting partners of the PWID. RR_{risk_red} refers to the relative risk of infection related to the PWID status regarding risk reduction interventions.

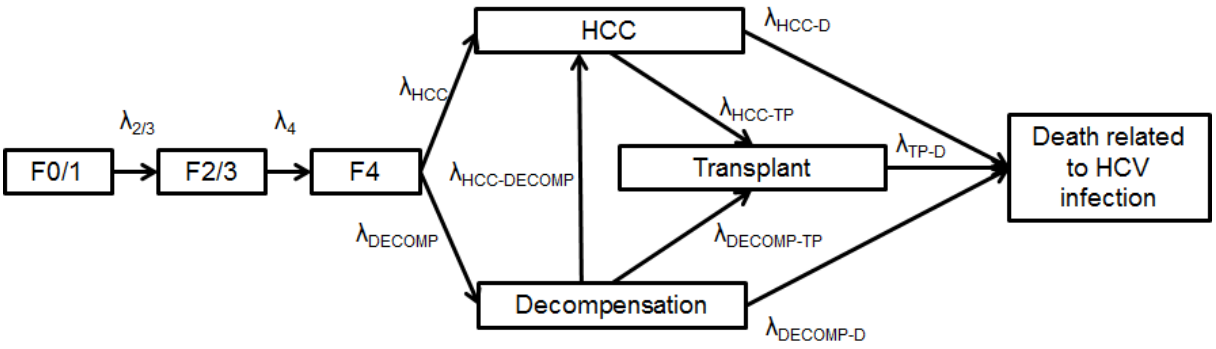

Figure 2 natural history of chronic hepatitis C in the model. F0/F1 refers to a F0 or F1 Metavir score; and F2/F3 to a F2 or F3 Metavir score. Each transition occurs according to exponential law. $\lambda_{TP\text{-}D}$ depends on the time since transplant: the mortality rate is higher during the first year.

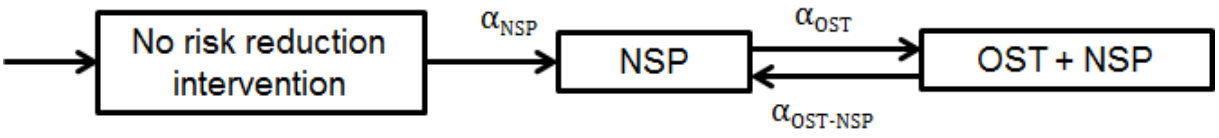

Figure 3 harm reduction interventions. NSP=Needle and syringe program, OST=Opioid substitution therapy. New PWID enter the model in the "no risk reduction intervention" compartment. Each transition occurs according to exponential law. $\alpha_{OST\text{-}NSP}$ depends on the existence of a previous OST among the PWID: the return under OST is faster than the first OST initiation.

Table 2 Key parameters for the model: initial population, infection and care.

Parameter	Value	References
Population size	20×524*	
Initial distribution infection and care		
Susceptible	57.2%	ANRS-Coquelicot (5), unpublished data
Acute hepatitis	0%*	
Non-diagnosed chronic hepatitis	9.2%	ANRS-Coquelicot, unpublished data
Diagnosed, non-linked to care chronic hepatitis C	11.3%	
Diagnosed and linked to care chronic hepatitis C	16.0%	
Under treatment	2.2%	
Non-responders after treatment	4.1%	
Initial distribution related to harm reduction interventions		
None	5.4%*	
NSP	8.9%*	
NSP+OST	85.7%	ANRS-Coquelicot (OST in active PWID), unpublished data
Infection rate by injecting partner in S'	0.184 y^{-1}partner^{-1}	Fitted by ABC to have a 12/100 p-y baseline incidence (21) – median value from western countires in absence of data in France
Relative risk of infection when under		
NSP	0.5	(24) For a high-coverage needle program (i.e. where a sterile syringe is available for 100% of the injections of the user)
NSP+OST	0.21	
Transition from "no risk reduction intervention" to NSP	1y*	
Transition from NSP to NSP+OST		
First time	0.5y*	
Next times	0.25y*	
Average time from chronic infection to diagnosis		
Current PWID	1.25 y	Derived from ANRS Coquelicot data (19)
Former PWID	1.45 y	
Average time before linkage to care	2.6 y	Derived from ANRS Coquelicot data (19)
Loss to follow-up rate	14%/y	(48)

Treatment: incoming DAAs regimens		
Duration	12 weeks	(7-10, 13-17, 49)
SVR rate – treatment naïve – all genotypes- clinical trials	95%	
Ratio of the effectiveness in real life to the efficacy in clinical trials	0.903	Derived from (50)

[*] Hypothesis
IBM: Individual-based model
SVR: Sustained virological response
PWID: People who inject drugs
y^{-1} : per year
HCC: Hepatocellular carcinoma
DAA: Direct-acting antiviral
HCV: Hepatitis C virus

Table 2 Annual mean costs (SD) attributable to chronic hepatitis C: ambulatory costs (never treated and after HCV treatment failure) and hospitalization costs (no death and in-hospital death)(3)

Liver disease stage	**Ambulatory costs (€)**		**Hospitalization costs (€)**	
	Never treated	**After treatment failure**	**No death**	**In-hospital death**
F0/F1	70 (10)	53 (12)	278 (1,087)	337 (1,377)
F2/F3	128 (22)	86 (15)		
F4	228 (20)	71 (18)	1,295 (3,732)	6,450 (11,422)
Decompensation	96 (21)		9,874 (12,246)	16,119 (17,778)
HCC	96 (21)		11,745 (11,634)	16,643 (14,137)
Liver transplant				
First year	96 (21)		56,021 (40,329)	90,712 (55,462)
Following years	96 (21)		5,445 (11,123)	15,911 (23,307)

Table S4 Utilities estimated in an HCV-infected German population according to disease stage (28, 29) and assumptions used in the model.

	HCV-RNA-positive	**HCV-RNA-negative***
F0/F1	0.931	0.95
F2/F3†	0.902	0.95
F4	0.872	0.89
Decompensated cirrhosis/HCC	0.794	0.81
Liver transplantation	0.843	0.843
Multiplied under IFN-free regimens	0.950	

*In case of SVR. †We conservatively assumed that the decrease in F2/F3 compartment correspond to that of F3 in Siebert *et al.* study.

Table 4 Results of the main analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs.

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (y)	Adjusted average life expectancy (sd) (QALYs)	Averge number of new infections (sd)	Average uumber of reinfections after SVR (sd)	ICER (€/QALY)
S1 – Reference (current practice)	25,598 (224)	18.30 (0.06)	16.57 (0.05)	3,271 (81)	872 (40)	
S2 – Improved risk reduction interventions	25,682 (214)	18.30 (0.06)	16.58 (0.06)	3,254 (74)	868 (36)	Extended dominance
S4 – Improved cascade of care	26,745 (194)	18.48 (0.05)	16.81 (0.05)	3,341 (93)	1,140 (48)	4,715
S5 – Combined S3 and S4	31,437 (270)	18.50 (0.06)	17.02 (0.06)	2,008 (86)	972 (54)	22,859
S6 – Combined S2 and S3 and S4	31,523 (259)	18.50 (0.06)	17.02 (0.05)	2,007 (86)	972 (57)	Dominated
S3 – Treatment initiation: fibrosis ≥F0	31,885 (346)	18.32 (0.05)	16.72 (0.05)	3,218 (113)	1,430 (66)	Dominated

sd : standard deviation ; y : year ; QALY : quality adjusted life-year

6.3 Annexes

SUPPLEMENTARY MATERIAL

S1: MODEL DETAILS AND PARAMETERS ESTIMATIONS

MODEL AND PARAMETERS

Population

The initial population of the model is a population of PWID in Paris area. As in a previous study, we supposed that the order of magnitude of this population is 10,000 (1, 2). The population is structured in 3 levels: each PWID is in a compartment in the transmission model, a position in the network and a life expectancy (excluding HCV mortality).

The initial age distribution is described in Table S1.

Table S1 Age distribution according to the gender in active (i.e. injection in the last month) PWID in 2011 from ANRS-Coquelicot study.

Age	Women	Men
20	1.4	0.1
22	6.2	1.5
23	5.0	1.8
24	10.3	2.7
25	0.1	1.1
26	1.5	0.7
27	0.7	5.9
28	1.8	0.5
29	1.1	3.0
30	5.3	2.9
31	5.6	8.3
32	0.0	3.3
33	3.5	1.9
34	0.1	4.7
35	1.0	1.9
36	2.9	4.8
37	17.8	4.4
38	0.6	5.5
39	5.7	6.8
40	1.5	7.0
41	4.7	4.6
42	0.0	1.5
43	0.0	2.7
44	6.4	5.5

45	0.2	2.3
46	4.9	1.6
47	3.4	0.8
48	3.4	0.3
49	1.4	5.0
50	0.0	2.1
51	3.6	1.2
53	0.0	0.2
54	0.0	0.0
55	0.0	1.3
56	0.0	0.5
59	0.0	1.6

Each compartment in the model corresponds to:

- A state concerning the risk reduction intervention in which he/she participates
- A state related to HCV infection and care
- For chronically HCV-infected PWID, a state in the natural history model

The possible states for each of these characteristics are described below.

Social network

Model

One of our objectives was to simulate possible pathways of HCV transmission in PWID by a random graph, i.e. a set of nodes connected by edges according to a probability distribution. Compared with mixed models, taking into account the social network allows to take the neighborhood size of individuals intro consideration and to propose more realistic estimations of infections parameters, for instance.

HCV is mainly transmitted by needles/syringes sharing in the PWID population; however paraphernalia sharing (e.g. filter, spoon) seems to play an important role too (3). To take into account the global risk of infection for a PWID, we chose, as previously described by Rolls *et al.*, to model the network of the sharing partners: two PWID are linked together if they inject together even without sharing needles/syringes (4). In this network, two PWID are linked if they reported "intraveneous drug use at the same place and time" in the previous 3 months.

A model is needed, because we need to generate networks of PWID in simulations. We chose a *household graph model* (5, 6). These models generate networks where individual from subgroups ("households") in which pairs have a high probability to be linked, while individuals belonging to different subgroups have a low probability to be linked.

Our model is constructed as follows :

1) In a population of *n* individual, we randomly assign each member to an household of size 1 (the individual is alone in his/her household), 2 or 5, with probabilities π_1, $\pi_2$or π_5.

2) Each couple of individuals belonging to the same household is considered is linked with an adge with probability depending of the type of household they belong to $p_{ij}, (i,j) \in \{1,2,5\}^2$

Probabilities p_{22} and p_{55} are considered higher than p_{12}, p_{15}, and p_{25}.

Parameters

For simplicity, we assumed that $p_{11} = 0$, because structure that would be formed if $p_{11} > 0$ would be similar to household of size 2. Thus, we needed to estimate the following parameters: π_1, π_2, π_5 and p_{12}, p_{15}, p_{22}, p_{25} and p_{55}.

For this purpose, we used Approximate Bayesian Computation (ABC). ABC is a bayesian method used to infer some parameters of a model without likelihood estimation (7). Briefly, the main idea of ABC is to fit the (possibly set of) parameter(s) θ of a model thanks to simulations and computation of a (possibly set of) statistic(s) $s_i, i = 1, \dots, N$ that are compared to the observed values on the data s_{obs}. More precisely, we drawn a model parameter sample $\theta_i, i = 1, \dots, N$ in a prior probability distribution. The models are simulated with these parameters is used to obtain the corresponding simulated statistics $s_i, i = 1, \dots, N$. Each parameter value is then weighted by $W_i = K_\delta(s_i - s_{obs})$, where K_δ is a smoothing kernel with tolerance threshold δ. The weighted sample gives the posterior probability distribution. We used a variant of the ABC algorithm with linear adjustement to correct θ_i given the other simulations: supposing a linear relation between θ and S, each θ_i is replaced by $\theta_i^* = \theta_i - \mathrm{b}(s_i - s_{obs})$, with b estimated by linear regression. This variant allows to obtain a tighter posterior distribution. For more details about ABC, the reader can refer to (8).

Due to the lack of data about PWID social networks in France, we used the data collected in a survey in Melbourne (Australia) (9). The data available was a network of 305 PWID in Melbourne (Australia). These data were obtained using snowball sampling (RDS): starting from an initial set of 151 PWID, each of them were asked to report a maximum of five injecting partner in the population. The investigators then tried to find these partners to make them participate in the survey, and ask them to report in turn their injecting partners, etc. The final obtained network was constituted of 305 PWID, of which 47 without identified partners. The total population size was estimated at 524 from this sample. This network is partial, due to the limitation in the number of reported injected partners.

To calibrate our household model from Melbourne data, we used ABC with the following process:

Step 1: A sample of 90,000 parameters values for the household graph model was drawn. The parameters p_{12}, p_{15}, p_{22}, $p_{25}$and p_{55} were drawn in uniform prior distributions in respectively [0, 0.2/250], [0, 0.05/250], [0, 0.2/250], [0, 0.05/250] and [0, 3/250]. The prior law distributions of π_1, $\pi_2$or π_5 were uniform distributions renormalized so that the distribution summed to 1 with respective means of 0.25, 0.25 and 0.5 respectively. The parameters for the prior distributions were chosen according to an exploratory descriptive analysis of the sample.

Step 2: For each set of parameters in the sample, we simulated a corresponding household graph of size 524. This value was the estimated size of the initial PWID community in which the snowball sample was drawn according to Rolls *et al.* (9).

Step 3: A snowball sampling process was simulated on each of these networks in the following manner (implemented in C++):

A. An initial set of 151 nodes was randomly chosen in the graph
B. For each of these nodes
    1. If the node's degree (i.e. the number of edges linked to the node) is inferior or equal to 5, all the neighbors of the index node are included in the snowball sample
    2. If the node's degree is superior to 5, 5 nodes are randomly and uniformly drawn among the neighbors to be included in the snowball sample
C. The same process is applied from B to the nodes newly included in the sample, until the sample size reached 305

Step 4: A set of summary statistics are computed for each snowball sample. These statistics are: the number of isolated nodes, the number of edges, the number of triangles in the network, the number of isolated couples and the diameter of the network (i.e. the maximum number of edges between two nodes of the network). This generates a set of inputs for the ABC constituted of N=90,000 summary statistics.

Step 5: We applied ABC using the package "abc" (10) of the statistical software R (11). The observed statistics in the Melbourne's snowball sample were: 47 isolated nodes, 263 edges, 61 triangles, 23 isolated couples, and a diameter of 17. We used an Epanechnikov kernel with a tolerance threshold corresponding to 10% of the simulations. $\pi_2$or π_5 values were logit-transformed to ensure final estimates between 0 and 1, and π_1 estimates was derived from $\pi_2$or π_5 to sum to 1.p_{12}, p_{15}, p_{22}, $p_{25}$and p_{55} were log-transformed to ensure their positivity. We applied a correction on the parameters values using linear regression, as explained below.

Step 6: The mean value of each posterior distribution was used as the final estimate for the corresponding parameter.

The results obtained were: $(\widehat{\pi_1},\widehat{\pi_2},\widehat{\pi_5}) = (0.26,0.237,0.503)$and $(\widehat{p_{12}},\widehat{p_{15}},\widehat{p_{22}},\widehat{p_{25}},\widehat{p_{55}}) = (3.42e^{-4}, 7.52e^{-5}, 3.20e^{-4}, 1.56e^{-4}, 2.48e^{-4})$.

We can see that according to these results, around 50% of the PWID belongs to a household of size 5. $\widehat{p_{12}}$ and $\widehat{p_{22}}$ are the highest values, implying the emergence of arborescent structures in the simulated graphs. The probabilities for people belonging to an household of 5 people to connect with people of other households $\widehat{p_{15}}$, $\widehat{p_{25}}$and $\widehat{p_{55}}$ are lower, suggesting that such household are more isolated. However with 5 people in each household, there are 5 times more chances to connect with other households.

Example

An example of simulated household graph is given Figure S1.

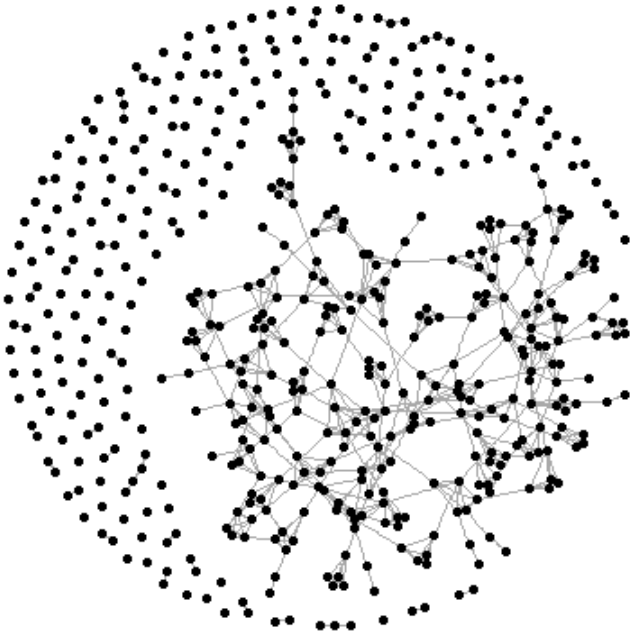

Figure S1 example of simulated household graph with N=524

Risk reduction interventions

We included the two main risk reduction interventions currently available in France: access to sterile injection equipment through harm reduction centers ("CAARUD"), risk reduction kits in pharmacy or via automatic dispensers; and opioid substitution therapies (buprenorphine or methadone). The model is represented Figure S2, and the parameters values are given Table S2.

The average duration between the first injection and the recruitment in NSP was not available in the medical literature. However, concerning HCV infection, PWID are known to be more risky during the first year of their injecting career (12, 13). We assumed that the lack of access to risk reduction interventions could explain this situation, and thus we assumed an average duration of 1 year between the first injection and the entry in NSP. The high proportion of active PWID currently under OST, and experts' opinions suggesting that NSP and OST are initiated almost simultaneously lead us to consider a very short duration before entering in the NSP+OST compartment (6 months). About 37% of PWID

under OST remain under treatment 10 months of the year, giving according to the survival function of the exponential distribution 2.32 years in average before cessation of OST (14). In addition, this data and the high proportion of PWID under OST suggest that the cessation of OST is short: we assumed a come-back under OST after 3 months. Relative risk of HCV infection in each compartment were estimated in a meta-analysis in (15). In this study NSP parameters were estimated considering a high-coverage needle program (i.e. where a sterile syringe is available for 100% of the injections of the user).

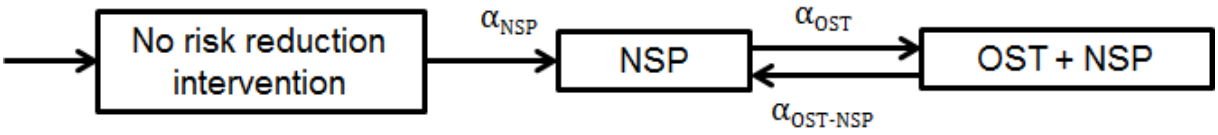

Figure S2 harm reduction interventions. NSP=Needle and syringe program, OST=Opioid substitution therapy. Each transition occurs according to exponential law. $\alpha_{OST-NSP}$ depends on the existence of a previous OST among the PWID: the return under OST is faster than the first OST initiation.

Natural history

The previously used model for chronic hepatitis C natural history included the fibrosis progression, the two cirrhosis complications (decompensated cirrhosis and HCC). We changed it to include hepatic transplant in cirrhosis complications, due to the high costs incurred. A representation of the model is given Figure S3. The corresponding parameters are described in Table S2.

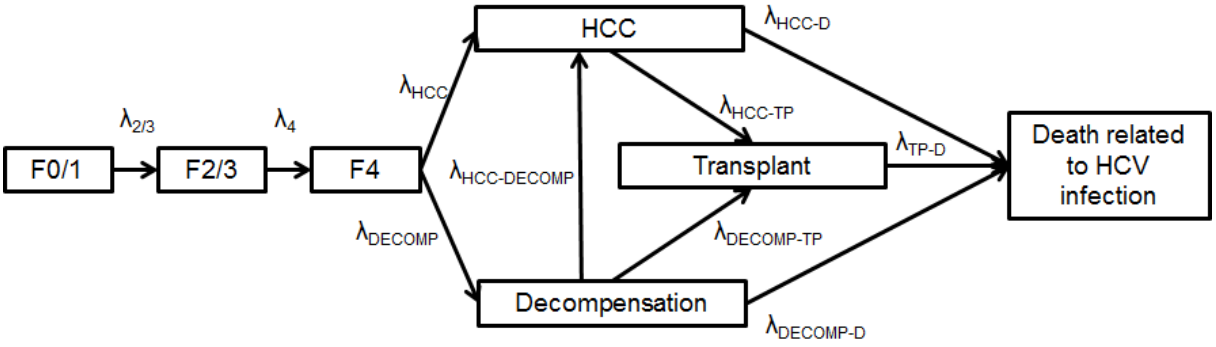

Figure S3 natural history of chronic hepatitis C in the model. F0/F1 refers to a F0 or F1 Metavir score; and F2/F3 to a F2 or F3 Metavir score. Each transition occurs according to exponential law. λ_{TP-D} depends on the time since transplant: the mortality rate is higher during the first year.

Infection and care

The model is represented in Figure S4. Briefly, starting from the susceptible state, an active (i.e. before cessation of injection) PWID can be infected with an infection rate depending on the number of his/her infectious injecting partners on the network and his/her status related to harm reduction

interventions. After the acute phase of hepatitis C he/she can spontaneously recover with probability and become susceptible again or progress to chronic hepatitis C. Then, he/she can be diagnosed at a rate that depends on his/her status related to injection: active or inactive injector. Once diagnosed, he/she can be linked to healthcare, and he/she can be lost to follow-up, or be treated if his/her Metavir score is between F2 and F4 (in the current practice). Then he/she can have SVR and become susceptible again or otherwise progress to "Non SVR", in which he/she can not be treated again. When a complication of cirrhosis occurs, a PWID is automatically linked to care.

Parameters values are given Table S2.

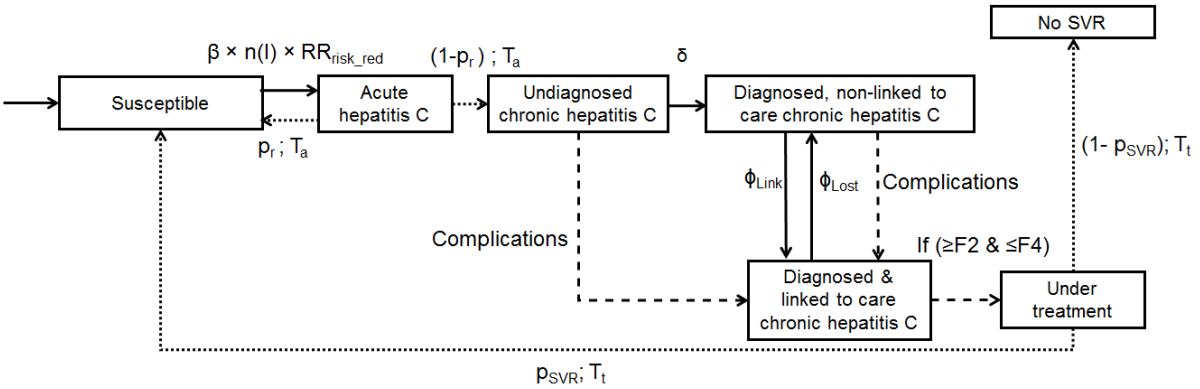

Figure S4 model for HCV infection and care. A new PWID enters the model as susceptible. Plain arrows correspond to transitions occurring according to exponential probability distributions. Dashed lines correspond to transition occurring after a fixed time with a given probability. Dotted lines correspond to transitions related to a transition in the natural history model. n(i) refers to the number of infectious injecting partners of the PWID. RR_{risk_red} refers to the relative risk of infection related to the PWID status regarding risk reduction interventions.

Cessation of drug injection and mortality non-related to HCV

The model takes also into account the cessation of injection: the duration of the injecting career is supposed to be 13.9 years (16, 17).

The mortality in the model depends on the gender, the age and the current injecting status (active injector or former injector). We assumed that the mortality for former injectors is similar to that of general French population, and we used the table of the mortality rates for the years 2012 in this case (18). For active injector, we applied a relative risk of 5.19 for men and 9.52 for women (19).

Table S2 Parameters for the model: initial population, infection, care and natural history

Parameter	Value	References
Population size	20×524*	
Initial distribution infection and care		
Susceptible	57.2%	ANRS-Coquelicot

Acute hepatitis	0%*	
Non-diagnosed chronic hepatitis	9.2%	ANRS-Coquelicot
Diagnosed, non-linked to care chronic hepatitis C	11.3%	
Diagnosed and linked to care chronic hepatitis C	16.0%	
Under treatment	2.2%	
Non-responders after treatment	4.1%	
Initial distribution in the natural history model		
F0/F1	35%	(20)
F2/F3	51%	
F4	14%	
Decompensated cirrhosis	0%*	
HCC	0%*	
Initial distribution related to harm reduction interventions		
None	5.4%*	Derived from (12)
NSP	8.9%*	
NSP+OST	85.7%	ANRS-Coquelicot (OST in active PWID)
Men among current PWID	75.5%	ANRS-Coquelicot
Infection rate by injecting partner in S'	0.184 $y^{-1}partner^{-1}$	Fitted by ABC to have a 12/100 p-y baseline incidence (21) – median value from western countires in absence of data in France
Relative risk of infection when under		
NSP	0.5	(15) For a high-coverage needle program (i.e. where a sterile syringe is available for 100% of the injections of the user)
NSP+OST	0.21	
Transition from "no risk reduction intervention" to NSP	1y*	
Transition from NSP to NSP+OST		
First time	0.5y*	
Next times	0.25y*	
Duration of acute hepatitis C	0.5 y	(22)
Probability of spontaneous recovery	26%	
Average time from chronic infection to diagnosis		
Current PWID	1.25 y	Derived from ANRS Coquelicot data (1)
Former PWID	1.45 y	
Average time before linkage to care	2.6 y	Derived from ANRS Coquelicot data (1)
Loss to follow-up rate	14%/y	(23)
Treatment: incoming DAAs regimens		
Duration	12 weeks	(24-34)

SVR rate – treatment naïve – all genotypes- clinical trials	95%	
Ratio of the effectiveness in real life to the efficacy in clinical trials	0.903	Derived from (20)
Duration of injecting career	13.9 y	(16, 17)
Transition rate F0/F1→ F2/F3	0.052 y^{-1}	(35)
Transition rate F2/F3→ F4 (λ_4)	0.054 y^{-1}	
Transition rate F4→Decompensated cirrhosis	0.04 y^{-1}	(36, 37)
Transition rate F4→HCC	0.021 y^{-1}	
Transition rate Decompensated cirrhosis→Death related to HCV	0.306 y^{-1}	
Transition rate HCC→Death related to HCV	0.433 y^{-1}	
Transition rate Decompensated cirrhosis→HCC	0.021 y^{-1}	
Transition rate Decompensated cirrhosis→Transplantation	0.128 y^{-1}	(38, 39)
Transition rate HCC→Transplantation	0.186 y^{-1}	
Transition rate Transplantation→Death related to HCV		
First year	0.174 y^{-1}	
Following years	0.033 y^{-1}	
Relative risk in patients achieving SVR in F4		
Death related to HCV infection	0.13	(40)
Decompensated cirrhosis	0.08	
HCC	0.27	

* Hypothesis
IBM: Individual-based model
SVR: Sustained virological response
PWID: People who inject drugs
$y^{-1:}$ per year
HCC: Hepatocellular carcinoma
DAA: Direct-acting antiviral
HCV: Hepatitis C virus

COSTS AND UTILITIES

Costs

In the analysis, we included all the relevant costs related to risk reduction interventions and chronic hepatitis C testing, healthcare and treatment on an annual basis.

Risk reduction interventions

NSP: Budget by PWID of the active file of French risk reduction centers (CAARUD) are estimated at 630€ annually (41), thus we used this estimate for PWID in NSP in our model.

OST: The average annual budget of French healthcare centers in addictology (CSAPA) is 746,472€ for an average active file of 574 PWID (42), thus we used an estimate at 1,300€ per PWID. In addition, based on the distribution of PWID on buprenorphine and methadone, the distribution between the princeps and generic form for buprenorphine delivery, the distribution between capsule and syrup for methadone, and the average posology for each of this treatment (from (14)) and the cost of each of product (from (43)) we estimated the annual cost on OST at 530€. The final estimate is thus 1,830€ for PWID in OST in the model.

Chronic hepatitis C related costs

Testing: the cost of a serology for PWID susceptible was set at 19.575€ (44). The annual cost depends on the testing rate delta assumed in the scenario.

Ressources consumption for HCV care: These costs were only taken into account for PWID linked to the healthcare system. We used estimates from French general population (45). These costs are summarized in Table S3.

Table S3 Annual mean costs (SD) attributable to chronic hepatitis C: ambulatory costs (never treated and after HCV treatment failure) and hospitalization costs (no death and in-hospital death) (45)

Liver disease stage	**Ambulatory costs (€)**		**Hospitalization costs (€)**	
	Never treated	**After treatment failure**	**No death**	**In-hospital death**
F0/F1	70 (10)	53 (12)	278 (1,087)	337 (1,377)
F2/F3	128 (22)	86 (15)		
F4	228 (20)	71 (18)	1,295 (3,732)	6,450 (11,422)
Decompensation	96 (21)		9,874 (12,246)	16,119 (17,778)
HCC	96 (21)		11,745 (11,634)	16,643 (14,137)
Liver transplant				
First year	96 (21)		56,021 (40,329)	90,712 (55,462)
Following years	96 (21)		5,445 (11,123)	15,911 (23,307)

Treatment: the cost of new antiviral therapies was assumed to be 46,000€ for a 12-weeks treatment, which is the current cost of the treatment by a combination ledipasvir+sofosbuvir at the time of the study (46). In addition, the healthcare cost for monitoring these treatments (physician consultations and laboratory tests) were estimated used French treatment guidelines to 740€.

Costs of implementation of the scenarios

Improvements in harm reduction interventions: as the annual cost we used for NSP and OST include the operating budget of the corresponding structures (CAARUD and CSAPA), we added no supplementary cost for the improvements of these interventions (corresponding to the opening of additional structures).

Treatment from F0: as we assumed in our analyses interferon free regimens with short treatment duration, we assumed that the treatment cost and healthcare monitoring costs would mainly be the cost of implementing this strategy.

Improvements in testing, linkage to care and adherence to treatment: based on a previous cost-effectiveness analysis about HIV screening in France (47), we estimated that the start-up cost of improving testing would mainly be the cost of training physicians working in CSAPA. Among the 70 CSAPA in Paris metropolitan area, considering an average of 9.6 employees/CSAPA including 16% of physicians, we estimated their number to be 40 (42). Considering a two-days training with 20 participants per training receiving 330€/day and instructors 1,500€/course, and 80% of acceptance, the cost is 29,400€ for this strategy.

In a similar way, the cost related to improvements in linkage to care would concern more healthcare workers: general practitionners (20,235) and gastroenterologists-hepatologists (840) (48); and CSAPA physicians were estimated at 12M€. This estimation represents probably an overestimation of the cost of this strategy, because the amount of physician that would be trained would probably be lower. However, in a conservative way we included this cost in the corresponding scenarios.

We made the hypothesis that with interferon free regimens and such shorter durations, an improvement in the adherence to treatment could occur relatively easily and we neglected the costs related.

Utilities

The measure of the quality of life was adjusted to take into account the impact of drug injection, chronic HCV infection and treatment with new DAAs.

Drug injection

For PWID before injection cessation, we adjusted the number of life years gained by a factor 0.9 (49).

Chronic hepatitis C related utilities

Due to the lack of data about French population and with new DAAs regimens, we used utilities estimated from an HCV-infected German population with dual therapy. The estimates are summarized Table S4.

Table S4 Utilities estimated in an HCV-infected German population according to disease stage (50, 51) and assumptions used in the model.

	HCV-RNA-positive	**HCV-RNA-negative***
F0/F1	0.931	0.95
F2/F3†	0.902	0.95
F4	0.872	0.89
Decompensated cirrhosis/HCC	0.794	0.81
Liver transplantation	0.843	0.843
Multiplied under IFN-free regimens	0.950	

*In case of SVR. †We conservatively assumed that the decrease in F2/F3 compartment correspond to that of F3 in Siebert *et al.* study.

Treatment

We assumed that the future HCV treatment will be injection-free DAAs regimens with few adverse events. Thus, by hypothesis we adjusted the number of life years gained by a factor 0.95 (52).

S2: SENSITIVITY ANALYSIS

In this section, we present the results obtained by changing the key parameters in the simulations.

Treatment cost

Table S5 Results of the main analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs. Compared with the main analysis, a 25% decrease was applied to the treatment cost.

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (y)	Adjusted average life expectancy (sd) (QALYs)	Averge number of new infections (sd)	Average uumber of reinfections after SVR (sd)	ICER (€/QALY)
S1 – Reference scenario	25,204 (221)	18.30 (0.06)	16.57 (0.05)	3,271 (81)	872 (40)	
S2 – Improved risk reduction interventions	25,288 (211)	18.30 (0.06)	16.58 (0.06)	3,254 (74)	868 (36)	Extended dominance
S4 – Improved cascade of care	25,577 (186)	18.48 (0.05)	16.81 (0.05)	3,341 (93)	1,140 (48)	1,225
S5 – Combined S3 and S4	29,758 (271)	18.50 (0.06)	17.02 (0.06)	2,008 (86)	972 (54)	20,366
S6 – Combined S2 and S3 and S4	29,842 (260)	18.50 (0.06)	17.02 (0.05)	2,007 (86)	972 (57)	Dominated
S3 – Treatment initiation: fibrosis ≥F0	31,402 (346)	18.32 (0.05)	16.72 (0.05)	3,218 (113)	1,430 (66)	Dominated

sd: standard deviation ; y: year ; QALY: quality adjusted life-year

Table S6 Results of the main analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs. Compared with the main analysis, a 50% decrease was applied to the treatment cost.

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (y)	Adjusted average life expectancy (sd) (QALYs)	Averge number of new infections (sd)	Average uumber of reinfections after SVR (sd)	ICER (€/QALY)
S4 – Improved cascade of care	24,409 (181)	18.48 (0.05)	16.81 (0.05)	3,341 (93)	1,140 (48)	
S1 – Reference scenario	24,810 (218)	18.30 (0.06)	16.57 (0.05)	3,271 (81)	872 (40)	Dominated
S2 – Improved risk reduction interventions	24,894 (211)	18.30 (0.06)	16.58 (0.06)	3,254 (74)	868 (36)	Dominated
S5 – Combined S3 and S4	28,078 (273)	18.50 (0.06)	17.02 (0.06)	2,008 (86)	972 (54)	17,873
S6 – Combined S2 and S3 and S4	28,162 (262)	18.50 (0.06)	17.02 (0.05)	2,007 (86)	972 (57)	Dominated
S3 – Treatment initiation: fibrosis ≥F0	30,919 (348)	18.32 (0.05)	16.72 (0.05)	3,218 (113)	1,430 (66)	Dominated

sd: standard deviation ; y: year ; QALY: quality adjusted life-year

Table S7 Results of the main analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs. Compared with the main analysis, a 75% decrease was applied to the treatment cost.

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (y)	Adjusted average life expectancy (sd) (QALYs)	Averge number of new infections (sd)	Average uumber of reinfections after SVR (sd)	ICER (€/QALY)
S4 – Improved cascade of care	23,241 (179)	18.48 (0.05)	16.81 (0.05)	3,341 (93)	1,140 (48)	
S1 – Reference scenario	24,416 (218)	18.30 (0.06)	16.57 (0.05)	3,271 (81)	872 (40)	Dominated
S2 – Improved risk reduction interventions	24,500 (212)	18.30 (0.06)	16.58 (0.06)	3,254 (74)	868 (36)	Dominated
S5 – Combined S3 and S4	26,398 (277)	18.50 (0.06)	17.02 (0.06)	2,008 (86)	972 (54)	15,380
S6 – Combined S2 and S3 and S4	26,481 (266)	18.50 (0.06)	17.02 (0.05)	2,007 (86)	972 (57)	Dominated
S3 – Treatment initiation: fibrosis ≥F0	30,436 (351)	18.32 (0.05)	16.72 (0.05)	3,218 (113)	1,430 (66)	Dominated

sd: standard deviation ; y: year ; QALY: quality adjusted life-year

Initial incidence

Table S8 Results of the main analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs. The initial incidence used was 22/100 p.y. (vs. 12/100 p.y. in the main analysis), corresponding to a study among PWID in Montréal, Canada (derived from local data – SurvUDI network (53)).

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (y)	Adjusted average life expectancy (sd) (QALYs)	Averge number of new infections (sd)	Average uumber of reinfections after SVR (sd)	ICER (€/QALY)
S1 – Reference scenario	26,420 (212)	18.27 (0.06)	16.50 (0.06)	4,689 (89)	1,444 (53)	
S2 – Improved risk reduction interventions	26,493 (244)	18.27 (0.05)	16.50 (0.05)	4,653 (90)	1,430 (51)	Extended dominance
S4 – Improved cascade of care	27,369 (194)	18.47 (0.05)	16.76 (0.05)	5,095 (111)	1,998 (72)	3,374
S3 – Treatment initiation: fibrosis ≥F0	37,722 (417)	18.27 (0.05)	16.62 (0.05)	5,801 (154)	3,028 (107)	Dominated
S6 – Combined S2 and S3 and S4	38,691 (539)	18.48 (0.05)	16.97 (0.05)	4,766 (199)	2,804 (145)	53,817
S5 – Combined S3 and S4	38,745 (549)	18.48 (0.06)	16.96 (0.05)	4,833 (193)	2,840 (141)	Dominated

sd: standard deviation ; y: year ; QALY: quality adjusted life-year

Table S9 Results of the main analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs. The initial incidence used was 42/100 p.y. (vs. 12/100 p.y. in the main analysis), corresponding to a study among PWID in London, United-Kingdom (54).

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (y)	Adjusted average life expectancy (sd) (QALYs)	Averge number of new infections (sd)	Average uumber of reinfections after SVR (sd)	ICER (€/QALY)
S1 – Reference scenario	27,152 (236)	18.23 (0.05)	16.43 (0.05)	5,887 (95)	2,006 (62)	
S2 – Improved risk reduction interventions	27,219 (235)	18.23 (0.05)	16.43 (0.05)	5,867 (98)	2,001 (65)	Extented dominance
S4 – Improved cascade of care	27,969 (211)	18.45 (0.05)	16.69 (0.05)	6,682 (128)	2,889 (89)	3,055
S3 – Treatment initiation: fibrosis ≥F0	44,265 (424)	18.22 (0.05)	16.51 (0.05)	8,695 (166)	5,086 (130)	Dominated
S6 – Combined S2 and S3 and S4	54,032 (794)	18.45 (0.06)	16.87 (0.06)	10,883 (320)	7,662 (275)	146,226
S5 – Combined S3 and S4	54,060 (845)	18.45 (0.05)	16.87 (0.05)	10,921 (320)	7,688 (275)	Dominated

sd: standard deviation ; y: year ; QALY: quality adjusted life-year

Mean time to diagnosis

Table S10 Results of the main analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs. The mean time to diagnosis was set at 2.0 years (vs. 1.25/1.45 years for active/inactive PWID in the main analysis) corresponding to a study among PWID in Montréal, Canada (derived from local data – SurvUDI network (53)).

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (y)	Adjusted average life expectancy (sd) (QALYs)	Averge number of new infections (sd)	Average uumber of reinfections after SVR (sd)	ICER (€/QALY)
S1 – Reference scenario	25,673 (205)	18.30 (0.06)	16.57 (0.05)	3,254 (79)	846 (39)	
S2 – Improved risk reduction interventions	25,721 (197)	18.29 (0.06)	16.56 (0.05)	3,235 (81)	840 (38)	Dominated
S4 – Improved cascade of care	26,745 (194)	18.48 (0.05)	16.81 (0.05)	3,341 (93)	1,140 (48)	4,335
S5 – Combined S3 and S4	31,437 (270)	18.50 (0.06)	17.02 (0.06)	2,008 (86)	972 (54)	22,859
S6 – Combined S2 and S3 and S4	31,523 (259)	18.50 (0.06)	17.02 (0.05)	2,007 (86)	972 (57)	Dominated
S3 – Treatment initiation: fibrosis ≥F0	31,593 (315)	18.30 (0.05)	16.70 (0.05)	3,251 (109)	1,412 (65)	Dominated

sd: standard deviation ; y: year ; QALY: quality adjusted life-year

Table S11 Results of the main analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs. The mean time to diagnosis was set at 7.8 years (vs. 1.25/1.45 years for active/inactive PWID in the main analysis) corresponding to a study among PWID in London, United-Kingdom (55).

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (y)	Adjusted average life expectancy (sd) (QALYs)	Averge number of new infections (sd)	Average uumber of reinfections after SVR (sd)	ICER (€/QALY)
S1 – Reference scenario	25,585 (226)	18.22 (0.06)	16.47 (0.05)	3,150 (70)	712 (31)	
S2 – Improved risk reduction interventions	25,757 (270)	18.21 (0.06)	16.47 (0.06)	3,124 (75)	704 (33)	Dominated
S4 – Improved cascade of care	26,745 (194)	18.48 (0.05)	16.81 (0.05)	3,341 (93)	1,140 (48)	3,357
S3 – Treatment initiation: fibrosis ≥F0	29,368 (321)	18.22 (0.06)	16.58 (0.06)	3,170 (87)	1,226 (48)	Dominated
S5 – Combined S3 and S4	31,437 (270)	18.50 (0.06)	17.02 (0.06)	2,008 (86)	972 (54)	22,859
S6 – Combined S2 and S3 and S4	31,523 (259)	18.50 (0.06)	17.02 (0.05)	2,007 (86)	972 (57)	Dominated

sd: standard deviation ; y: year ; QALY: quality adjusted life-year

Mean time to linkage to care

Table S12 Results of the main analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs. The mean time to linkage to care was set at 4.0 years (vs. 2.6 years in the main analysis).

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (y)	Adjusted average life expectancy (sd) (QALYs)	Averge number of new infections (sd)	Average uumber of reinfections after SVR (sd)	ICER (€/QALY)
S1 – Reference scenario	25,675 (216)	18.25 (0.06)	16.51 (0.06)	3,213 (75)	787 (34)	
S2 – Improved risk reduction interventions	25,737 (206)	18.26 (0.06)	16.52 (0.05)	3,195 (70)	780 (36)	Extended dominance
S4 – Improved cascade of care	26,745 (194)	18.48 (0.05)	16.81 (0.05)	3,341 (93)	1,140 (48)	3,534
S3 – Treatment initiation: fibrosis ≥F0	31,099 (299)	18.28 (0.06)	16.66 (0.06)	3,282 (105)	1,387 (67)	Dominated
S5 – Combined S3 and S4	31,437 (270)	18.50 (0.06)	17.02 (0.06)	2,008 (86)	972 (54)	22,859
S6 – Combined S2 and S3 and S4	31,523 (259)	18.50 (0.06)	17.02 (0.05)	2,007 (86)	972 (57)	Dominated

sd: standard deviation ; y: year ; QALY: quality adjusted life-year

Loss to follow-up rate

Table S13 Results of the main analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs. The annual loss to follow-up rate was set at 20%/year (vs. 14%/year in the main analysis).

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (y)	Adjusted average life expectancy (sd) (QALYs)	Averge number of new infections (sd)	Average uumber of reinfections after SVR (sd)	ICER (€/QALY)
S1 – Reference scenario	25,675 (216)	18.25 (0.06)	16.51 (0.06)	3,213 (75)	787 (34)	
S2 – Improved risk reduction interventions	25,737 (206)	18.26 (0.06)	16.52 (0.05)	3,195 (70)	780 (36)	Extended dominance
S4 – Improved cascade of care	26,745 (194)	18.48 (0.05)	16.81 (0.05)	3,341 (93)	1,140 (48)	3,534
S3 – Treatment initiation: fibrosis ≥F0	31,099 (299)	18.28 (0.06)	16.66 (0.06)	3,282 (105)	1,387 (67)	Dominated
S5 – Combined S3 and S4	31,437 (270)	18.50 (0.06)	17.02 (0.06)	2,008 (86)	972 (54)	22,859
S6 – Combined S2 and S3 and S4	31,523 (259)	18.50 (0.06)	17.02 (0.05)	2,007 (86)	972 (57)	Dominated

sd: standard deviation ; y: year ; QALY: quality adjusted life-year

Table S14 Results of the main analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs. The annual loss to follow-up rate was set at 30%/year (vs. 14%/year in the main analysis) by authors' choice.

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (y)	Adjusted average life expectancy (sd) (QALYs)	Averge number of new infections (sd)	Average uumber of reinfections after SVR (sd)	ICER (€/QALY)
S1 – Reference scenario	24,943 (227)	18.3 (0.06)	16.57 (0.05)	3,259 (75)	861 (38)	
S2 – Improved risk reduction interventions	25,009 (240)	18.29 (0.06)	16.56 (0.05)	3,233 (81)	852 (40)	Dominated
S4 – Improved cascade of care	26,745 (194)	18.48 (0.05)	16.81 (0.05)	3,341 (93)	1,140 (48)	7,271
S5 – Combined S3 and S4	31,437 (270)	18.50 (0.06)	17.02 (0.06)	2,008 (86)	972 (54)	22,859
S6 – Combined S2 and S3 and S4	31,523 (259)	18.50 (0.06)	17.02 (0.05)	2,007 (86)	972 (57)	Dominated
S3 – Treatment initiation: fibrosis ≥F0	31,925 (308)	18.32 (0.06)	16.72 (0.06)	3,222 (109)	1,429 (65)	Dominated

sd: standard deviation ; y: year ; QALY: quality adjusted life-year

Risk of reinfection following a SVR

Table S15 Results of the main analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs. The risk of reinfection per infected injecting partner β was divided by 3 after a previous infection successfully treated (56, 57).

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (y)	Adjusted average life expectancy (sd) (QALYs)	Averge number of new infections (sd)	Average uumber of reinfections after SVR (sd)	ICER (€/QALY)
S1 – Reference scenario	25,533 (231)	18.31 (0.06)	16.58 (0.06)	3,103 (76)	726 (36)	
S2 – Improved risk reduction interventions	25,558 (221)	18.30 (0.06)	16.58 (0.05)	3,084 (75)	720 (34)	Dominated
S4 – Improved cascade of care	26,697 (195)	18.48 (0.05)	16.82 (0.05)	3,152 (80)	970 (39)	4,847
S5 – Combined S3 and S4	31,155 (295)	18.50 (0.05)	17.02 (0.05)	1,877 (84)	852 (53)	22,493
S6 – Combined S2 and S3 and S4	31,243 (310)	18.50 (0.06)	17.02 (0.06)	1,872 (95)	852 (59)	Dominated
S3 – Treatment initiation: fibrosis ≥F0	31,475 (309)	18.32 (0.06)	16.73 (0.05)	3,005 (101)	1,237 (56)	Dominated

sd: standard deviation ; y: year ; QALY: quality adjusted life-year

Risk reduction coverage

Table S16 Results of the main analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs. The initial distribution and transition rates in the risk reduction interventions model were changed for a worst case: initial distribution in NSP=15% and in NSP+OST=50% vs. 8.9% and 85.7% respectively in the main analysis.

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (y)	Adjusted average life expectancy (sd) (QALYs)	Averge number of new infections (sd)	Average uumber of reinfections after SVR (sd)	ICER (€/QALY)
S1 – Base case	24,440 (223)	18.30 (0.05)	16.57 (0.05)	3,423 (86)	915 (43)	
S4 – Improved cascade of care	25,580 (182)	18.49 (0.05)	16.82 (0.05)	3,515 (94)	1,204 (51)	4,549
S2 – Improved risk reduction interventions	25,682 (214)	18.30 (0.06)	16.58 (0.06)	3,254 (74)	868 (36)	Dominated
S5 – Combined S3 and S4	30,786 (336)	18.50 (0.06)	17.02 (0.06)	2,202 (107)	1,061 (65)	25,404
S3 – Treatment initiation: fibrosis ≥F0	31,119 (323)	18.31 (0.06)	16.72 (0.05)	3,410 (116)	1,513 (68)	Dominated
S6 – Combined S2 and S3 and S4	31,523 (259)	18.50 (0.06)	17.02 (0.05)	2,007 (86)	972 (57)	Dominated

sd: standard deviation ; y: year ; QALY: quality adjusted life-year

Table S17 Results of the main analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs. The initial distribution and transition rates in the risk reduction interventions model were changed for a worst case: relative risk of seroconversion in NSP=0.9 vs. 0.5 in the main analysis (hypothetic values); relative risk of seroconversion in NSP+OST=0.48 vs. 0.21 in the main analysis (from (15), with NSP coverage <100% + OST); initial distribution in NSP=15% and in NSP+OST=50% vs. 8.9% and 85.7% respectively in the main analysis.

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (y)	Adjusted average life expectancy (sd) (QALYs)	Averge number of new infections (sd)	Average uumber of reinfections after SVR (sd)	ICER (€/QALY)
S1 – Base case	24,757 (217)	18.29 (0.06)	16.53 (0.06)	4,061 (84)	1,200 (43)	
S4 – Improved cascade of care	25,795 (186)	18.48 (0.06)	16.79 (0.05)	4,237 (94)	1,579 (58)	4,049
S2 – Improved risk reduction interventions	25,843 (208)	18.29 (0.06)	16.54 (0.06)	3,965 (80)	1,171 (45)	Dominated
S5 – Combined S3 and S4	32,216 (367)	18.50 (0.06)	17.01 (0.05)	2,774 (117)	1,431 (79)	29,493
S3 – Treatment initiation: fibrosis ≥F0	32,908 (346)	18.31 (0.06)	16.69 (0.05)	4,236 (119)	2,030 (78)	Dominated
S6 – Combined S2 and S3 and S4	33,014 (359)	18.49 (0.06)	17.01 (0.05)	2,661 (119)	1,367 (82)	Dominated

sd: standard deviation ; y: year ; QALY: quality adjusted life-year

Table S18 Results of the scenario S1 in absence of risk reduction interventions.

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (y)	Adjusted average life expectancy (sd) (QALYs)	Averge number of new infections (sd)	Average uumber of reinfections after SVR (sd)
S1 – Base case	25,122 (223)	18.27 (0.06)	16.49 (0.05)	4,747 (95)	1,549 (58)

sd: standard deviation ; y: year ; QALY: quality adjusted life-year

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7 Estimation non-paramétrique des indices de Sobol pour l'analyse de sensibilité de modèles complexes

7.1 Résumé

Dans les études de modélisation, l'incertitude portant sur la valeur des paramètres peut-être importante. L'utilisation de valeurs moyennes ou médianes provenant de la littérature est courante, mais ces estimations sont sujettes à des incertitudes. Dans le cas de la modélisation en épidémiologie, par exemple, ces valeurs sont le plus souvent inférées à partir des données d'enquêtes épidémiologiques, et donc d'un échantillon de la population. L'estimation est alors associée à un intervalle d'incertitude : intervalle de confiance à 95%, intervalle interquartile, etc. De plus, plusieurs valeurs différentes sont parfois disponibles pour un même paramètre. C'est le cas lorsque plusieurs études ont été publiées sur un même sujet. Ces variations peuvent s'expliquer par de nombreux facteurs. La taille ou la sélection des échantillons, ainsi que les époques et lieux de ces études ont une influence sur les estimations. Les designs des études (étude rétrospective ou prospective, étude transversale ou cohorte, etc.) sont associés à différents biais, et vont donc également avoir un impact sur les sorties du modèle. Il est donc important de déterminer la robustesse des conclusions obtenues malgré ces incertitudes. Pour des modèles complexes, le nombre de paramètres peut-être important, et simuler, de manière exhaustive, le modèle sous chaque jeu de paramètres possible entraîne rapidement des temps de calcul importants.

Une alternative consiste à essayer d'identifier les variables dont l'incertitude entraine la plus grande variation sur les sorties du modèle afin de limiter le nombre de ces analyses complémentaires. C'est le but de l'analyse de sensibilité.

Dans le cadre de la modélisation en épidémiologie, une pratique courante consiste à effectuer une analyse de sensibilité déterministe univariée : on effectue des simulations en prenant comme valeur de paramètre les bornes de l'intervalle d'incertitude, un paramètre à la fois, afin d'estimer l'ampleur de la variation obtenue sur les sortie du modèle. Un graphe « Tornado » permet alors de représenter les résultats de ces analyses. C'est la méthode que nous avons utilisé dans les études présentées aux chapitres 3 et 4 de cette thèse. Cette méthode suppose une variation monotone des valeurs des sorties en fonction de chaque paramètre, puisque seules des estimations ponctuelles aux extrémités des intervalles d'incertitude sont effectuées.

Une autre méthode consiste à effectuer une analyse de sensibilité probabiliste par le calcul des indices de Sobol (Sobol 1990; Sobol 2001).

Considérons un modèle déterministe de la forme $y = f(x)$, avec $f: \mathbb{R}^p \to \mathbb{R}$ le modèle, y la sortie du modèle, et $x = (x^1, \dots, x^p)$ l'ensemble des valeurs des p paramètres du modèle. Pour prendre en compte l'incertitude liée à l'estimation des paramètres, considérons x comme une réalisation d'un ensemble de variables aléatoire indépendantes $X = (X^1, \dots, X^p)$, dont les distributions sont choisies pour refléter l'incertitude. Notons $Y = f(X)$ la variable aléatoire qu'est devenue la sortie du modèle. L'indice de Sobol d'ordre 1 pour le paramètre $i \in \{1, \dots, p\}$ est défini par :

$$S_i = \frac{Var(\mathbb{E}[Y|X_i])}{Var(Y)}$$

S_i peut-être interprété comme la part de la variance de Y expliquée par la variable X_i considérée indépendamment des autres variables. C'est un indice de sensibilité correspondant au paramètre i pris isolément. On peut également définir des indices d'ordre supérieur, par exemple les indices d'ordre 2, correspondant à la sensibilité du modèle à l' interaction entre deux variables $X_i, X_j, (i,j) \in \{1,\dots,p\}^2$:

$$S_{ij} = \frac{Var(\mathbb{E}[Y|X_i, X_j])}{Var(Y)} - S_i - S_i$$

On peut également définir l'indice de sensibilité totale de la variable $X_i, i \in \{1,\dots,p\}$ correspondant à la sensibilité du modèle par rapport à la variable X_i :

$$S_{T_i} = \sum_{\substack{i \in J \\ J \subset \{1,\dots,p\}}} S_J$$

Les estimateurs classiques pour les indices de Sobol sont basés sur des méthodes de Monte-Carlo (Saltelli et al. 2004; Saltelli et al. 2008). Les estimateurs de Jansen en sont un exemple (Jansen 1999). Toutefois, ces estimateurs nécessitent un grand nombre de réplications du modèle. Classiquement, l'analyse de sensibilité se fait de la manière suivante : on estime les indices de Sobol d'ordre 1 et les indices totaux. La différence entre S_{T_i} et S_i correspond à la sensibilité du modèle par rapport aux termes d'interaction, donc si la nécessité d'estimer ces termes est déterminée en fonction des résultats obtenus. Avec les estimateurs de Jansen, l'estimation des indices d'ordre 1 et totaux nécessite $N(p+1)$ simulations du modèle, et une valeur de $N = 10\,000$ est recommandée (Saltelli et al. 2008). Dans le cas de modèles complexes, une telle quantité de simulations peut rapidement entrainer un temps de calcul excessif.

De plus, si les estimateurs basés sur des méthodes de Monte-Carlo sont bien documentés dans le cas de modèles déterministes, ce n'est pas le cas dans un modèle aléatoire. Un tel modèle peut-être défini de la manière suivante :

$$Y = f(X, \epsilon)$$

Avec ϵ la variable source (« seed ») du générateur de nombres pseudo aléatoire. L'introduction de cette variable dans modèle introduit des nouveaux indices de Sobol (correspondant à cette nouvelle source d'aléa dans le modèle) par rapport à laquelle Y va avoir un comportement chaotique, ce qui pose la question de l'estimation par des méthodes de Monte-Carlo dans ce cas (Marrel et al. 2012).

L'objectif de l'étude présentée dans ce chapitre est de proposer deux estimateurs alternatifs non-paramétriques pour les indices de Sobol d'ordre 1 et d'en étudier la convergence. Le premier estimateur est basé sur l'estimateur de Nadaraya-Watson, un estimateur à noyau de l'espérance conditionnelle (Nadaraya 1964). L'erreur quadratique moyenne de cet estimateur a été étudiée par Solìs et al. (Solìs 2014), qui ont mis en évidence un effet *elbow*, dépendant de la régularité de la densité jointe du vecteur (Y, X). Il est nécessaire de déterminer la fenêtre h de l'estimateur à noyaux, ce qui est problématique, la

densité jointe étant à priori inconnu. Le deuxième estimateur est un estimateur original et basé sur la décomposition ondelettes de la fonction $x \mapsto \mathbb{E}[Y|X_i = x]$. Cet estimateur est adaptatif, contrairement à l'etimateur de Nadaray-Watson qui nécessite de fixer une fenêtre h. Dans l'article qui suit, nous avons étudié l'erreur quadratique moyenne de cet estimateur, qui montre également un effet *elbow*.

Des premiers résultats numériques ont été obtenus en comparant les estimateurs de Jansen et de Nadaraya-Watson sur deux exemples tests : la fonction d'Ishigami, pour laquelle les valeurs théoriques des indices de Sobol sont connues, et un modèle SIR. Ces résultats, encore préliminaires, montrent que l'estimateur non-paramétrique aboutit à un biais plus important, mais à un écart quadratique moyen moins important que l'estimateur de Jansen, tout en nécessitant moins de simulations du modèle. Finalement, nous avons appliqué l'estimateur de Nadaraya-Watson à l'analyse de sensibilité de notre modèle de transmission du VHC chez les UDI présenté au chapitre 3. Les résultats sont consistants avec ceux que nous avions obtenus grâce au Tornado.

Ce travail est en cours, la version de l'article présentée dans ce manuscrit et un document de travail.

7.2 Article 6

Nonparametric adaptive estimation of order 1 Sobol indices in stochastic models, with an application to Epidemiology

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Abstract

The global sensitivity analysis is a set of methods aiming at quantifying the influence of the uncertainty about the inputs parameters of a model on the variability of the responses (e.g. Saltelli et al. (2008)). In a deterministic framework, i.e. when the same inputs values give always the same outputs values, the estimation of the Sobol indices is a commonly-used method. This method is based on the variance decomposition aiming at estimating the contribution of each parameter (or combination of parameters) on the variance of the response. We consider here the estimation of the Sobol indices of order 1, which are usually estimated by replicated simulations of the model. In the case of a stochastic framework, i.e. when the model response is not unique for a same input parameter set due to random numbers generation in the model, metamodels are often used to approximate the mean and the dispersion of the response by deterministic functions thus allowing to recover the classical deterministic framework. We propose a new non-parametric estimator without the need of defining a metamodel to estimate the Sobol indices of order 1. The estimator is based on warped wavelets and it is adaptative in the regularity of the model. The convergence of the mean square error to zero, when the number of simulations of the model tend to infinity, is computed and an elbow effect is shown, depending on the regularity of the model.

Keywords: Sensitivity analysis in a stochastic framework; Sobol indices of order 1; adaptive non-parametric inference; warped wavelets; Nadaraya-Watson estimator; model selection; applications to epidemiology; SIR model; spread of the Hepatitis Virus C among drug users.
MSC2010: 49Q12; 62G08; 62P10.

1 Sobol indices

In a mathematical model where the output $y \in \mathbb{R}$ depends on a set of $p \in \mathbb{N}$ input parameters $x = (x_1, ...x_p) \in \mathbb{R}^p$ through the relation $y = f(x)$, there are various ways to measure the influence of the input x_ℓ, for $\ell \in \{1, \dots, p\}$, on y. In this article, we are interested in Sobol indices [20], which are based on an ANOVA decomposition. These indices have been proposed to take into account the uncertainty on the input parameters that are here considered as a realisation of a set of independent random variables $X = (X_1, ...X_p)$, with a known distribution.

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Denoting by $Y = f(X)$ the random response, the first order Sobol indices can be defined for $\ell \in \{1, \dots, p\}$ by

$$S_\ell = \frac{\mathrm{Var}\big(\mathbb{E}[Y \mid X_\ell]\big)}{\mathrm{Var}(Y)}. \tag{1.1}$$

This first order index S_ℓ correspond to the sensitivity of the model to X_ℓ alone. Higher order indices can also be defined using ANOVA decomposition : considering $(\ell, \ell') \in \{1, \dots, p\}$, we can define the second order sensitivity, corresponding to the sensitivity of the model to the interaction between X_ℓ and $X_{\ell'}$ index by

$$S_{\ell\ell'} = \frac{\mathrm{Var}\big(\mathbb{E}[Y \mid X_\ell, X_{\ell'}]\big)}{\mathrm{Var}(Y)} - S_\ell - S_{\ell'} \tag{1.2}$$

We can also define the total sensitivity indices by

$$S_{T_\ell} = \sum_{L \subset \{1,\dots,p\} \,|\, \ell \in L} S_L. \tag{1.3}$$

As the estimation of the Sobol indices can be computer time consuming, a usual practice consists in estimating the first order and total indices, to assess 1) the sensitivity of the model to each parameter taking alone and 2) the possible interactions, which are quantified by the difference between the total order and the first order index for each parameter. Several numerical procedures to estimate the Sobol indices have been proposed, in particular by Jansen [12] (see also [18, 19]). These estimators, that we recall in the sequel, are based on Monte-Carlo simulations of $(Y, X_1 \dots X_p)$.

The literature focuses on deterministic relations between the input and output parameters. In a stochastic framework where the model response Y is not unique for given input parameters, few works have been done, randomness being usually limited to input variables. Assume that:

$$Y = f(X, \varepsilon), \tag{1.4}$$

where $X = (X_1, \dots X_p)$ still denotes the random variables modelling the uncertainty of the input parameters and where ε is a noise variable. When noise is added in the model, the classical estimators do not always work: Y can be chaotic regarding the value of ε. Moreover, this variable is not always controllable by the user.

When the function f is linear, we can refer to [7]. For general cases, it is possible to add the seed of the noise as an additional input parameter and compute classical estimators, or to propose a meta-model, i.e. a deterministic function approximating the mean and the dispersion of the response by deterministic functions allows to come back in the classical deterministic framework (e.g. Janon et al. [11], Marrel et al. [16]). We study here another point of view, which is based on the non-parametric statistical estimation of the term $\mathrm{Var}\big(\mathbb{E}[Y \mid X_\ell]\big)$ appearing in the numerator of (1.1). We propose here a new approach based on the Nadaraya-Watson kernel regression or on wavelet decompositions. The kernel estimator presented in the sequel has been introduced independently from us by Solís [21]. An advantage of these non-parametric estimators is that their computations requires less simulations of the model. For Jansen estimators, the number of calls of f required to compute the sensitivity indices is $n(p+2)$, where n is the number of independent random vectors $(Y^i, X_1^i, \dots X_p^i)$ $(i \in \{1, \dots n\})$ that are sampled for the Monte-Carlo, making the estimation of the sensitivity indices time-consuming for sophisticated models with many parameters. In addition, for the non-parametric estimators, the convergence of the mean square error to zero may be faster than for Monte-Carlo estimators, depending on the regularity of the model.

In a first section, we present the non-parametric estimators of the Sobol indices of order 1 in the case of the stochastic model (1.4) and study their convergence rates. These estimators are then computed and compared for toy examples introduced by Ishigami [10]. We then address models from Epidemiology. First, the stochastic continuous-time SIR model is considered, in which the population of size N is divided into three compartments: the susceptibles, infectious and removed individuals (see e.g. [1] for an introduction). Infections and removals occur at random times whose laws depend on the composition of the population and on the infection and removal parameters λ and μ as input variables. The output variable Y can be the prevalence or the incidence at a given time T for instance. Y naturally depends on λ, μ and on the randomness underlying the occurrence of random times. Then, we consider a stochastic multi-level epidemic model for the transmission of Hepatitis C virus (HCV) among people who inject drugs (PWID) that has been introduced by Cousien et al. [6]. This model describes an individual-based population of PWID that is structured by compartments showing the state of individuals in the heath-care system and by a contact-graph indicating who inject with whom. Additionally the advance of HCV in each patient is also taken into account. The input variables are the different parameters of the model. Ouputs depend on these inputs, on the randomness of event occurrences and on the randomness of the social graph. We compare the sensitivity analysis performed by estimating the Sobol indices of order 1 with the naive sensitivity analysis performed in [6] by letting the parameters vary in an *a priori* chosen windows.

In the sequel, C denotes a constant that can vary from line to line.

2 A non-parametric estimator of the Sobol indices of order 1

Denoting by $V_\ell = \mathbb{E}\big(\mathbb{E}^2(Y \mid X_\ell)\big)$, we have:

$$S_\ell = \frac{V_\ell - \mathbb{E}(Y)^2}{\mathrm{Var}(Y)}, \tag{2.1}$$

which can be approximated by

$$\widehat{S}_\ell = \frac{\widehat{V}_\ell - \bar{Y}^2}{\widehat{\sigma}^2_Y} \tag{2.2}$$

where

$$\bar{Y} = \frac{1}{n}\sum_{j=1}^{n} Y_j \text{ and } \widehat{\sigma}^2_Y = \frac{1}{n}\sum_{j=1}^{n}(Y_j - \bar{Y})^2$$

are the empirical mean and variance of Y. In this article, we propose 2 approximations $\widehat{V}_\ell$ of V_ℓ, based on Nadaraya-Watson and on warped wavelet estimators. At an advanced stage of this work, we learned that the Nadaraya-Watson-based estimator of Sobol indices of order 1 had also been proposed and studied in the PhD of Solis [21]. Using a result on estimation of covariances by Loubes et al. [15], they obtain an elbow effect. However their estimation is not adaptative. For the warped wavelet estimator, we propose a model selection procedure based on a work by Laurent and Massart [14] to make the estimator adaptative.

2.1 Definitions

Assume that we have n independent couples $(Y^i, X^i_1, \dots X^i_p)$ in $\mathbb{R} \times \mathbb{R}^p$, for $i \in \{1, \dots, n\}$, generated by (1.4). Let us start with the kernel-based estimator:

Definition 2.1. *Let $K : \mathbb{R} \mapsto \mathbb{R}$ be a kernel such that $\int_{\mathbb{R}} K(u)du = 1$ and ..... Let $h > 0$ be a window and let us denote $K_h(x) = K(x/h)/h$. An estimator of S_ℓ for $\ell \in \{1, \dots p\}$ is:*

$$\widehat{S}_\ell^{(NW)} = \frac{\frac{1}{n}\sum_{i=1}^n \left(\frac{\sum_{j=1}^n Y_j K_h(X_\ell^j - X_\ell^i)}{\sum_{j=1}^n K_h(X_\ell^j - X_\ell^i)}\right)^2 - \bar{Y}^2}{\widehat{\sigma}_Y^2}. \tag{2.3}$$

This estimator is based on the Nadaraya-Watson estimator of $\mathbb{E}(Y \mid X_\ell = x)$ given by (e.g. [24])

$$\frac{\sum_{j=1}^n Y_j K_h(X_\ell^j - x)}{\sum_{j=1}^n K_h(X_\ell^j - x)}.$$

Replacing this expression in (2.2) provides $\widehat{S}_\ell^{(NW)}$. As mentioned before, this estimator has also been proposed by Solís [21].

Our second estimator is based on a warped wavelet decomposition of $\mathbb{E}(Y \mid X_\ell = x)$. For introduction to such decomposition, refer to [4, 13]. Let us denote by G_ℓ the cumulative distribution function of X_ℓ.

Let $(\psi_{jk})_{j\geq -1, k\in\mathbb{Z}}$ be a Hilbert wavelet basis of L^2. In the sequel, we denote by $\langle f, g\rangle = \int_{\mathbb{R}} f(u)g(u)du$, for $f, g \in L^2$, the usual scalar product of L^2. The wavelet ψ_{-10} is the father wavelet, and for $k \in \mathbb{Z}$, $\psi_{-1k}(x) = \psi_{-10}(x-k)$. The wavelet ψ_{00} is the mother wavelet, and for $j \geq 0$, $k \in \mathbb{Z}$, $\psi_{jk}(x) = 2^{j/2}\psi_{00}(2^j x - k)$.

Definition 2.2. *Let us define for $j \geq -1$, $k \in \mathbb{Z}$,*

$$\widehat{\beta}_{jk}^\ell = \frac{1}{n}\sum_{i=1}^n Y_i \psi_{jk}(G_\ell(X_\ell^i)). \tag{2.4}$$

Then, we define the (block thresholding) estimator of $\widehat{S}_\ell$, for $J_n := \left[\log_2\left(\frac{\sqrt{n}}{\log(n)}\right)\right]$, as:

$$\widehat{S}_\ell^{(WW)} = \frac{\widehat{\theta}_\ell - \bar{Y}^2}{\widehat{\sigma}_Y^2}, \tag{2.5}$$

$$\text{where } \widehat{\theta}_\ell = \sum_{j=-1}^{J_n}\Big[\sum_{k\in\mathbb{N}}\left(\widehat{\beta}_{jk}^\ell\right)^2 - w(j)\Big]\mathbb{1}_{\sum_{k\in\mathbb{N}}\left(\widehat{\beta}_{jk}^\ell\right)^2 \geq w(j)} \tag{2.6}$$

$$\text{with } w(j) = K'2^j \text{ so that } pen(\mathcal{J}) = \sum_{j\in\mathcal{J}} w(j) = K\Big(\frac{2^{J_{max}}}{n} + \frac{x_\mathcal{J}}{n}\Big) \tag{2.7}$$

where K and K' are positive constants, where $J_{max} := \max\mathcal{J}$ and where

$$x_\mathcal{J} = J_{max}\log(2). \tag{2.8}$$

Notice for the proofs that for $x_\mathcal{J}$ as in (2.8),

$$\limsup_{n\to+\infty}\frac{1}{n}\sum_{\mathcal{J}\subset\{-1,\dots,J_n\}} e^{-x_\mathcal{J}}2^{2J_{\max}} < +\infty. \tag{2.9}$$

Indeed, for a given $J_{\max} \leq J_n$ there are $2^{J_{\max}+1}$ subsets $\mathcal{J} \subset \{-1, \dots J_n\}$ such that $\max\mathcal{J} = J_{\max}$. Thus:

$$\sum_{\mathcal{J}\subset\{-1,\dots,J_n\}} e^{-x_\mathcal{J}}2^{2J_{\max}} = C + C'\sum_{J_{\max}=0}^{J_n} 2^{J_{\max}}2^{-J_{\max}}2^{2J_{\max}} = C2^{2J_n} = C\frac{n}{\log^2(n)},$$

where C in the first equality corresponds to the case $\mathcal{J} = \{-1\}$.

An expression of the constant K appears in the proofs of Section 4 (where the mean square error is studied). However this constant is hard to compute in practice and depends on inequalities that are maybe not optimal. Indeed, the proof is concentrated on the orders in n and in the dimension of the model corresponding to $\mathcal{J}$, not on obtaining the best constants. For applications, the constant K appearing in the penalty $\mathrm{pen}(\mathcal{J})$ can be chosen by a slope heuristic approach (see e.g. [2]) explained at the end of the section.

Let us present the idea explaining the estimator proposed in Definition 2.2. Let us introduce centered random variables η_ℓ such that

$$Y = f(X, \varepsilon) = \mathbb{E}(Y \mid X_\ell) + \eta_\ell. \tag{2.10}$$

Let $g_\ell(x) = \mathbb{E}(Y \mid X_\ell = x)$ and $h_\ell(u) = g_\ell \circ G_\ell^{-1}(u)$. h_ℓ is a function from $[0,1] \mapsto \mathbb{R}$ that belong to L^2 since $Y \in L^2$. Then

$$h_\ell(u) = \sum_{j \geq -1} \sum_{k \in \mathbb{Z}} \beta_{jk}^\ell \psi_{jk}(u), \quad \text{with} \quad \beta_{jk}^\ell = \int_0^1 h_\ell(u)\psi_{jk}(u)du = \int_{\mathbb{R}} g_\ell(x)\psi_{jk}(G_\ell(x))G_\ell(dx). \tag{2.11}$$

Notice that the sum in k is finite because the function h_ℓ has compact support in $[0,1]$. It is then natural to estimate $h_\ell(u)$ by

$$\widehat{h}_\ell = \sum_{j \geq -1} \sum_{k \in \mathbb{Z}} \widehat{\beta}_{jk}^\ell \psi_{jk}(u), \tag{2.12}$$

and we then have:

$$\begin{aligned} V_\ell = \mathbb{E}\big(\mathbb{E}^2(Y \mid X_\ell)\big) &= \int_{\mathbb{R}} G_\ell(dx)\Big(\sum_{j \geq -1} \sum_{k \in \mathbb{Z}} \beta_{jk}^\ell \psi_{jk}\big(G_\ell(x)\big)\Big)^2 = \int_0^1 \Big(\sum_{j \geq -1} \sum_{k \in \mathbb{Z}} \beta_{jk}^\ell \psi_{jk}(u)\Big)^2 du \\ &= \sum_{j \geq -1} \sum_{k \in \mathbb{Z}} \big(\beta_{jk}^\ell\big)^2 = \|h_\ell\|_2^2. \end{aligned} \tag{2.13}$$

Adaptive estimation of $\|h_\ell\|_2^2$ has been studied in [14], which provides the block thresholding estimator $\widehat{\theta}_\ell$ in the Definition 2.2. The idea is: 1) to sum the terms $\big(\beta_{jk}^\ell\big)^2$, for $j \geq 0$, by blocks $\{(j,k),\ k \in \mathbb{Z}\}$ for $j \in \{-1, \ldots, J_n\}$ with a penalty $w(j)$ for each block to avoid choosing too large js, 2) to cut the blocks that do not sufficiently contribute to the sum, in order to obtain statistical adaptation.

Notice that

$$\widehat{\theta}_\ell = \sup_{\mathcal{J} \subset \{-1,0,\ldots,J_n\}} \sum_{j \in \mathcal{J}} \Big[\sum_{k \in \mathbb{N}} \big(\widehat{\beta}_{jk}^\ell\big)^2 - w(j)\Big] = \sup_{\mathcal{J} \subset \{-1,0,\ldots,J_n\}} \sum_{j \in \mathcal{J}} \sum_{k \in \mathbb{N}} \big(\widehat{\beta}_{jk}^\ell\big)^2 - \mathrm{pen}(\mathcal{J}). \tag{2.14}$$

In view of this identity, $\widehat{\theta}_\ell$ can be seen as an estimator of V_ℓ resulting from a model selection on the choice of the blocks $\{(j,k),\ k \in \mathbb{Z}\}$, $j \in \{-1, \ldots, J_n\}$ that are kept, with the penalty function $\mathrm{pen}(\mathcal{J}) = \sum_{j \in \mathcal{J}} w(j)$, for $\mathcal{J} \subset \{-1, \ldots, J_n\}$.

For a given K appearing in the definition of the penalty function pen (2.7), let us denote by $\mathcal{J}_K$ the subset of indices j of $\{-1, \ldots J_n\}$ achieving the supremum in the r.h.s. of (2.14). Plotting $\mathrm{Card}(\mathcal{J}_K)$ as a function of K, the slope heuristic tells us to choose K as value where the curve has a sudden decrease.

2.2 Statistical properties

In this Section, we are interested in the rate of convergence to zero of the mean square error (MSE) $\mathbb{E}\big((S_\ell - \widehat{S}_\ell)^2\big)$. Let us consider the generic estimator $\widehat{S}_\ell$ defined in (2.2), where $\widehat{V}_\ell$ is an estimator of $V_\ell = \mathbb{E}(\mathbb{E}^2(Y \mid X_\ell))$. We first start with a Lemma stating that the MSE can be obtained from the rate of convergence of $\widehat{V}_\ell$ to V_ℓ. Then, we recall the result of Solís [21], where an elbow effect for the MSE is shown when the regularity of the density of (X_ℓ, Y) varies. The case of the warped wavelet estimator is studied at the end of the section.

Lemma 2.3. *Consider the generic estimator $\widehat{S}_\ell$ defined in* (2.2)*. Then there is a constant C such that:*

$$\mathbb{E}\big((S_\ell - \widehat{S}_\ell)^2\big) \leq \frac{C}{n} + \frac{4}{Var(Y)^2}\mathbb{E}\Big[\big(\widehat{V}_\ell - V_\ell\big)^2\Big]. \tag{2.15}$$

Proof. From (2.1) and (2.2),

$$\begin{aligned}\mathbb{E}\big((S_\ell - \widehat{S}_\ell)^2\big) =& \mathbb{E}\Big[\Big(\frac{V_\ell - \mathbb{E}(Y)^2}{\mathrm{Var}(Y)} - \frac{\widehat{V}_\ell - \bar{Y}^2}{\widehat{\sigma}^2_{\bar{Y}}}\Big)^2\Big] \\ \leq& 2\mathbb{E}\Big[\Big(\frac{\mathbb{E}(Y)^2}{\mathrm{Var}(Y)} - \frac{\bar{Y}^2}{\widehat{\sigma}^2_{\bar{Y}}}\Big)^2\Big] + 2\mathbb{E}\Big[\Big(\frac{V_\ell}{\mathrm{Var}(Y)} - \frac{\widehat{V}_\ell}{\widehat{\sigma}^2_{\bar{Y}}}\Big)^2\Big]. \end{aligned} \tag{2.16}$$

The first term in the right hand side (r.h.s.) is in C/n. For the second term in the right hand side of (2.16):

$$\mathbb{E}\Big[\Big(\frac{V_\ell}{\mathrm{Var}(Y)} - \frac{\widehat{V}_\ell}{\widehat{\sigma}^2_{\bar{Y}}}\Big)^2\Big] \leq 2\mathbb{E}\Big[\widehat{V}_\ell^2\Big(\frac{1}{\mathrm{Var}(Y)} - \frac{1}{\widehat{\sigma}^2_{\bar{Y}}}\Big)^2\Big] + \frac{2}{\mathrm{Var}(Y)^2}\mathbb{E}\Big[\big(\widehat{V}_\ell - V_\ell\big)^2\Big]. \tag{2.17}$$

The first term in the r.h.s. is also in C/n, which concludes the proof. ■

2.2.1 MSE for the Nadaraya-Watson estimator

Using the preceding Lemma, Loubes Marteau and Solís prove an elbow effect for the estimator $\widehat{S}_\ell^{(NW)}$. Let us introduce $\mathcal{H}(\alpha, L)$, for $\alpha, L > 0$, the set of functions ϕ of class $[\alpha]$, whose derivative $\phi^{([\alpha])}$ is $\alpha - [\alpha]$ Hölder continuous with constant L.

Proposition 2.4 (Loubes Marteau and Solís [21, 15])**.** *Assume that $\mathbb{E}(X_\ell^4) < +\infty$, that the joint density $\phi(x, y)$ of (X_ℓ, Y) belongs to $\mathcal{H}(\alpha, L)$, for $\alpha, L > 0$ and that the marginal density of X_ℓ, ϕ_ℓ belongs to $\mathcal{H}(\alpha', L')$ for $\alpha' > \alpha$ and $L' > 0$. Then:*
If $\alpha \geq 2$, there exists a constant $C > 0$ such that

$$\mathbb{E}\big((S_\ell - \widehat{S}_\ell)^2\big) \leq \frac{C}{n}.$$

If $\alpha < 2$, there exists a constant $C > 0$ such that

$$\mathbb{E}\big((S_\ell - \widehat{S}_\ell)^2\big) \leq C\big(\frac{\log^2 n}{n}\big)^{\frac{2\alpha}{\alpha+2}}.$$

For smooth functions ($\alpha \geq 2$), Loubes et al. recover a parametric rate, while they still have a nonparametric one when $\alpha < 2$. Their result is based on (2.15) and a bound for $\mathbb{E}\Big[\big(\widehat{V}_\ell - V_\ell\big)^2\Big]$ given by [15, Th. 1], whose proof is technical. Since their result is not adaptive, they require the knowledge of the window h for numerical implementation. Our purpose is to provide a similar result for the warped wavelet adaptive estimator, with a shorter proof.

2.2.2 MSE for the warped wavelet estimator

Let us introduce first some additional notation. We define, for $\mathcal{J} \subset \{-1, \dots, J_n\}$, the projection $h_{\mathcal{J},\ell}$ of h on the subspace spanned by $\{\psi_{jk}, \text{ with } j \in \mathcal{J},\ k \in \mathbb{Z}\}$ and its estimator $\widehat{h}_{\mathcal{J},\ell}$:

$$h_{\mathcal{J},\ell}(u) = \sum_{j\in\mathcal{J}} \sum_{k\in\mathbb{Z}} \beta_{jk}^{\ell} \psi_{jk}(u) \tag{2.18}$$

$$\widehat{h}_{\mathcal{J},\ell}(u) = \sum_{j\in\mathcal{J}} \sum_{k\in\mathbb{Z}} \widehat{\beta}_{jk}^{\ell} \psi_{jk}(u). \tag{2.19}$$

We also introduce the estimator of V_ℓ for a fixed subset of resolutions $\mathcal{J}$:

$$\widehat{\theta}_{\mathcal{J},\ell} = \sum_{j\in\mathcal{J}} \sum_{k\in\mathbb{N}} \big(\widehat{\beta}_{jk}^{\ell}\big)^2. \tag{2.20}$$

The estimators $\widehat{\beta}_{jk}$ and $\widehat{\theta}_{\mathcal{J},\ell}$ have natural expressions in term of the empirical process $\gamma_n(dx)$ defined as follows:

Definition 2.5. *The empirical measure associated with our problem is:*

$$\gamma_n(dx) = \frac{1}{n} \sum_{i=1}^{n} Y_i \delta_{G_\ell(X_\ell^i)}(dx) \tag{2.21}$$

where $\delta_a(dx)$ denotes the Dirac mass in a.
For a measurable function f, $\gamma_n(f) = \frac{1}{n}\sum_{i=1}^n Y_i f\big(G_\ell(X_\ell^i)\big)$. We also define the centered integral of f with respect to $\gamma_n(dx)$ as:

$$\bar{\gamma}_n(f) = \gamma_n(f) - \mathbb{E}\big(\gamma_n(f)\big) \tag{2.22}$$

$$= \frac{1}{n} \sum_{i=1}^{n} \Big(Y_i f\big(G_\ell(X_\ell^i)\big) - \mathbb{E}\big[Y_i f\big(G_\ell(X_\ell^i)\big)\big] \Big). \tag{2.23}$$

Using the empirical measure $\gamma_n(dx)$, we have:

$$\widehat{\beta}_{jk}^{\ell} = \gamma_n\big(\psi_{jk}\big) = \beta_{jk}^{\ell} + \bar{\gamma}_n\big(\psi_{jk}\big).$$

Let us introduce the correction term

$$\zeta_n = 2\bar{\gamma}_n\big(h_\ell\big) \tag{2.24}$$

$$= 2\Big[\frac{1}{n}\sum_{i=1}^{n} Y_i h_\ell\big(G_\ell(X_\ell^i)\big) - \mathbb{E}\Big(Y_1 h_\ell\big(G_\ell(X_\ell^1)\big)\Big)\Big]$$

$$= 2\Big[\frac{1}{n}\sum_{i=1}^{n} h_\ell^2\big(G_\ell(X_\ell^i)\big) - \|h_\ell\|_2^2\Big] + \frac{2}{n}\sum_{i=1}^{n} \eta_\ell^i h_\ell\big(G_\ell(X_\ell^i)\big). \tag{2.25}$$

Theorem 2.6. *Let us assume that the random variables Y are bounded by a constant M, and let us choose a father and a mother wavelets ψ_{-10} and ψ_{00} that are continuous with compact support (and thus bounded). The estimator $\widehat{\theta}_\ell$ defined in (2.6) is almost surely finite, and:*

$$\mathbb{E}\Big[\big(\widehat{\theta}_\ell - V_\ell - \zeta_n\big)^2\Big] \le C \inf_{\mathcal{J}\subset\{-1,\dots,J_n\}} \Big(\|h_\ell - \widehat{h}_{\mathcal{J},\ell}\|_2^4 + \frac{2^{J_{max}}}{n^2} \Big) + \frac{C'}{n\log^2(n)}, \tag{2.26}$$

for constants C and $C' > 0$.

We deduce the following corollary from the estimate obtained above. Let us consider the Besov space $\mathcal{B}(\alpha,2,\infty)$ of functions $h=\sum_{j\geq -1}\sum_{k\in\mathbb{Z}}\beta_{jk}\psi_{jk}$ of L^2 such that

$$|h|_{\alpha,2,\infty}:=\sum_{j\geq 0}2^{j\alpha}\sqrt{\sup_{0<v\leq 2^{-j}}\int_0^{1-v}|h(u+v)-h(u)|^2du}<+\infty.$$

For a $h\in\mathcal{B}(\alpha,2,\infty)$ and $h_{\mathcal{J}}$ its projection on $\mathrm{Vect}\{\psi_{jk},\ j\in\mathcal{J}=\{-1,\dots J_{\max}\},\ k\in\mathbb{Z}\}$, we have the following approximation result from [9, Th. 9.4].

Proposition 2.7 (Härdle Kerkyacharian Picard and Tsybakov)**.** *Assume that the wavelet function ψ_{-10} has compact support and is of class $\mathcal{C}^N$ for an integer $N>0$. Then, if $h\in\mathcal{B}(\alpha,2,\infty)$ with $\alpha<N+1$,*

$$\sup_{\mathcal{J}\subset\mathbb{N}\cup\{-1\}}2^{\alpha Jmax}\|h-h_{\mathcal{J}}\|_2=\sup_{\mathcal{J}\subset\mathbb{N}\cup\{-1\}}2^{\alpha Jmax}\Big(\sum_{j\geq Jmax}\sum_{k\in\mathbb{Z}}\beta_{jk}^2\Big)^{1/2}<+\infty. \tag{2.27}$$

Notice that Theorem 9.4 of [9] requires assumptions that are fulfilled when ψ_{-10} has compact support and is smooth enough (see comment after the Corol. 8.2 of [9]).

Corollary 2.8. *If ψ_{-10} has compact support and is of class $\mathcal{C}^N$ for an integer $N>0$ and if h_ℓ belongs to a ball of radius $R>0$ of $\mathcal{B}(\alpha,2,\infty)$ for $0<\alpha<N+1$, then*

$$\sup_{h\in\mathcal{B}(\alpha,2,\infty)}\mathbb{E}\Big[\big(\widehat{\theta}_\ell-V_\ell\big)^2\Big]\leq Cn^{-\frac{8\alpha}{\alpha+1}}. \tag{2.28}$$

As a consequence, we obtain the following elbow effect:
If $\alpha\geq\frac{1}{4}$, there exists a constant $C>0$ such that

$$\mathbb{E}\big((S_\ell-\widehat{S}_\ell)^2\big)\leq\frac{C}{n}.$$

If $\alpha<\frac{1}{4}$, there exists a constant $C>0$ such that

$$\mathbb{E}\big((S_\ell-\widehat{S}_\ell)^2\big)\leq Cn^{-\frac{8\alpha}{4\alpha+1}}.$$

The proof of Theorem 2.6 is postponed to Section 4. Let us remark that in comparison with the result of Loubes et al. [15], the regularity assumption is on the function h_ℓ rather than on the joint density $\phi(x,y)$ of (X_ℓ,Y). The adaptivity of our estimator is then welcomed since the function h_ℓ is *a priori* unknown. Remark that in application, the joint density $\phi(x,y)$ also has to be estimated and hence has an unknown regularity. For very regular functions $\alpha\to+\infty$, we recover a rate of convergence in n^{-2} in both cases.

Notice that in the case when $\alpha>1/4$, we can show from the estimate of Th. 2.6 that:

$$\lim_{n\to+\infty}n\mathbb{E}\Big[\big(\widehat{\theta}_\ell-V_\ell-\zeta_n\big)^2\Big]=0, \tag{2.29}$$

which yields that $\sqrt{n}\big(\widehat{\theta}_\ell-V_\ell-\zeta_n\big)$ converges to 0 in L^2. Since $\sqrt{n}\zeta_n$ converges in distribution to $\mathcal{N}\Big(0,4\mathrm{Var}\big(Y_1h_\ell(G_\ell(X_\ell^1))\big)\Big)$ by the central limit theorem, we obtain that:

$$\lim_{n\to+\infty}\sqrt{n}\big(\widehat{\theta}_\ell-V_\ell\big)=\mathcal{N}\Big(0,4\mathrm{Var}\big(Y_1h_\ell(G_\ell(X_\ell^1))\big)\Big), \tag{2.30}$$

in distribution.

The result of Corollary 2.8 is stated for functions h_ℓ belonging to $\mathcal{B}(\alpha,2,\infty)$, but the generalization to other Besov space might be possible.

2.3 Numerical tests on toy models

We start with considering a toy model called the Ishigami function and defined as:

$$Y = f(X_1, X_2, X_3) = \sin(X_1) + 7\sin(X_2)^2 + 0.1\ X_3^4 \sin(X_1) \tag{2.31}$$

where X_i are independent uniform random variables in $[-\pi, \pi]$ (see e.g. [10, 18]).

Firstly, we consider this model with (X_1, X_2, X_3) as input parameters and compute the associated Sobol indices. For the Ishigami function, all the Sobol sensitivity indices are known.

$$S_1 = 0.3139, \qquad S_2 = 0.4424, \qquad S_3 = 0.$$

Secondly, following Marrel et al. [16], we consider the case where (X_1, X_2) are the input parameters and X_3 a nuisance random parameter. However, the Sobol indices have the same values as in the standard case.

In both cases, we compare the Nadaraya-Watson estimator of the Sobol indices of order 1 with the Jansen estimator [12] that is one of the classical estimator found in the literature (for the case of outputs that are deterministic functions of the inputs). The numerical implementation of the wavelet estimator is a work in progress. The Jansen estimator is based on the mixing of two replications of the sample $(Y, X_1, \ldots, X_p)$, as described below.

Let us consider two samples $(X_1^{(1),i}, ..., X_p^{(1),i},\ i \in \{1, \ldots n\})$ and $(X_1^{(2),i}, ..., X_p^{(2),i},\ i \in \{1, \ldots n\})$ of i.i.d. p-uplets distributed as $(X_1, \ldots X_p)$. The Jansen estimators for the first order Sobol indices are, $\forall \ell \in 1, ..., p$:

$$\widehat{S}_\ell = \widehat{\sigma}_Y^2 - \frac{1}{2n}\sum_{i=1}^{n}\left(f(X_1^{(2),i}, ..., X_p^{(2),i}) - f(X_1^{(1),i}, ..., X_{\ell-1}^{(1),i}, X_\ell^{(2),i}, X_{\ell+1}^{(1),i}, \ldots, X_p^{(1),i})\right)^2 \tag{2.32}$$

The total order sensitivity indices are estimated by:

$$\widehat{S}_{T_\ell} = \frac{1}{2n}\sum_{i=1}^{n}\left(f(X_1^{(1),i}, ..., X_p^{(1),i}) - f(X_1^{(1),i}, ..., X_{\ell-1}^{(1),i}, X_\ell^{(2),i}, X_{\ell+1}^{(1),i}, \ldots, X_p^{(1),i})\right)^2 \tag{2.33}$$

Notice that the estimation of the Sobol indices using Jansen estimators requires $N(p+2)$ simulations of the model. We computed the non-parametric estimators first from a sample of size n, then from a sample of size $(p+2)n$ to have a similar number of simulations of the model. We used $n = 10,000$ and we performed 1,000 replications to estimate the bias and MSE for each estimator. For the Nadaraya-Watson estimator, we choose $h = 0.01$. For the warped wavelet estimator, we applied a constant penality of 0.01. We used the classical Haar wavelet basis: the father wavelet is $\psi_{-10} = \mathbf{1}_{[0,1]}$, and the mother wavelet $\psi_{-00} = \mathbf{1}_{[0,1/2]} - \mathbf{1}_{[1/2,1]}$.

Table 1: *Estimates of the bias and MSE for the parameters X_1, X_2 and X_3 in the Ishigmami function, for 1,000 replications and $n = 10,000$*

Method	$\mathbb{E}[\hat{S}_1 - S_1]$	$\mathbb{E}[(\hat{S}_1 - S_1)^2]$	$\mathbb{E}[\hat{S}_2 - S_2]$	$\mathbb{E}[(\hat{S}_2 - S_2)^2]$	$\mathbb{E}[\hat{S}_3 - S_3]$	$\mathbb{E}[(\hat{S}_3 - S_3)^2]$
Jansen, $n(p+1)$	9.9e-4	1.8e-4	3.2e-5	1.0e-4	8.6e-4	5.6e-4
Nadaraya-Watson, n	6.6e-3	8.8e-5	4.4e-3	8.1e-5	9.5e-3	9.3e-5
Nadaraya-Watson, $n(p+1)$	1.5e-3	1.1e-5	3.4e-4	1.6e-5	2.0e-3	4.3e-6

We can see that in the deterministic framework results Table 1 that for the 3 indices, the mean bias is higher for the Nadaraya-Watson estimator, even when the same number of simulation

Table 2: *Estimates of the bias and MSE for the parameters X_1 and X_2 in the Ishigmami function, when X_3 is considered as a pertubation parameter, for 1,000 replications and $n = 10,000$*

Method	$\mathbb{E}[\hat{S}_1 - S_1]$	$\mathbb{E}[(\hat{S}_1 - S_1)^2]$	$\mathbb{E}[\hat{S}_2 - S_2]$	$\mathbb{E}[(\hat{S}_2 - S_2)^2]$
Jansen, $n(p+1)$	-5.6e-4	2.0e-4	-7.8e-4	1.8e-4
Nadaraya-Watson, n	5.8e-3	7.8e-5	4.7e-3	8.4e-5
Nadaraya-Watson, $n(p+1)$	1.6e-3	1.2e-5	6.8e-4	1.5e-5

were computed $n(p+1)$. However, with the non-parametric estimator, the MSE was lower with the Nadaraya-Watson, even with five times less simulations of the model available. The results are similar in the stochastic framework Table 2, with the exception of the estimation of S_2 for which, with the same number of model simulations, the bias is comparable for Jansen and Nadaraya Watson (-7.8e-4 vs. 6.8e-4).

3 Sobol indices for epidemiological problems

We now consider two stochastic individual-based models of epidemiology in continuous time. In both cases, the population is of size N and divided into compartments. Input parameters are the rates describing the times that individuals stay in each compartment. These rates are usually estimated from epidemiological studies or clinical trials, but there can be uncertainty on their values. The restricted size of the sample in these studies brings uncertainty on the estimates, which are given with uncertainty intervals (classically, a 95% confidence interval). Different studies can provide different estimates for the same parameters. The study populations can be subject to selection biases. In the case of clinical trials where the efficacy of a treatment is estimated, the estimates can be optimistic compared with what will be the effectiveness in real-life, due to the protocol of the trials. It is important to quantify how theses uncertainty on parameters estimations could impact the results and the conclusion of a modelling study.

3.1 SIR model and ODE metamodels

In the first model, we consider the usual SIR model, with three compartments: susceptibles, infectious and removed (e.g. [1]). We denote by S_t^N, I_t^N and R_t^N the respective sizes of the corresponding sub-populations at time $t \geq 0$, with $S_t^N + I_t^N + R_t^N = N$. At the population level, infections occur at the rate $\frac{\lambda}{N} S_t^N I_t^N$ and removals at the rate μI_t^N. The idea is that to each pair of susceptible-infectious individuals a random independent clock with parameter λ/N is attached and to each infectious individual an independent clock with parameter μ is attached. The input parameters are the rates λ and μ. The outpout parameter is the final size of the epidemic, i.e. at a time $T > 0$ where $I_T^N = 0$, $Y = (I_T^N + R_T^N)/N$.

It is possible to describe the evolution of $(S_t^N/N, I_t^N/N, R_t^N/N)_{t\geq 0}$ by a stochastic differential equation driven by Poisson point measures and it is known that when $N \to +\infty$, this stochastic process converges in $\mathbb{D}(\mathbb{R}_+, \mathbb{R}^3)$ to the unique solution $(s_t, i_t, r_t)_{t\geq 0}$ of the following system of ordinary differential equations (e.g. [1, 23]):

$$\begin{cases} \frac{ds}{dt} = -\lambda s_t i_t \\ \frac{di}{dt} = \lambda s_t i_t - \mu i_t \\ \frac{dr}{dt} = \mu i_t. \end{cases}$$

The fluctuations associated with this convergence have also been established. The limiting equations provide a natural deterministic approximating meta-model (recall [16]) for which sen-

sitivity indices can be computed.

In this section, we applied the Jansen estimator and the Nadaraya-Watson estimator to the estimation of the first order Sobol indices of S_λ and S_μ. We applied these estimators to the SIR stochastic process and to SIR deterministic model (as a metamodel approximating the stochastic process) described above.

In a first example, we simulated a close population of 1200 individuals, with $S_0^{1200} = 1190$, $I_0^{1200} = 10$ and $R_0^{1200} = 0$. We choose this high population size to ensure the convergence of the simulations in the stochastic process to the solution of the ordinary differential equation system. The parameters distribution were Beta(2,2) distributions renormalized to have $\lambda/N \in [1/15000, 3/15000]$ and $\mu \in [1/15, 3/15]$.

In a second example, to increase the influence of ε on the output Y, we decreased the population size to 120 individuals, ith $S_0^{120} = 119$, $I_0^{120} = 1$ and $R_0^{120} = 0$ and parameters drawn from Beta(2,2) distributions renormalized to have $\lambda/N \in [1/1500, 3/1500]$ and $\mu \in [1/15, 3/15]$.

The smoothed distributions of the first order Sobol indices are presented below, for 1,000 replications of the estimators and $n = 10,000$ are presented Figures 1 and 2 .

For the determistic framework, the results are similar for S_λ, with for Jansen $\hat{S}_\lambda = 0.45$ (standard deviation=8.1e-3) and $\hat{S}_\lambda^{(NW)} = 0.45$ (6.9e-3); $\hat{S}_\mu = 0.50$ (7.7e-3) and $\hat{S}_\mu^{(NW)} = 0.50$ (7.2e-3). We can however underline that the estimation of the Sobol indice with Jansen estimators required 40,000 simulations of the model vs. 10,000 for the Nadaraya-Watson estimator. For the stochastic model with $N = 1,200$, we obtained similar results, but the Sobol indices were lower, due to the contribution of the randomness of the model to the variance of Y: $\hat{S}_\lambda = 0.38$ (9.6e-3) and $\hat{S}_\lambda^{(NW)} = 0.38$ (7.6e-3); $\hat{S}_\mu = 0.46$ (8.6e-3) and $\hat{S}_\mu^{(NW)} = 0.45$ (7.8e-3).

However, when we increased the contribution of the randomness to the variance of Y by considering a smaller population (120 individuals), the results were different: for Jansen $\hat{S}_\lambda = 0.063$ (0.022) and $\hat{S}_\lambda^{(NW)} = 0.087$ (5.4e-3); $\hat{S}_\mu = 0.12$ (0.021) and $\hat{S}_\mu^{(NW)} = 0.13$ (7.3e-3). We can not compare the two estimators in absence of theoritical values for the Sobol indices, but we can see that for small values, the two estimators provides different values, with the Nadaraya-Watson giving higher mean estimates but tighter distributions than the Jansen estimator.

3.2 Application to the spread of HVC among drug users

Chronic hepatitis C is a major cause of liver failure in the world, responsible of approximately 500,000 deaths annually [25]. Hepatitis C is a bloodborne disease, and the transmission remains high in people whi inject drugs (PWID) due to injecting equipment sharing [22]. Until recently, the main approaches to decrease HCV transmission among PWID in high income countries relied on injection prevention and on risk reduction measures (access to sterile equipment, opioid substitution therapies, etc.). The arrival of highly effective antiviral treatments offers the opportunity to use the treatment as a mean to prevent HCV transmission, by treating infected PWID before they have transmitted the infection [8].

In this context, a stochastic, individual-based dynamic model was used to assessed the impact of the treatment on HCV transmission in PWID in Paris area [5]. This model included HCV transmission on a random graph modelling PWID social network, the cascade of care of chronic hepatitis C and the progression of the liver disease. A brief description of the model for HCV infection and cascade of care is available in 3, for a detailled description and the details of the parameters values with their uncertainty intervals, the reader can refer to [5].

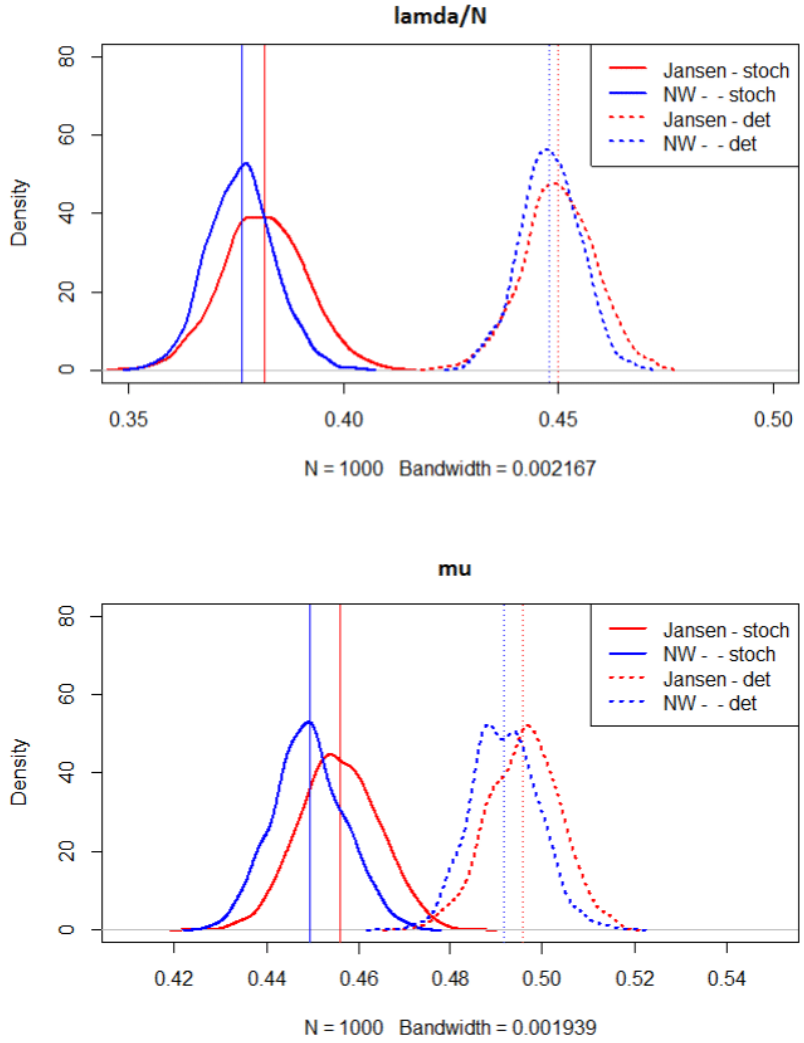

Figure 1: *Smoothed densities of the first order sensitivity indices estimates for λ/N and μ in a deterministic (dotted lines) and in a stochastic (plain lines) SIR model, with $N = 1,200$ individuals.*

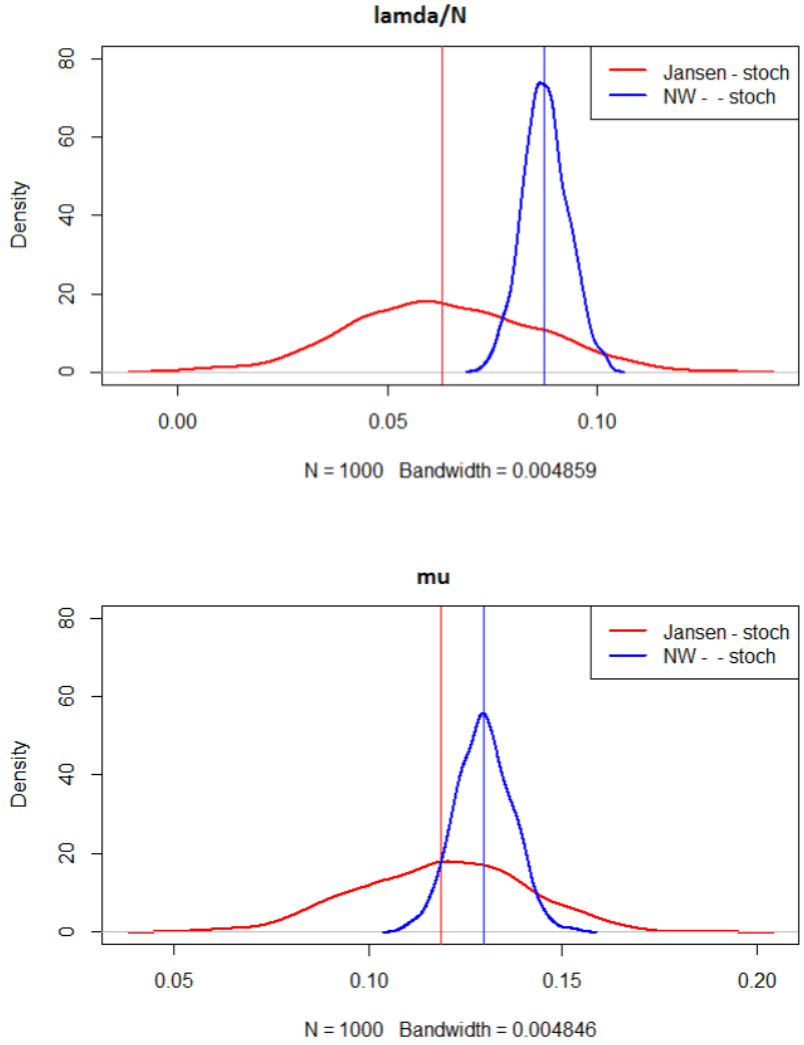

Figure 2: *Smoothed densities of the first order sensitivity indices estimates for λ/N and μ in a stochastic (plain lines) SIR model, with $N = 120$ individuals.*

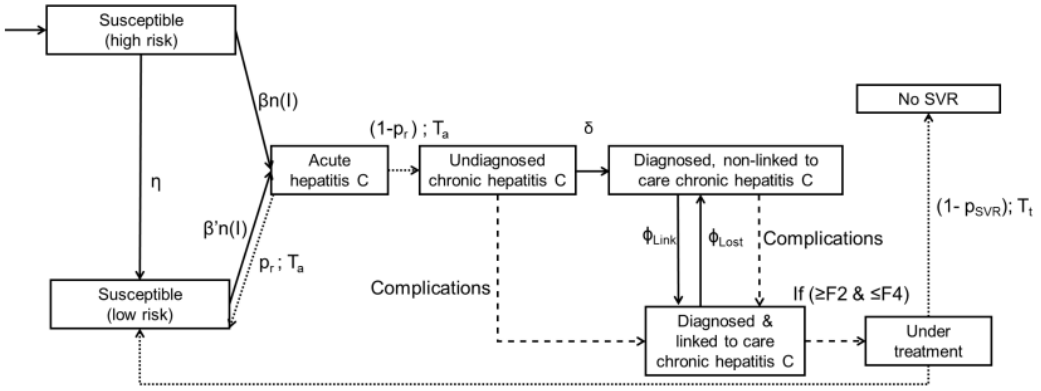

Figure 3: *Diagram flow of infection and cascade of care modelling for HCV infection among PWID. Greek letters refer to rates, p_r and p_{SVR} to probabilities and T_a and T_t to (deterministic) time before leaving the compartment. β depends on the status of the PWID with respect to the risk reduction measures (access to sterile injecting equipment, access to substitution therapies). n_i denotes the number of infected injecting partners of the PWUID. δ depends on the status of the PWID with respect to injection: active or inactive injector (i.e. before or after the cessation of injection). The liver disease progression is quantified by a score (score Metavir for the fibrosis progression) between F0 and F4 (cirrhosis). "Complications" refers to the two cirrhosis complications: decompensated cirrhosis and hepatocellular carcinoma*

The parameter values used in this analysis were mainly provided by epidemiological studies and were subject to uncertainty. This kind of model requires high computing time, and thus the sensitivity analysis using Monte-Carlo estimators of Sobol indices is difficult, due to the number of simulations needed. We estimated Sobol indices using the Nadaraya-Watson non-parametric estimator, and with Y the prevalence after 10 years of simulation, and with uniform distributions on the uncertainty interval for each parameter. We used $n = 10,000$ simulations of the model. For comparison, we also represented the sensitivity using a Tornado diagram, classically used in epidemiology. A Tornado diagram is built using the extremal values of the uncertainty interval for each parameter. The model is simulated Y by changing the mean parameter value by the extremal values, one at a time. The other parameters values are let at their mean value (i.e. the value from the main analysis). Then, the parameters are sorted by decreasing width of the interval of Y values, and the deviation from the main analysis result is represented in a bar plot.

Results are presented Figure 4 With the Tornado diagram, the most sensitive parameters are the infection rate per infected injecting partner, the transition rate from a fibrosis score of F0/F1 to a score of F2/F3 and the combination of the linkage to care/loss to follow-up rate (which were varied together to estimate the impact of the uncertainty about the linkage to care of PWID). With the Sobol indices, we obtained consistent results. However, as the Sobol indices can be interpreted as the contribution of each parameter to this variance. We can thus see that a large part of the variance of Y is explained by the infection rate per infected partner alone, with a Sobol index of 0.59, and by the transition rate from a fibrosis score of F0/F1 to a score of F2/F3, with a Sobol index of 0.31. Other parameters contribute only marginally, and particularly linkage to care/loss to follow-up rate, wich represent only 4% of the whole variance, according to these results. However, the sum of all the sensitivity indices estimated was 1.20, which is > 1.

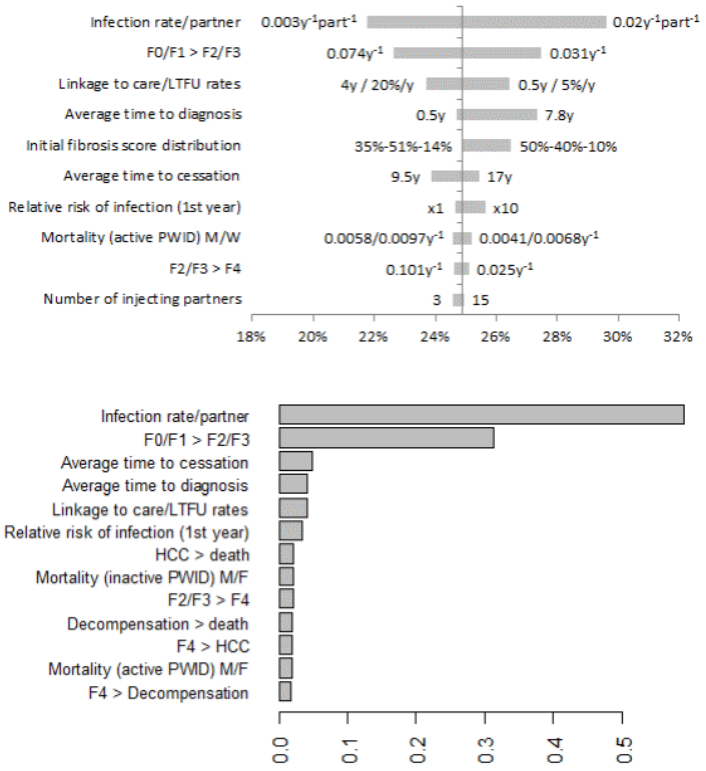

Figure 4: *Tornado diagram (upper figure), and Sobol indices estimated using the Nadaraya-Watson estimator and sorted by decreasing value (lower figure). The values represented on the Tornado diagram are the extremal values of the uncertainty interval for each parameter. LTFU=loss to follow-up, HCC=Hepatocellular carcinoma, M=Male, F=Female. "Cessation" refers to the cessation of the injections. "F0/F1 > F2/F3" refers to the transition rate from a fibrosis score F0 or F1 to a fibrosis score F2 or F3 (and similarly for other rates).*

4 Proofs

4.1 Proof of Theorem 2.6

We follow the scheme of the proof of Theorem 1 in [14]. The main difficulty here is that we are not in a Gaussian framework and that we use the empirical process $\bar{\gamma}_n$, which introduces much technical difficulties.
In the sequel, C denotes a constant that can vary from line to line.

Using Lemma 2.3, we concentrate on the MSE $\mathbb{E}\big((\widehat{\theta}_\ell - V_\ell)^2\big)$. First, we will prove that:

$$\mathbb{E}\Big[\Big(\widehat{\theta}_\ell - V_\ell - \zeta_n\Big)_+^2\Big] \leq \inf_{\mathcal{J}\subset\{-1,\dots,J_n\}} \mathbb{E}\Big[\Big(-\widehat{\theta}_{\mathcal{J},\ell} + V_\ell + \zeta_n\Big)_+^2\Big] + \frac{C}{n\log^2(n)}, \tag{4.1}$$

where $\widehat{\theta}_{\mathcal{J},\ell}$ has been defined in (2.14). Then, considering the first term in the r.h.s. of (4.1), we prove:

$$\mathbb{E}\Big[\Big(-\widehat{\theta}_{\mathcal{J},\ell} + V_\ell + \zeta_n\Big)_+^2\Big] \leq C\Big(\|h_\ell - h_{\mathcal{J},\ell}\|_2^4 + \frac{\log^2(n) + 2^{J\max}}{n^2}\Big) \tag{4.2}$$

Step 1:
From (2.14), and letting $A_{\mathcal{J}} = \widehat{\theta}_{\mathcal{J},\ell} - V_\ell - \zeta_n$, we have:

$$\widehat{\theta}_\ell - V_\ell - \zeta_n = \sup_{\mathcal{J}\subset\{-1,\dots,J_n\}} A_{\mathcal{J}}.$$

Since

$$\Big|\sup_{\mathcal{J}} A_{\mathcal{J}}\Big| \leq \max\Big[\sup_{\mathcal{J}} (A_{\mathcal{J}})_+, \inf_{\mathcal{J}} (A_{\mathcal{J}})_-\Big],$$

we have that

$$\begin{aligned}\mathbb{E}\Big(\sup_{\mathcal{J}} A_{\mathcal{J}}^2\Big) &\leq \sum_{\mathcal{J}\subset\{-1,\dots,J_n\}} \mathbb{E}\Big((A_{\mathcal{J}})_+^2\Big) + \inf_{\mathcal{J}\subset\{-1,\dots,J_n\}} \mathbb{E}\Big((A_{\mathcal{J}})_-^2\Big) \\ &\leq \sum_{\mathcal{J}\subset\{-1,\dots,J_n\}} \mathbb{E}\Big((A_{\mathcal{J}})_+^2\Big) + \inf_{\mathcal{J}\subset\{-1,\dots,J_n\}} \mathbb{E}\Big((V_\ell - \widehat{\theta}_{\mathcal{J},\ell} + \zeta_n)_+^2\Big). \end{aligned} \tag{4.3}$$

The second term correspond to what appears in (4.1) and will be treated in Step 4. Let us consider the first term of the r.h.s. We start by rewriting

$$\begin{aligned} A_{\mathcal{J}} =& \widehat{\theta}_{\mathcal{J},\ell} - V_\ell - \zeta_n \\ =& \|\widehat{h}_{\mathcal{J},\ell}\|_2^2 - \mathrm{pen}(\mathcal{J}) - \|h_\ell\|_2^2 - \zeta_n \\ =& \big(\|\widehat{h}_{\mathcal{J},\ell} - h_{\mathcal{J},\ell}\|_2^2 + \|h_{\mathcal{J},\ell}\|_2^2 + 2\langle \widehat{h}_{\mathcal{J},\ell} - h_{\mathcal{J},\ell}, h_{\mathcal{J},\ell}\rangle\big) \\ & - \big(\|h_\ell - h_{\mathcal{J},\ell}\|_2^2 + \|h_{\mathcal{J},\ell}\|_2^2 + 2\langle h_\ell - h_{\mathcal{J},\ell}, h_{\mathcal{J},\ell}\rangle\big) - \zeta_n - \mathrm{pen}(\mathcal{J}) \\ =& \|\widehat{h}_{\mathcal{J},\ell} - h_{\mathcal{J},\ell}\|_2^2 + 2\langle \widehat{h}_{\mathcal{J},\ell} - h_{\mathcal{J},\ell}, h_{\mathcal{J},\ell}\rangle - \|h_\ell - h_{\mathcal{J},\ell}\|_2^2 - \zeta_n - \mathrm{pen}(\mathcal{J}), \end{aligned} \tag{4.4}$$

since $\langle h_\ell - h_{\mathcal{J},\ell}, h_{\mathcal{J},\ell}\rangle = 0$ by definition of $h_{\mathcal{J},\ell}$ as projection of h_ℓ on the subspace generated by $\{\psi_{jk},\ j\in\mathcal{J},\ k\in\mathbb{Z}\}$.

Thus:

$$\begin{aligned}\mathbb{E}\Big((A_{\mathcal{J}})_+^2\Big) \leq\ & 2\mathbb{E}\Big(\big(\|\widehat{h}_{\mathcal{J},\ell} - h_{\mathcal{J},\ell}\|_2^2 - \mathrm{pen}_1(\mathcal{J})\big)^2\Big) \\ & + 2\mathbb{E}\Big(\big(2\langle \widehat{h}_{\mathcal{J},\ell} - h_{\mathcal{J},\ell}, h_{\mathcal{J},\ell}\rangle - \|h_\ell - h_{\mathcal{J},\ell}\|_2^2 - \zeta_n - \mathrm{pen}_2(\mathcal{J})\big)^2\Big). \end{aligned} \tag{4.5}$$

where

$$\mathrm{pen}_1(\mathcal{J}) = \frac{K2^{J\max}}{n}, \text{ and } \mathrm{pen}_2(\mathcal{J}) = \frac{4M^2 x_{\mathcal{J}}}{n} + \frac{4M^2\|\varphi_{\mathcal{J}}\|_\infty^2 x_{\mathcal{J}}^2}{n^2}. \tag{4.6}$$

Step 2: Upper bound of the first term in the r.h.s. of (4.5)

Reformulation of $\|\widehat{h}_{\mathcal{J},\ell} - h_{\mathcal{J},\ell}\|_2^2$

The first term in the r.h.s. of (4.4) is the approximation error of $h_{\mathcal{J}}$ by $\widehat{h}_{\mathcal{J},\ell}$ and equals

$$\|\widehat{h}_{\mathcal{J},\ell} - h_{\mathcal{J},\ell}\|_2^2 = \sum_{j\in\mathcal{J}}\sum_{k\in\mathbb{Z}} \big(\widehat{\beta}_{jk} - \beta_{jk}\big)^2 = \sum_{j\in\mathcal{J}}\sum_{k\in\mathbb{Z}} \bar{\gamma}_n\big(\psi_{jk}\big)^2.$$

To control it, let us introduce, for coefficients $a = (a_{jk},\ -1 \le j \le J_n,\ k \in \mathbb{Z})$, the set $\mathcal{F}_{1,\mathcal{J}} = \{\sum_{j\in\mathcal{J}}\sum_{k\in\mathbb{Z}} a_{jk}\psi_{jk},\ a_{jk} \in \mathbb{Q},\ \|a\|_2 \le 1\}$, which is countable and dense in the unit ball of $L^2([0,1])$:

$$\begin{aligned}
\Big(\sum_{j\in\mathcal{J}}\sum_{k\in\mathbb{Z}} \bar{\gamma}_n\big(\psi_{jk}\big)^2\Big)^{1/2} &= \sup_{\|a\|_2\le 1}\Big|\sum_{j\in\mathcal{J}}\sum_{k\in\mathbb{Z}} a_{jk}\bar{\gamma}_n\big(\psi_{jk}\big)\Big| \\
&= \sup_{\|a\|_2\le 1}\Big|\bar{\gamma}_n\Big(\sum_{j\in\mathcal{J}}\sum_{k\in\mathbb{Z}} a_{jk}\psi_{jk}\Big)\Big| \\
&= \sup_{f\in\mathcal{F}_{1,\mathcal{J}}}\big|\bar{\gamma}_n(f)\big| := \chi_n(\mathcal{J}).
\end{aligned} \tag{4.7}$$

Let us introduce, for $\rho > 0$,

$$\Omega_{\mathcal{J}}(\rho) = \big\{\forall j \in \mathcal{J},\ \sum_{k\in\mathbb{Z}}\big|\bar{\gamma}_n(\psi_{jk})\big| \le \rho 2^{-j/2}\big\}. \tag{4.8}$$

Then, to upper bound the first term in (4.5), we can write:

$$\mathbb{E}\Big(\big(\|\widehat{h}_{\mathcal{J},\ell} - h_{\mathcal{J},\ell}\|_2^2 - \mathrm{pen}_1(\mathcal{J})\big)^2\Big) \le 2A_1(\mathcal{J}) + 2A_2(\mathcal{J}) \tag{4.9}$$

where

$$A_1(\mathcal{J}) = \mathbb{E}\Big(\big(\chi_n^2(\mathcal{J})\mathbb{1}_{\Omega_{\mathcal{J}}(\rho)} - \mathrm{pen}_1(\mathcal{J})\big)^2\Big), \quad \text{and} \quad A_2(\mathcal{J}) = \mathbb{E}\Big(\chi_n^4(\mathcal{J})\mathbb{1}_{\Omega_{\mathcal{J}}^c(\rho)}\Big). \tag{4.10}$$

The upper bounds of $A_1(\mathcal{J})$ and $A_2(\mathcal{J})$ make the object of the remainder of Step 2. We use ideas developed in [3]. To upper bound $A_1(\mathcal{J})$, we use the identity

$$A_1(\mathcal{J}) = \int_0^{+\infty} t\ \mathbb{P}\big(\chi_n^2(\mathcal{J})\mathbb{1}_{\Omega_{\mathcal{J}}(\rho)} - \mathrm{pen}_1(\mathcal{J}) > t\big)\ dt, \tag{4.11}$$

and look for deviation inequalities of $\chi_n^2(\mathcal{J})\mathbb{1}_{\Omega(\mathcal{J})(\rho)}$. Then, estimates of the probability of $\Omega_{\mathcal{J}}^c(\rho)$ are studied to control $A_2(\mathcal{J})$.

Deviation inequality for $\sup_{a\in\Lambda_{\mathcal{J}}}\big|\bar{\gamma}_n(f)\big|$

The supremum in (4.7) is obtained for

$$\bar{a}_{jk} = \frac{\bar{\gamma}_n(\psi_{jk})}{\chi_n(\mathcal{J})}. \tag{4.12}$$

On the set $\Omega_{\mathcal{J}}(\rho) \cap \{\chi_n(\mathcal{J} > z\}$, for a constant $z > 0$ that shall be fixed in the sequel, we have for all $j \in \mathcal{J}$,

$$\sum_{k\in\mathbb{Z}} |\bar{a}_{jk}| = \frac{\sum_{k\in\mathbb{Z}} |\bar{\gamma}_n(\psi_{jk})|}{\chi_n(\mathcal{J})} \leq \frac{\rho 2^{-j/2}}{z}.$$

As a consequence, on the set $\Omega_{\mathcal{J}}(\rho) \cap \{\chi_n(\mathcal{J}) > z\}$, we can restrict the research of the optima to the set

$$\Lambda_{\mathcal{J}} = \big\{a = (a_{jk})_{j\geq -1, k\in\mathbb{Z}} \in \mathbb{Q}^{\{-1,\dots\}\times\mathbb{Z}},\ a_{jk} = 0 \text{ if } j \notin \mathcal{J},\ \sum_{k\in\mathbb{Z}} |a_{jk}| \leq \frac{\rho 2^{-j/2}}{z} \text{ if } j \in \mathcal{J}\big\},$$

which is countable.

We can then use Talagrand inequality (see [17, p.170]) to obtain that for all $\eta > 0$ and $x > 0$,

$$\mathbb{P}\Big(\sup_{a\in\Lambda_{\mathcal{J}}} |\bar{\gamma}_n(f)| \geq (1+\eta)\mathbb{E}\big(\sup_{a\in\Lambda_{\mathcal{J}}} |\bar{\gamma}_n(f)|\big) + \sqrt{2\nu_n x} + \big(\frac{1}{3} + \frac{1}{\eta}\big) b_n x\Big) \leq e^{-x}, \tag{4.13}$$

where $\mathbb{E}\big(\sup_{a\in\Lambda_{\mathcal{J}}} |\bar{\gamma}_n(f)|\big)$ and where ν_n and b_n can be chosen respectively as $\nu_n = M^2/n$ and $b_n = 2M\|\psi\|_\infty \rho \mathrm{Card}(\mathcal{J})/nz$. Indeed, ν_n is an upper bound of:

$$\frac{1}{n} \sup_{a\in\Lambda_{\mathcal{J}}} \mathrm{Var}\Big(Y_1 \sum_{j\in\mathcal{J}} \sum_{k\in\mathbb{Z}} a_{jk}\psi_{jk}\big(G_\ell(X_\ell^1)\big)\Big) \leq \frac{M^2}{n} \sup_{a\in\Lambda_{\mathcal{J}}} \Big\| \sum_{j\in\mathcal{J}} \sum_{k\in\mathbb{Z}} a_{jk}\psi_{jk}\Big\|_2^2 \leq \frac{M^2}{n}, \tag{4.14}$$

from the definition of $\Lambda_{\mathcal{J}}$. As for the term b_n, it can be obtained from:

$$\begin{aligned}
&\frac{1}{n} \sup_{a\in\Lambda_{\mathcal{J}}} \sup_{(u,y)\in[0,1]\times\mathbb{R}} \Big| y \sum_{j\in\mathcal{J}} \sum_{k\in\mathbb{Z}} a_{jk}\psi_{jk}(u) - \mathbb{E}\Big(Y_1 \sum_{j\in\mathcal{J}} \sum_{k\in\mathbb{Z}} a_{jk}\psi_{jk}\big(G_\ell(X_\ell^1)\big)\Big)\Big| \\
\leq &\frac{2M}{n} \sum_{j\in\mathcal{J}} \sum_{k\in\mathbb{Z}} |a_{jk}| 2^{j/2} \|\psi\|_\infty \leq \frac{2M\|\psi\|_\infty}{n} \sum_{j\in\mathcal{J}} \frac{\rho 2^{-j/2}}{z} 2^{j/2} = \frac{2M\|\psi\|_\infty \rho\ \mathrm{Card}(\mathcal{J})}{n\ z}.
\end{aligned} \tag{4.15}$$

For the expectation in the r.h.s. in the probability, we have:

$$\begin{aligned}
\mathbb{E}\big(\sup_{a\in\Lambda_{\mathcal{J}}} |\bar{\gamma}_n(f)|\big) \leq \mathbb{E}\big(\chi_n(\mathcal{J})\big) &\leq \sqrt{\mathbb{E}\big(\chi_n^2(\mathcal{J})\big)} = \sqrt{\sum_{j\in\mathcal{J}} \sum_{k\in\mathbb{Z}} \mathbb{E}\big(\bar{\gamma}_n^2(\psi_{jk})\big)} \\
&= \sqrt{\sum_{j\in\mathcal{J}} \sum_{k\in\mathbb{Z}} \frac{1}{n} \mathrm{Var}\big(Y_1 \psi_{jk}(G_\ell(X_\ell^1))\big)} \leq M\sqrt{\frac{2^{J\max}}{n}}
\end{aligned} \tag{4.16}$$

by using the Cauchy-Schwarz inequality and the fact that $\|\psi_{jk}\|_2^2 = 1$.

Because $\sup_{a\in A_{\mathcal{J}}} |\bar{\gamma}_n(f)| \geq \chi_n(\mathcal{J}) \mathbb{1}_{\Omega_{\mathcal{J}}(\rho)\cap\{\chi_n(\mathcal{J}>z\}}$, Equations (4.13)-(4.16) become:

$$\mathbb{P}\Big(\chi_n(\mathcal{J}) \mathbb{1}_{\Omega_{\mathcal{J}}(\rho)\cap\{\chi_n(\mathcal{J})>z\}} \geq (1+\eta)M\sqrt{\frac{2^{J\max}}{n}} + \sqrt{\frac{2M^2 x}{n}} + \big(\frac{1}{3}+\frac{1}{\eta}\big)\frac{2M\|\psi\|_\infty \rho\ \mathrm{Card}(\mathcal{J})}{n\ z} x\Big) \leq e^{-x}.$$

Choosing $z = \sqrt{\frac{2x}{n}}\big(\frac{1}{3} + \frac{1}{\eta}\big)\|\psi\|_\infty$, we obtain:

$$\mathbb{P}\Big(\chi_n(\mathcal{J}) \mathbb{1}_{\Omega_{\mathcal{J}}(\rho)\cap\{\chi_n(\mathcal{J})>z\}} \geq (1+\eta)M\sqrt{\frac{2^{J\max}}{n}} + (1+\rho)M\mathrm{Card}(\mathcal{J})\sqrt{\frac{2x}{n}}\Big) \leq e^{-x}.$$

Choosing $\rho = \left(\frac{1}{3} + \frac{1}{\eta}\right)\|\psi\|_\infty$, we can get rid of the constraint $\{\chi_n(\mathcal{J}) > z\}$ to evaluate the above probability and choosing $x = x_\mathcal{J} + \xi$:

$$\begin{aligned}\mathbb{P}\Big(\chi_n^2(\mathcal{J})\mathbb{1}_{\Omega_\mathcal{J}(\rho)} - \frac{1}{n}\Big[&(1+\eta)^2M^2 2^{J_{\max}} + 2(1+\rho)^2\mathrm{Card}^2(\mathcal{J})x_\mathcal{J} \\ &+ 2(1+\rho)(1+\eta)M^2 2^{\frac{J_{\max}+1}{2}}\mathrm{Card}(\mathcal{J})\sqrt{x_\mathcal{J}}\Big)\Big] \geq h_\mathcal{J}(\xi)\Big) \\ &\leq e^{-x_\mathcal{J}}e^{-\xi},\end{aligned}$$

where

$$h_\mathcal{J}(\xi) = \frac{2(1+\rho)M^2\ \mathrm{Card}(\mathcal{J})}{n}\Big[(1+\rho)\mathrm{Card}(\mathcal{J})\xi + (1+\eta)2^{\frac{J_{\max}+1}{2}}\sqrt{\xi}\Big]. \tag{4.17}$$

The square bracket in the l.h.s. inside the probability can be upper bounded by $n\mathrm{pen}_1(\mathcal{J}) = K2^{J_{\max}}$, for a certain constant K that depends on $x_\mathcal{J}$, since $\mathrm{Card}(\mathcal{J}) \leq J_{\max}$ and since $x^2 \leq 2^x$ for all integers $x \geq 1$. Then:

$$\mathbb{P}\Big(\chi_n^2(\mathcal{J})\mathbb{1}_{\Omega_\mathcal{J}(\rho)} - \mathrm{pen}_1\big(\mathcal{J}\big) \geq h_\mathcal{J}(\xi)\Big) \leq e^{-x_\mathcal{J}}e^{-\xi}. \tag{4.18}$$

From this and (4.11),

$$A_1(\mathcal{J}) \leq \int_0^{+\infty} te^{-x}e^{-h_\mathcal{J}^{-1}(t)}dt.$$

To upper bound the r.h.s., we have to lower bound $h_\mathcal{J}^{-1}(t)$ and hence upper bound $h_\mathcal{J}(t)$. The square bracket in (4.17) can be upper bounded by

$$\begin{cases} 2\sqrt{2}(1+\eta)2^{\frac{J_{\max}}{2}}\sqrt{\xi} & \text{if} \quad \xi \leq 2\Big(\frac{1+\eta}{1+\rho}\Big)^2\frac{2^{J_{\max}}}{\mathrm{Card}^2\mathcal{J}} \\ 2(1+\rho)\mathrm{Card}\mathcal{J}\xi & \text{if} \quad \xi > 2\Big(\frac{1+\eta}{1+\rho}\Big)^2\frac{2^{J_{\max}}}{\mathrm{Card}^2\mathcal{J}}. \end{cases}$$

Then, for $t \geq 0$:

$$h_\mathcal{J}^{-1}(t) \geq \begin{cases} \frac{n^2t^2}{32(1+\rho)^2M^2\mathrm{Card}^2\mathcal{J}(1+\eta)^2 2^{J_{\max}}} & \text{if} \quad t \leq \frac{8M^2(1+\eta)^2 2^{J_{\max}}}{n} \\ \frac{nt}{4(1+\rho)^2M^2\mathrm{Card}^2\mathcal{J}} & \text{if} \quad t > \frac{8M^2(1+\eta)^2 2^{J_{\max}}}{n}. \end{cases}$$

As a consequence,

$$\begin{aligned} A_1(\mathcal{J}) \leq &\int_0^{\frac{8M^2(1+\eta)^2 2^{J_{\max}}}{n}} te^{-x_\mathcal{J}}\exp\Big(-\frac{n^2t^2}{32(1+\rho)^2M^2\mathrm{Card}^2\mathcal{J}(1+\eta)^2 2^{J_{\max}}}\Big)dt \\ &+ \int_{\frac{8M^2(1+\eta)^2 2^{J_{\max}}}{n}}^{+\infty} te^{-x_\mathcal{J}}\exp\Big(-\frac{nt}{4(1+\rho)^2M^2\mathrm{Card}^2\mathcal{J}}\Big)dt \\ \leq &e^{-x_\mathcal{J}}\frac{32(1+\rho)^2M^2\mathrm{Card}^2\mathcal{J}(1+\eta)^2 2^{J_{\max}}}{2n^2}\Big[1 - \exp\Big(-\frac{2M^2(1+\eta)^2 2^{J_{\max}}}{(1+\rho)^2\mathrm{Card}^2\mathcal{J}}\Big)\Big] \\ &+ e^{-x_\mathcal{J}}\frac{16(1+\rho)^2M^4\mathrm{Card}^2\mathcal{J}\Big(2(1+\eta)^2 2^{J_{\max}} + (1+\rho)^2\mathrm{Card}^2\mathcal{J}\Big)}{n^2}\exp\Big(-\frac{2(1+\eta)^2 2^{J_{\max}}}{(1+\rho)^2\mathrm{Card}^2\mathcal{J}}\Big) \\ \leq &\frac{C2^{2J_{\max}}}{n^2}e^{-x_\mathcal{J}}. \end{aligned} \tag{4.19}$$

From the choice of $x_\mathcal{J}$ (2.8), we deduce that

$$\sum_{\mathcal{J}\subset\{-1,\dots,J_n\}} A_1(\mathcal{J}) \leq \frac{C2^{2J_n}}{n^2} = \frac{C}{n\log^2(n)}. \tag{4.20}$$

Upper bound of $A_2(\mathcal{J})$

For the term $A_2(\mathcal{J})$ of (4.9), noting that:

$$|\bar{\gamma}_n(\psi_{jk})| \leq M2^{j/2}\|\psi\|_\infty + M2^{-j/2}\int_{\mathbb{R}}\psi(u)du,$$

we have for a constant C that depends only on the choice of ψ_{-10} and ψ_{00}:

$$A_2(\mathcal{J}) \leq \Big[C\sum_{j\in\mathcal{J}}\Big(M2^{j/2}\|\psi\|_\infty + M2^{-j/2}\int_{\mathbb{R}}\psi(u)du\Big)^2\Big]^2 \times \mathbb{P}\Big(\Omega_{\mathcal{J}}^c(\eta)\Big). \tag{4.21}$$

Since:

$$\sum_{i=1}^n \mathbb{E}\Big[\Big(\frac{Y_i\psi_{jk}\big(G_\ell(X_\ell^i)\big) - \mathbb{E}\big(Y_1\psi_{jk}(G_\ell(X_\ell^1))\big)}{n}\Big)^2\Big] = \frac{\mathrm{Var}\big(Y_1\psi_{jk}(G_\ell(X_\ell^1))\big)}{n} \leq \frac{M^2}{n},$$
$$\Big|\frac{Y_i\psi_{jk}\big(G_\ell(X_\ell^i)\big) - \mathbb{E}\big(Y_1\psi_{jk}(G_\ell(X_\ell^1))\big)}{n}\Big| \leq \frac{2M2^{j/2}\|\psi\|_\infty}{n} \text{ a.s.}$$

then we have by Bernstein's inequality (e.g. [17]):

$$\mathbb{P}\big(|\bar{\gamma}_n(\psi_{jk})| \geq \rho 2^{-j/2}\big) \leq 2\exp\Big(-\frac{n\rho^2 2^{-j}}{2\big(M^2 + 2M\|\psi\|_\infty\rho\big)}\Big).$$

As a consequence,

$$\begin{aligned}\sum_{\mathcal{J}\subset\{-1,\dots J_n\}} A_2(\mathcal{J}) \leq& \sum_{\mathcal{J}\subset\{-1,\dots J_n\}} 2^{2J_{\max}}\mathbb{P}\Big(\exists(j,k)\in\mathcal{J}\times\mathbb{Z},\ |\bar{\gamma}_n(\psi_{jk})| \geq \rho 2^{-j/2}\Big)\\ \leq& C\sum_{\mathcal{J}\subset\{-1,\dots J_n\}} 2^{3J_{\max}}\exp\Big(-\frac{n\rho^2 2^{-J_{\max}}}{2\big(M^2+2M\|\psi\|_\infty\rho\big)}\Big).\end{aligned} \tag{4.22}$$

which is smaller than C/n^2 for sufficiently large n, as $J_{\max} \leq J_n = \log_2(\sqrt{n})$.

Step 3: Upper bound of the second term in the r.h.s. of (4.5)

For the terms 2 to 4 of (4.4),

$$\begin{aligned}&2\langle\widehat{h}_{\mathcal{J},\ell} - h_{\mathcal{J},\ell}, h_{\mathcal{J},\ell}\rangle - \|h_\ell - h_{\mathcal{J},\ell}\|_2^2 - \zeta_n - \mathrm{pen}_2(\mathcal{J})\\ =&2\sum_{j\in\mathcal{J}}\sum_{k\in\mathbb{Z}}\bar{\gamma}_n\big(\psi_{jk}\big)\beta_{jk}^\ell - \|h_\ell - h_{\mathcal{J},\ell}\|_2^2 - 2\bar{\gamma}_n\big(h_\ell\big) - \mathrm{pen}_2(\mathcal{J})\\ =&2\bar{\gamma}_n\Big(\sum_{j\in\mathcal{J}}\sum_{k\in\mathbb{Z}}\beta_{jk}^\ell\psi_{jk}\Big) - \|h_\ell - h_{\mathcal{J},\ell}\|_2^2 - 2\bar{\gamma}_n\big(h_\ell\big) - \mathrm{pen}_2(\mathcal{J})\\ =&2\bar{\gamma}_n\big(h_{\mathcal{J},\ell} - h_\ell\big) - \|h_\ell - h_{\mathcal{J},\ell}\|_2^2 - \mathrm{pen}_2(\mathcal{J}) \qquad (4.23)\\ \leq&\Big(\frac{\bar{\gamma}_n\big(h_{\mathcal{J},\ell} - h_\ell\big)}{\|h_\ell - h_{\mathcal{J},\ell}\|_2}\Big)^2 - \mathrm{pen}_2(\mathcal{J}) = \bar{\gamma}_n^2\Big(\frac{h_{\mathcal{J},\ell} - h_\ell}{\|h_\ell - h_{\mathcal{J},\ell}\|_2}\Big) - \mathrm{pen}_2(\mathcal{J}), \qquad (4.24)\end{aligned}$$

by using the identity $2ab - b^2 \leq a^2$. Setting $\varphi_{\mathcal{J}} = \frac{h_{\mathcal{J},\ell} - h_\ell}{\|h_\ell - h_{\mathcal{J},\ell}\|_2}$ and using Bernstein's formula (see [17, p.25]), we have for all $x > 0$:

$$\mathbb{P}\Big(\bar{\gamma}_n\big(\varphi_{\mathcal{J}}\big) \geq \sqrt{\frac{2M^2}{n}x} + \frac{2M\|\varphi_{\mathcal{J}}\|_\infty}{n}x\Big) \leq e^{-x}. \tag{4.25}$$

Setting $x_{\mathcal{J}}+\xi$ as x in the above inequality and using that $(a+b)^2 \le 2a^2+2b^2$, this implies that

$$\mathbb{P}\Big(\bar{\gamma}_n^2(\varphi_{\mathcal{J}}) - \mathrm{pen}_2(\mathcal{J}) \ge r_n(\xi)\Big) \le e^{-x_{\mathcal{J}}} e^{-\xi}, \tag{4.26}$$

where $\mathrm{pen}_2(\mathcal{J})$ has been defined in (4.6) and

$$r_n(x,\xi) = \frac{4M^2\|\varphi_{\mathcal{J}}\|_\infty^2 \xi^2}{n^2} + \frac{4M^2\xi}{n}.$$

Then,

$$\begin{aligned}
&\mathbb{E}\Big(\big(2\langle \widehat{h}_{\mathcal{J},\ell} - h_{\mathcal{J},\ell}, h_{\mathcal{J},\ell}\rangle - \|h_\ell - h_{\mathcal{J},\ell}\|_2^2 - \zeta_n - \mathrm{pen}_2(\mathcal{J})\big)_+^2\Big) \\
\le &\mathbb{E}\Big(\Big[\bar{\gamma}_n^2(\varphi_{\mathcal{J}}) - \mathrm{pen}_2(\mathcal{J})\Big]^2\Big) \\
\le &C\int_0^{+\infty} t\ \mathbb{P}\big(\big|\bar{\gamma}_n^2(\varphi_{\mathcal{J}}) - \mathrm{pen}_2(\mathcal{J})\big| > t\big)dt \\
\le &Ce^{-x_{\mathcal{J}}}\int_0^{+\infty} t\ \exp\Big(-\frac{n}{2\|\varphi_{\mathcal{J}}\|_\infty^2}\big(\sqrt{1+\frac{t\|\varphi_{\mathcal{J}}\|_\infty^2}{M}}-1\big)\Big)dt \le \frac{Ce^{-x_{\mathcal{J}}}}{n^2}.
\end{aligned} \tag{4.27}$$

The last inequality stems from the behaviour of the integrand when t is close to 0.

Gathering the results of Steps 1 to 3, we have by (4.9) and (4.5) that the first term in the r.h.s. of (4.3) is smaller than $C/(n\log^2(n))$. This proves (4.1).

Step 4:

Let us now consider the term $\mathbb{E}\Big[\Big(-\widehat{\theta}_{\mathcal{J},\ell}+V_\ell+\zeta_n\Big)_+^2\Big]$ in (4.1). From (4.4) and (4.23):

$$\begin{aligned}
&\mathbb{E}\Big[\big(-\widehat{\theta}_{\mathcal{J},\ell}+V_\ell+\zeta_n\big)_+^2\Big] \\
=&\mathbb{E}\Big(\big(\|h_\ell - h_{\mathcal{J},\ell}\|_2^2 - \|\widehat{h}_{\mathcal{J},\ell} - h_{\mathcal{J},\ell}\|_2^2 + 2\bar{\gamma}_n\big(h_\ell - h_{\mathcal{J},\ell}\big) + \mathrm{pen}(\mathcal{J})\big)_+^2\Big) \\
\le &4\Big(\|h_\ell - h_{\mathcal{J},\ell}\|_2^4 + 4\mathbb{E}\Big(\bar{\gamma}_n^2\big(h_\ell - h_{\mathcal{J},\ell}\big)\Big) + \mathbb{E}\Big(\Big[\|\widehat{h}_{\mathcal{J},\ell} - h_{\mathcal{J},\ell}\|_2^2 - \mathrm{pen}_1(\mathcal{J})\Big]_+^2\Big) + \mathrm{pen}_2^2(\mathcal{J})\Big),
\end{aligned} \tag{4.28}$$

where $D_{\mathcal{J}}$ has been defined in (4.2).

For the second term in the r.h.s. of (4.28), we have:

$$\begin{aligned}
\mathbb{E}\Big(\bar{\gamma}_n^2\big(h_\ell - h_{\mathcal{J},\ell}\big)\Big) =&\mathrm{Var}\Big(\bar{\gamma}\big(h_\ell - h_{\mathcal{J},\ell}\big)\Big) \\
\le &\frac{1}{n}\mathbb{E}\Big(Y_1^2\big(h_\ell(G_\ell(X_\ell^1)) - h_{\mathcal{J},\ell}(G_\ell(X_\ell^1))\big)^2\Big) \le \frac{M^2\|h_\ell - h_{\mathcal{J},\ell}\|_2^2}{n} \\
\le &C\big(\frac{1}{n^2} + \|h_\ell - h_{\mathcal{J},\ell}\|_2^4\big)
\end{aligned} \tag{4.29}$$

by using that $2ab \le a^2+b^2$ for the last inequality.

The third term in the r.h.s. of (4.28) has been treated in (4.9) precedingly. We established an upper bound in $2^{J_{\max}}/n^2$. The fourth term, $\mathrm{pen}_2^2(\mathcal{J})$ is in $x_{\mathcal{J}}^2/n^2 \le C\log^2(n)/n^2$ from (4.6). Gathering these results, we obtain (4.2) and then (2.26).

4.2 Proof of Corollary 2.8

Plugging (4.2) in (4.1), and using that

$$\mathbb{E}\big(\zeta_n^2\big) = \frac{2}{n}\mathrm{Var}\Big(Y_1 h_\ell\big(G_\ell(X_\ell^1)\big)\Big) \leq \frac{2M^2\|h_\ell\|_2^2}{n}, \tag{4.30}$$

we obtain:

$$\mathbb{E}\Big[\big(\widehat{\theta}_\ell - V_\ell\big)^2\Big] \leq C\Big[\inf_{\mathcal{J}\subset\{-1,\dots,J_n\}}\Big(\|h_\ell - h_{\mathcal{J},\ell}\|_2^4 + \frac{2^{J_{\max}}}{n^2}\Big) + \frac{1+\|h_\ell\|_2^2}{n}\Big]. \tag{4.31}$$

If $h_\ell \in \mathcal{B}(\alpha, 2, \infty)$, then from Proposition 2.7, we have for $\mathcal{J} = \{-1, \dots, J_{\max}\}$ that $\|h_\ell - h_{\mathcal{J},\ell}\|_2^4 \leq 2^{-4\alpha\ J_{\max}}$. Thus, for subsets $\mathcal{J}$ of the form considered, the infimum is attained when choosing $J_{\max} = \frac{2}{4\alpha+1}\log_2(n)$, which yield an upper bound in $n^{8\alpha/(4\alpha+1)}$.

For h_ℓ in a ball of radius R, $\|h_\ell\|_2^2 \leq R^2$, and we can find an upper bound that does not depend on h. Because the last term in (4.31) is in $1/n$, the elbow effect is obtained by comparing the order of the first term in the r.h.s. ($n^{8\alpha/(4\alpha+1)}$) with $1/n$ when α varies. □

A Properties of $\widehat{\beta}_{jk}$

Lemma A.1.

$$\lim_{n\to+\infty}\sqrt{n}\big(\widehat{\beta}_{jk}^\ell - \beta_{jk}^\ell\big) = \mathcal{N}\Big(0,\, Var\big(Y\psi_{jk}\big(G_\ell(X_\ell)\big)\big)\Big) \tag{A.1}$$

where

$$Var\big(Y\psi_{jk}\big(G_\ell(X_\ell)\big)\big) = Var\big(g_\ell(X_\ell)\psi_{jk}\big(G_\ell(X_\ell)\big)\big) + \mathbb{E}\big(\eta_\ell^2\psi_{jk}^2(G_\ell(X_\ell))\big).$$

Proof. Recall that $Y^i = g_\ell(X_\ell^i) + \eta_\ell^i$. Then:

$$\begin{aligned}\widehat{\beta}_{jk}^\ell =& \frac{1}{n}\sum_{i=1}^n g_\ell(X_\ell^i)\psi_{jk}\big(G_\ell(X_\ell^i)\big) + \frac{1}{n}\sum_{i=1}^n \eta_\ell^i\psi_{jk}\big(G_\ell(X_\ell^i)\big)\\ =&\beta_{jk}^\ell + \frac{1}{n}\sum_{i=1}^n\Big(g_\ell(X_\ell^i)\psi_{jk}\big(G_\ell(X_\ell^i)\big) - \mathbb{E}\big(g_\ell(X_\ell)\psi_{jk}(G_\ell(X_\ell))\big)\Big) + \frac{1}{n}\sum_{i=1}^n \eta_\ell^i\psi_{jk}\big(G_\ell(X_\ell^i)\big).\end{aligned}$$

The second term in the r.h.s. is a biais term due to the approximation of β_{jk}^ℓ, defined as an integral, by a mean. The third term is due to the noise between Y^i and $g_\ell(X_\ell^i)$. The third term is centered as $\mathbb{E}(\eta_\ell \mid X_\ell) = 0$. Since the observations are i.i.d., we have by the central limit theorem that

$$\lim_{n\to+\infty}\frac{1}{\sqrt{n}}\sum_{i=1}^n\begin{pmatrix} g_\ell(X_\ell^i)\psi_{jk}\big(G_\ell(X_\ell^i)\big) - \mathbb{E}\big(g_\ell(X_\ell)\psi_{jk}(G_\ell(X_\ell))\big) \\ \frac{1}{n}\sum_{i=1}^n \eta_\ell^i\psi_{jk}\big(G_\ell(X_\ell^i)\big)\end{pmatrix} = \mathcal{N}(0,\Sigma) \tag{A.2}$$

with

$$\Sigma = \begin{pmatrix}\mathrm{Var}\big(g_\ell(X_\ell)\psi_{jk}\big(G_\ell(X_\ell)\big)\big) & 0\\ 0 & \mathrm{Var}\big(\eta_\ell\psi_{jk}\big(G_\ell(X_\ell)\big)\end{pmatrix}.$$

We have

$$\begin{aligned}\mathrm{Var}\big(g_\ell(X_\ell)\psi_{jk}\big(G_\ell(X_\ell)\big)\big) =& \mathbb{E}\big(g_\ell^2(X_\ell)\psi_{jk}^2\big(G_\ell(X_\ell)\big)\big) - \beta_{jk}^2\\ =& \int_0^1\big(\sum_{jk}\beta_{jk}\psi_{jk}(u)\big)^2\psi_{jk}^2(u)du - \beta_{jk}^2,\end{aligned}$$

and as $\mathbb{E}(\eta_\ell \mid X_\ell) = 0$, we have

$$\mathrm{Var}\big(\eta_\ell \psi_{jk}(G_\ell(X_\ell))\big) = \mathbb{E}\big(\eta_\ell^2 \psi_{jk}^2(G_\ell(X_\ell))\big) = \int_{\mathbb{R}} \mathbb{E}\big(\eta_\ell^2 \mid X_\ell = G_\ell^{-1}(2^{-j}(v+k))\big)\ \psi^2(v)dv.$$

Using the Slutsky lemma concludes the proof. ■

B Sobol indices

The Sobol indices are based on the following decomposition for f (see Sobol [20]). We recall the formulas here, with the notation X_{p+1} for the random variable ε:

$$Y = f(X_1, \dots, X_p, \varepsilon) = f_0 + \sum_{\ell=1}^{p+1} f_\ell(X_\ell) + \sum_{1 \le \ell_1 < \ell_2 \le p+1} f_{\ell_1 \ell_2}(X_{\ell_1}, X_{\ell_2}) + \cdots + f_{1,\dots,p+1}(X_1, \dots, X_p, \varepsilon) \tag{B.1}$$

where $\quad f_0 = E[Y], \quad f_\ell(X_\ell) = E[Y|X_\ell] - E[Y],$
$f_{\ell_1\ell_2}(X_{\ell_1}, X_{\ell_2}) = E[Y|X_{\ell_1}, X_{\ell_2}] - E[Y|X_{\ell_1}] - E[Y|X_{\ell_2}] - E[Y], \quad \dots$

Then, the variance of Y can be written as:

$$\mathrm{Var}(Y) = \sum_{\ell=1}^{p+1} V_\ell + \sum_{1 \le \ell_1 < \ell_2 \le p+1} V_{\ell_1\ell_2} + \cdots + V_{1\dots p+1} \tag{B.2}$$

where

$$V_\ell = \mathrm{Var}(E[Y|X_\ell]), \qquad V_{\ell_1\ell_2} = \mathrm{Var}(E[Y|X_{\ell_1}, X_{\ell_2}]) - V_{\ell_1} - V_{\ell_2}, \dots$$
$$V_{1\dots p+1} = \mathrm{Var}(Y) - \sum_{\ell=1}^{p+1} V_\ell - \sum_{1 \le \ell_1 < \ell_2 \le p+1} V_{\ell_1\ell_2} - \cdots - \sum_{1 \le \ell_1 < \cdots < \ell_p \le p+1} V_{\ell_1 \dots \ell_p} \tag{B.3}$$

The first order indices are then defined as:

$$S_\ell = V_\ell / \mathrm{Var}(Y) = \mathrm{Var}(E[Y|X_\ell])/\mathrm{Var}(Y) \tag{B.4}$$

S_ℓ corresponds to the part of the variance that can be explained by the variance of Y due to the variable X_ℓ alone. In the same manner, we define the second order indices, third order indices, etc. by dividing the variance terms by $\mathrm{Var}(Y)$.

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8 Discussion

Dans cette partie section, nous allons discuter des résultats obtenues dans les différentes études de cette thèse et de l'apport de celles-ci pour l'aide à la décision dans ce problème particulier de l'hépatite C chez les UDI en France. Les méthodologies utilisées, ainsi que les problèmes rencontrés sont également discutés. Enfin, la dernière sous-section évoque les perspectives de ce travail, et les prolongements envisageables.

8.1 Bilan : réduire le fardeau de l'hépatite C chez les UDI

8.1.1 La réduction des risques

Dans l'article 2, nous avons démontré que l'amélioration de l'accès au matériel stérile ou aux traitements de substitution aux opiacés, en divisant par deux le temps moyen d'accès à ces interventions, ne permettait qu'une amélioration modeste de la durée de vie ajustée sur la qualité. De plus, l'amélioration de l'accès à la réduction des risques combinée avec une amélioration de l'ensemble de la cascade de soins (dépistage, lien aux soins et adhérence au traitement ; traitement à partir de F0) n'a pas apporté d'amélioration de la durée de vie par rapport à une amélioration de la cascade de soins seule.

Dans les faits, si l'accès au matériel d'injection stérile débuté en France en 1987 par la vente libre de seringues en pharmacie, et les traitements de substitution aux opiacés introduits plus tardivement ont permis une amélioration importante de la santé des UDI, particulièrement en réduisant la transmission du VIH, l'impact sur la transmission du VHC a été beaucoup plus modéré (Jauffret-Roustide et al. 2006). Dans l'étude ANRS-Coquelicot, un effet de cohorte est visible pour le VIH chez les usagers de drogues (par voie injectable et/ou nasale) nés au début des années 70 et donc les premiers touchés par ces interventions de réduction des risques, mais pas pour le VHC (Jauffret-Roustide et al. 2009). Pour le VHC, la séroprévalence demeure à environ 65% malgré l'introduction de ces mesures, tandis que pour le VIH, elle décroît de 17% à 8%. Cette différence d'impact peut s'expliquer par le risque de transmission de ces deux virus lors de l'utilisation de matériel d'injection infecté : le VHC étant plus résistant que le VIH, le risque de transmission est environ 10 fois plus élevé (MacDonald et al. 1996) et donc une force d'infection élevée (Pollack 2001; Murray et al. 2003; Hutchinson et al. 2006; Coutin et al. 2010).

Cette force d'infection élevée a deux conséquences. Premièrement, lorsque l'on étudie une cohorte, comme nous l'avons fait dans l'analyse coût-efficacité du chapitre 6, une grande part des individus (42.8% initialement, chiffre dérivé de l'étude ANRS-Coquelicot) sont déjà atteints d'hépatite C. Une amélioration de l'accès à la réduction des risques ne peut donc finalement avoir un impact que pour la proportion restante de la population. Une étude de modélisation portant sur une population d'UDI aux Pays-Bas est arrivée à la même conclusion, c'est-à-dire que les interventions de réduction des risques devraient cibler les individus les moins à risque de la population pour être efficace, les individus les plus à risque étant déjà, pour la plupart, infectés par le VHC (de Vos et al. 2013). Toutefois, dans notre étude,

l'impact d'améliorations des interventions de réduction des risques sur les infections chez les UDI « incidents », c'est-à-dire les individus qui arrivent dans la population au cours des simulations (et ne font donc par partie de la cohorte initiale), n'a pas été évalué. Les infections évitées dans ces futurs générations d'UDI pourraient permettre un gain d'efficacité de cette stratégie, mais sur un plus long terme.

Deuxièmement, la transmission du VHC continue à exister même si les pratiques à risques (partage de matériel d'injection) persistent à un faible niveau. Il est donc nécessaire d'assurer la continuité de l'accès au matériel d'injection stérile et aux traitements de substitution. En France, près de 14 millions de seringues ont été distribuées ou vendues en 2008 (Expertise collective INSERM 2010), et 85% des UDI actifs (injecteurs dans le dernier mois) ont été sous traitement de substitution durant les 6 derniers mois (données non-publiées de l'enquête ANRS-Coquelicot). Ces données suggèrent un taux de couverture des interventions de réduction des risques élevé en France. Toutefois, ces chiffres masquent une certaine difficulté à assurer la permanence de ces interventions pour les UDI concernés. Ramenées au nombre estimé d'injecteurs actifs en France (81 000), les 14 millions de seringues distribuées correspondent à 170 seringues par injecteurs (Expertise collective INSERM 2010), soit environ une seringue pour deux jours. Il est difficile d'estimer le nombre de seringues requis pour couvrir les besoins des usagers, mais parmi les injecteurs actifs, 13% déclarent avoir partagé une seringues et 74% avoir réutilisé leurs seringues dans le dernier mois (Jauffret-Roustide 2009), ce qui suggère que ce nombre est insuffisant. En ce qui concerne la substitution, des problèmes de compliance surviennent également : une étude de l'Observatoire Français des Drogues et Toxicomanies (OFDT) a démontré que parmi les UDI substitués, seuls 37% le sont au moins 10 mois dans l'année (Brisacier et al. 2013). D'autres études en France confirment cette faible adhérence aux traitements de substitution (Roux et al. 2009; Dupouy et al. 2013). De plus, l'accès à la substitution permet de diminuer la fréquence d'injection, mais la pratique peut malgré tout persévérer. De ce point de vue, une revue regroupant les données provenant de 6 études au Royaume-Uni a estimé l'impact d'une couverture complète par les mesures de réduction des risques (i.e. individu sous substitution et participant à un programme d'accès aux seringues couvrant 100% des injections). Le partage de seringues dans le dernier mois chez les individus concernés n'était inférieur que de 52% à celui reporté par les UDI sous réduction des risques minimale (i.e. non-substitué et n'ayant pas assez de seringues pour couvrir leurs besoins) (Turner et al. 2011). Ce chiffre donne donc une idée des limites de ces interventions de réduction des risques dans le cadre du VHC. Enfin, les usagers les plus marginalisés sont plus difficiles à recruter dans les enquêtes épidémiologiques, celles-ci recrutant la plupart du temps parmi la population fréquentant des structures de réduction des risques, de soin ou d'hébergement. Cette population cachée, qui ne fréquente pas les structures, induit donc probablement à une estimation optimiste de la situation.

Toutefois, notre étude montre qu'une haute couverture des interventions de réduction des risques est malgré tout bénéfique, et que maintenir le niveau de réduction des risques actuel est une nécessité. En effet, l'analyse de sensibilité de l'étude coût-efficacité présentée au chapitre 6 montre qu'un moindre

niveau de réduction des risques aboutirait à 25% d'infections en plus (50% en cas d'absence totale de réduction des risques). De plus, toujours en analyse de sensibilité, l'efficacité d'améliorations de la réduction des risques en complément d'amélioration de la cascade de soins variait grandement selon le niveau d'incidence initial. Nous avons évalué une stratégie combinée consistant à améliorer la réduction des risques, l'ensemble de la cascade de soins, et à traiter dès F0, avec les paramètres suivants : 0.25 ans (vs. 1 an pour la pratique actuelle) pour la durée moyenne entre le début de l'injection et la participation à un programme d'accès au matériel d'injection ; 0.25 ans (vs. 0.5 dans la pratique actuelle) pour la durée moyenne entre le début de la participation à un programme d'accès au matériel d'injection et l'accès aux traitements de substitution ; 0.5 ans (vs. 1.25/1.45 ans pour les injecteurs actifs/inactifs dans la pratique actuelle) pour la durée moyenne entre le passage à la chronicité et le diagnostic 0.5 ans (vs. 2.6 ans dans la pratique actuelle) pour la durée moyenne avant lien aux soins après le diagnostic ; 5%/an (vs. 14%/an dans la pratique actuelle) pour taux annuel de perte de vue ; 95% (vs. 86% dans la pratique actuelle) pour le taux de RVS. Cette stratégie combinée, dans l'analyse principale, donnait des résultats similaires au scénario combinant une amélioration de la cascade de soins avec un traitement dès F0. Ajouter une amélioration de la réduction des risques n'apportait donc pas d'amélioration de l'espérance de vie. Toutefois, lorsque nous avons considéré une incidence de départ plus élevée (22/100 p.a, l'incidence des séroconversions dans la population UDI de Montréal, d'après les données du réseau SurvUDI (Leclerc et al. 2011) vs. 12/100 p.a dans l'analyse principale), ajouter cette amélioration des interventions de réduction des risques permettait une augmentation supplémentaire de l'espérance de vie de 0.21 QALY (+0.47 QALY par rapport à la pratique actuelle). Ce scénario était de plus coût-efficace, avec un ICER de 53 000€/QALY par rapport à une amélioration de la cascade de soin seule. En augmentant encore l'incidence initiale jusqu'à des niveaux très élevés (à 42/100 p.a, correspondant à une estimation à Londres (Judd et al. 2005)), l'écart entre ces deux scénarios croissait (+0.28 QALY), mais le scénario incluant une amélioration de la réduction des risques ne devenait plus coût-efficace par rapport à une amélioration de la cascade de soin seule, avec un ICER de 146 000€/QALY), le nombre de réinfections devenant alors très élevé (7 600 réinfections contre 2 000 dans le scénario de la pratique actuelle).

Ces résultats suggèrent qu'aux taux actuels de couverture des interventions de réduction des risques, il existe un intervalle d'incidence en dessous duquel améliorer la réduction des risques en complément d'une stratégie de type TasP a peu d'impact à cause du faible nombre d'infections évitées, à l'intérieur duquel cette amélioration a un impact important sur la mortalité et est coût-efficace, et en dehors duquel le coût-efficacité n'est pas assuré à cause du nombre élevé de réinfections. Dans notre analyse principale, nous avons pris en compte une incidence de 12/100 p.a, qui est une estimation médiane pour les pays à haut-revenus, en l'absence de données françaises récentes. Toutefois, une estimation réalisée entre mars 1999 et juillet 2000 à partir d'une cohorte d'UDI dans le Nord et l'Est de la France avait estimé cette incidence des séroconversion chez les UDI à 9/100 p.a. (Lucidarme et al. 2004), donc une incidence du

même ordre. Une estimation plus récente de l'incidence serait nécessaire afin de déterminer la place exacte de la France par rapport à l'intervalle d'incidence mentionné plus haut.

8.1.2 Treatment as Prevention (TasP)

Avec l'arrivée des nouveaux antiviraux, le « Treatment as Prevention » (ou TasP), c'est-à-dire l'utilisation du traitement dans une perspective collective, pour empêcher la transmission de la maladie, est avancé comme une solution pour réduire le fardeau de la maladie, éliminer l'hépatite C (atteindre une incidence nulle (Dowdle 1998)), voir l'éradiquer (atteindre une prévalence nulle (Dowdle 1998)) (Delfraissy 2013; Grebely et al. 2013; Hagan et al. 2013).

Le chapitre 3 de la présente thèse démontre que, si l'objectif est de réduire de manière importante la transmission de la maladie par l'utilisation du traitement, des améliorations importantes de la cascade de soins de l'hépatite C sont nécessaires. Premièrement, l'initiation du traitement ne doit pas être réservée aux stades de fibrose modérés à sévères (supérieur à F2), mais doit se faire le plus tôt possible, dès F0 idéalement. L'étude sur la population d'UDI en Île-de-France est assez explicite : le seul fait de permettre l'accès au traitement aux patientsà partir de F0 (au lieu de F2 dans le scénario de référence) permettait de diviser par deux l'incidence et la prévalence du VHC dans la population après 10 ans. L'étude portant sur la population UDI de Montréal, évaluant des scénarios différents, a abouti à des résultats encore plus parlants : traiter systématiquement tous les UDI diagnostiqués et liés aux soins, mais uniquement lorsque le stade de fibrose est supérieur à F2, ne permettait pas d'atteindre la même réduction de prévalence et d'incidence après 10 ans de simulation que traiter seulement 20% de ces individus annuellement indépendamment de leur stade de fibrose.

Traiter dès F0 est donc nécessaire si l'on veut diminuer de manière importante le fardeau de la maladie, mais pas suffisant. Combiner cette stratégie avec des améliorations de la cascade de soins (dépistage, liens aux soins et traitement), était indispensable. Dans le chapitre 6, ce scénario était le plus efficace sur la transmission du VHC avec plus de 1 200 infections évitées dans une population de 10 480 UDI. Dans l'étude du chapitre 3, un scénario similaire, mais prenant en compte un taux de RVS maximum de 90% dans les essais cliniques, permettait d'atteindre une prévalence de 7% après 10 ans, contre 25% avec la cascade de soins actuelle. A noter par ailleurs que traiter dès F0 n'avait par contre qu'un impact modéré sur la morbidité/mortalité associée à l'hépatite C avec environ 7% de complications évitées après 40 ans (comparativement à une limitation de l'accès au traitement aux stades F2 et supérieurs). Encore une fois, combiner cette stratégie avec des améliorations du reste de la cascade de soins était incontournable pour parvenir à diviser par deux le nombre de complications après 40 ans. Enfin traiter dès F0 sans améliorer le reste de la cascade de soins n'était pas coût-efficace dans l'étude présentée au chapitre 6. Cette situation peut s'expliquer par le coût élevé des nouveaux traitements (46 000€ pour 12 semaines de traitement, pour la combinaison lédipasvir + sofosbuvir (Legifrance 2015)) et à la possibilité de réinfection (le nombre de réinfection étant de 1 430 en moyenne dans la cohorte contre 872 dans le scénario de la pratique actuelle). Pour être coût-efficace, améliorer le reste de la cascade de

soins (dépistage, lien aux soins et adhérence au traitement) était nécessaire : lorsque l'on diminuait le temps moyen entre le passage à la chronicité et le diagnostic à 6 mois (contre 1.25/1.45 ans pour les injecteurs actifs/inactifs dans le scénario de base), que l'on diminuait le temps entre le diagnostic et le lien aux soins à 6 mois (contre 2.6 ans dans le scénario de base), que l'on considérait un taux de perte de vue de 5%/an (contre 14%/an dans le scénario de base) et un taux de RVS de 95% (contre 87% dans le scénario de base), l'espérance de vie ajustée était en moyenne de 17.02 QALY (+0.45 QALY par rapport au scénario de base), pour un ratio coût-efficacité incrémental (ICER) d'environ 20 000€/QALY par rapport à une amélioration de la cascade de soin seule, largement en dessous du seuil de coût-efficacité recommandé par l'OMS. Pour cette institution, une stratégie est considérée comme très coût-efficace si l'ICER inférieur au PIB par habitant (environ 30 000€ en France (World Bank 2014)), et comme coût-efficace si inférieur à 3 fois le PIB par habitant (World Health Organization 2003).

Une stratégie de TasP est donc une option intéressante pour réduire le fardeau de l'hépatite C chez les UDI. Toutefois, la mise en application de cette stratégie soulève de nombreux problèmes. La nécessité d'améliorer l'ensemble de la cascade de soins nécessiterait une réflexion approfondie sur les méthodes à utiliser.

D'abord, lorsqu'il s'agit d'améliorer le dépistage, les liens avec le système de soins ou l'adhérence aux traitements antiviraux se pose la question des moyens à mettre en œuvre. Le fait que les nouveaux antiviraux permettent des durées de traitement plus courtes (12 semaines contre 24 à 48 semaines auparavant), présentent moins d'effets indésirables et sont moins contraignants (existence de régimes de traitement sans injections d'interférons) (Micallef et al. 2006; NICE 2006; Sulkowski et al. 2011; Lawitz et al. 2013; Afdhal et al. 2014; Sulkowski et al. 2014; Lawitz et al. 2015) devrait permettre d'obtenir une certaine amélioration de l'adhérence au traitement dans les années à venir. En ce qui concerne le dépistage, la France est déjà l'un des pays obtenant les meilleurs résultats dans ce domaine avec environ 90% d'UDI infectés connaissant leur infection (Meffre et al. 2010). Toutefois, d'autres améliorations sont possibles. L'utilisation de tests utilisant une goutte de sang séché (tests « buvard ») ou des tests rapides d'orientation diagnostique (TROD) pourrait offrir de nouvelles possibilités de dépistage (Haute Autorité de Santé 2014). Ces tests bon marché, faciles d'utilisation et ne nécessitant pas d'équipement spécifique, offrent de nouvelles possibilités, par exemple la mise en place d'un dépistage communautaire dans les structures fréquentées par les UDI comme les CARUUD et en CSAPA, hors des structures médicales traditionnelles. L'accès à ces tests ne nécessitant pas de prise de sang permettrait probablement une meilleure acceptation du dépistage chez les UDI, l'accès veineux pour un prélèvement sanguin pouvant être difficile chez certains individus (Haute Autorité de Santé 2014). Une revue systématique, publiée en 2015 met en évidence un impact positif des tests sur buvard sur la fréquence de dépistage (Coats et al. 2015). Une étude de modélisation a par ailleurs démontré que l'utilisation de ce type de test dans les services d'addictologie serait coût-efficace en Angleterre (Martin et al. 2013). L'utilisation des TROD offre également une possibilité d'améliorer les liens avec les soins par une stratégie de « point-of-care testing », c'est-à-dire le dépistage à proximité des lieux de soins afin

de permettre, grâce à la rapidité des résultats (moins d'une heure), une orientation immédiate de l'individu vers les soins. Toujours en ce qui concerne les liens avec le système de soins, l'Ecosse a investi depuis 2008 43 millions de livres pour favoriser le lien des UDI avec le système de soins et effectuer des campagnes d'information et de conseil auprès des professionnels. Les résultats ont été visibles : la proportion d'UDI ayant consulté un spécialiste dans les 12 mois suivant le diagnostic de leur hépatite C est passé de 32% avant 2008 à 45% par la suite (McDonald et al. 2014). Pour comparaison, dans notre modèle, pour la population UDI en Île-de-France, la probabilité de lien aux soins durant la première année est de 32% également (loi exponentielle de taux de transition 1/2.6 années^{-1}). Bien que ne permettant d'atteindre l'objectif fixé dans nos études, c'est-à-dire un lien aux soins dans les 6 mois suivant le diagnostic, il s'agit d'une piste intéressante pour améliorer graduellement l'accès aux soins.

Ensuite, parce que même si améliorer la cascade de soins et traiter les patients dès F0 est coût-efficace, le nombre important de malades à traiter pourrait entraîner un impact budgétaire important à court terme. Dans l'étude présentée au chapitre 3, sur une population de 10 000 UDI en Île-de-France, le nombre de traitement atteint 4 000 après seulement 3 années de simulations sous ce scénario. Le coût du traitement par sofosbuvir + lédipasvir étant de 46 000 euros pour 12 semaines (Legifrance 2015), le coût engendré serait donc de 185 millions d'euros sur 3 ans pour cette seule population et en ne prenant en compte que le coût du médicament. En effet, les aspects logistiques sont également à prendre en compte. Traiter massivement les UDI pour l'hépatite C, même avec des modalités de traitement plus courtes et moins contraignantes, nécessiterait d'accroître la capacité d'accueil des services spécialisés, afin d'assurer l'évaluation et le suivi de ces malades.

8.1.3 Généralisation des résultats à d'autre contextes et sensibilité du modèle

Dans le chapitre 4, nous avons modélisé l'effet d'une stratégie de TasP sur la population d'UDI actifs à Montréal. Nous y avons favorisé l'utilisation de données locales, afin de reproduire au mieux la cascade de soins dans ce contexte. La population d'étude est différente de celle que nous avions définie pour les études en Île-de-France : à Montréal, nous avons défini un injecteur « actif » comme un individu ayant pratiqué l'injection au cours des 6 derniers mois, contre 1 mois dans le modèle en population française. De plus, l'initiation du traitement dans cette version du modèle n'était pas dépendante de la sévérité de la maladie hépatique, mais d'un taux annuel d'initiation du traitement. Les recommandations au Québec ne font pas intervenir, à l'heure actuelle, le stade de fibrose, mais une prise de décision sur une base individuelle (Myers et al. 2015). Pourtant le taux de traitement est très faible : parmi les UDI qui se savent infectés par le VHC, seuls 12% ont déjà reçu un traitement (Leclerc et al. 2011). Les obstacles à l'initiation du traitement sont nombreux : les troubles psychiatriques, les autres comorbidités et les conditions de vie précaires sont identifiés comme des barrières à la décision d'initier le traitement (Moirand et al. 2007). Dans cette étude, il ne s'agissait pas d'étudier l'impact de recommandations sur une stratégie, mais plutôt d'un accès élargi au traitement chez les UDI de Montréal.

Les scénarios ont donc été adaptés, notamment en faisant varier le taux d'initiation du traitement chez les individus déjà diagnostiqués et suivi par le système de soins de 5%/an à 10%/an, puis 20% par an, en combinaison ou non avec des améliorations de la cascade de soins : dépistage à 6 mois après le passage à la chronicité (contre 2 ans dans la pratique actuelle), lien aux soins à 6 mois après le diagnostic (contre 1.7 ans dans la pratique actuelle), un taux de perte de vue de 5%/an (contre 10%/an dans le scénario de référence) et un taux de RVS de 90% (contre 81% dans la pratique actuelle). Ces améliorations sont les mêmes que celles supposées dans l'étude sur la population d'UDI d'Île-de-France, mais à partir de la cascade de soins de Montréal, où le dépistage est un peu moins rapide (2 ans après le passage à la chronicité contre 1.25/1.45 ans en France chez les UDI actifs/inactifs) et le lien aux soins meilleurs (lien aux soins 1.7 ans après le diagnostic et 10% de perdus de vue chaque année contre respectivement 2.6 ans et 14%/an pour la France).

Les résultats ont démontré que le taux d'initiation du traitement est le paramètre critique du modèle : augmenter ce taux de 5%/an à 10%/an, puis 20%/an, permettant d'obtenir en moyenne une incidence à 10 ans de 8.1/100 personne-années (p.a) et 6.4/100 p.a respectivement (9.4/100 p.a dans la pratique actuelle), une prévalence à 10 ans de 47.5% et 36.6% respectivement (55.8% dans la pratique actuelle), et une diminution du nombre de complications de la cirrhose (décompensation ou carcinome hépatocellulaire) de 21% et 37% respectivement par rapport à la pratique actuelle. Améliorer le dépistage, le lien aux soins ou l'adhérence au traitement seul n'avait qu'un faible impact, mais combiner toutes ces améliorations avec un taux de traitement augmenté à 20%/an était l'intervention la plus efficace, avec une incidence moyenne à 10 ans de 4.3/100 p.a (vs. 9.4/100 p.a dans la pratique actuelle), une prévalence moyenne à 10 ans de 24% (vs. 55.8% dans la pratique actuelle) et une diminution du nombre de complications de la cirrhose de 54% par rapport à la pratique actuelle.

On peut donc établir des parallèles avec les résultats obtenus en France : premièrement, l'initiation du traitement est l'étape de la cascade sur laquelle une amélioration est la plus susceptible d'amener à une diminution de la prévalence et de l'incidence ; et deuxièmement, seule une amélioration de l'ensemble de la cascade de soins permet un certain contrôle de l'épidémie de VHC.

Les recommandations concernant les nouveaux traitements antiviraux sont en cours de discussion, et leur prix élevé 55,000$ canadiens pour 12 semaines dans le cas du sofosbuvir (Régie de l'assurance maladie du Québec 2015)) soulève, comme en France, des questions sur le traitement des stades de fibroses F0 à F2. Nous avons donc également évalué un scénario où le traitement était initié uniquement en fonction du stade de fibrose, comme dans le modèle en population française : tous les individus liés aux soins et avec un score de fibrose supérieur ou égal à F2 initiaient automatiquement le traitement. Dans ce scénario, les résultats obtenus en terme de transmission du VHC n'était pas aussi bon que lorsque le taux d'initiation du traitement était de 20%, mais indépendamment du stade de fibrose, avec une incidence à 10 ans de 7.3/100 p.a en moyenne et une prévalence à 10 ans de 44.3%, contre 6.4/100 p.a et 36.6% respectivement. Traiter tous les infectés avec un score de fibrose modéré à sévère était donc moins efficace pour diminuer la transmission que de traiter une petite fraction des infectés, mais

indépendamment de leur stade de fibrose. Ces résultats, comme ceux obtenus chez les UDI en Île-de-France, montrent qu'un accès au traitement restreint aux stades de fibrose les plus sévères est incompatible avec l'objectif d'élimination du VHC.

Ces résultats montrent une possibilité de généralisation des résultats à d'autres contextes. Toutefois, cette généralisation dépend de la cascade de soins du pays considéré. A titre d'exemple dans l'étude présentée au chapitre 3 sur l'impact d'améliorations de la cascade de soins chez les UDI d'Île-de-France, l'analyse de sensibilité a démontré qu'en prenant un temps moyen entre le passage à la chronicité et le diagnostic de 7.8 ans (1.25/1.45 ans chez les injecteurs actifs/inactifs en France), correspond au contexte du Royaume-Uni (Martin et al. 2013), améliorer le dépistage seul pourrait devenir une stratégie intéressante, ce changement entraînant 10% de complications de la cirrhose en plus après 40 ans par rapport au scénario de référence. Améliorer le dépistage, dans l'étude en population française, était pourtant le scénario le moins efficace, et conduisait à des résultats similaires à ceux obtenus avec la cascade de soins actuelle. La généralisation des résultats est donc conditionnée à une certaine similarité dans la cascade de soins de l'hépatite C.

8.2 La modélisation individu-centrée pour l'aide à la décision en santé publique

8.2.1 Intérêt de l'approche pour l'aide à la décision

En ce qui concerne la problématique du VHC chez les UDI, la modélisation individu-centrée avec représentation du réseau social par un graphe n'a connu qu'un développement récent. Dans le cadre de la problématique de l'hépatite C chez les UDI, ce type de modèle n'a été que très peu exploité. Les premiers essais dans ce domaines ont eu lieu en 2006, avec une étude en population écossaise (Hutchinson et al. 2006), et depuis 2011, avec les travaux publiés par une équipe australienne sur la population UDI de Melbourne (Rolls et al. 2011; Rolls et al. 2013; Hellard et al. 2014; Hellard et al. 2015). Pourtant, les possibilités offertes par ce type de modèles pour l'aide à la décision en santé publique sont nombreuses.

Premièrement, les modèles individu-centrés permettent une exploitation statistique des résultats du modèle. C'est notamment le cas au chapitre 6, où nous avons effectué une analyse coût-efficacité sur une cohorte d'UDI simulée grâce au modèle. La simulation des trajectoires individuelles a permis l'estimation des durées de vie moyennes, ainsi que des coûts moyens sur l'ensemble de la durée de vie. Dans les recommandations de traitement les interventions de santé publiques deviennent de plus en plus spécifiques et individualisées : l'évaluation d'interventions ciblant les individus en fonction de leurs caractéristiques va donc prendre une place de plus en plus importante. Dans le cadre des études présentées dans cette analyse, nous nous sommes concentrés sur un traitement antiviral correspondant aux caractéristiques « moyennes » des nouveaux traitements antiviraux : 85% de RVS dans les essais cliniques pour 12 semaines de traitements. Toutefois, le grand nombre de molécules à venir conduit à des recommandations de traitement de plus en plus complexes, faisant intervenir le génotype de

l'individu, son historique de traitement (présence ou non d'un antécédent de traitement), et la sévérité de la maladie (Association Française pour l'Etude du Foie 2015). L'évaluation de ces recommandations, particulièrement dans un contexte de concurrence entre les traitements commercialisés, va devenir un enjeu au cours des prochaines années.

L'utilisation de modèles stochastiques permet également d'évaluer l'importance de l'aléa dans la population, et de quantifier les risques de survenue de différents évènements dans la population. L'étude présentée au chapitre 5, portant sur l'estimation de probabilités d'évènements rares, en est un exemple. Le chapitre 5 présente différentes méthodes d'estimation de probabilité de survenue d'évènements rares dans un modèle probabiliste, avec pour application l'estimation d'une probabilité d'élimination du VHC chez les UDI en Île-de-France par une stratégie de TasP. D'autres exemples d'applications sont cités dans cet article : estimer la probabilité pour une épidémie de dépasser une taille donnée, ou de persister au-delà d'un certain horizon temporelle, etc. L'utilisation de modèles déterministes, dont les résultats représentent des trajectoires moyennes et ne prennent pas en compte l'aléa dans les trajectoires épidémiques, ne permettent pas ce type d'évaluation.

8.2.2 Obstacles et problèmes rencontrés

Le faible nombre d'articles utilisant l'approche individu-centrée pour modéliser l'épidémie de VHC chez les UDI peut s'expliquer par les problèmes rencontrés lors de la construction et de l'utilisation des modèles individu-centrés. Premièrement, la modélisation individu-centrée consistant à simuler un ensemble de trajectoires individuelles, les temps de calcul deviennent rapidement élevés. De plus, la nature stochastique de ce type de modèles implique d'effectuer un grand nombre de réplications pour assurer la convergence des résultats. Il est donc nécessaire d'avoir accès à des structures de calcul intensif. Pour les études présentées dans cette thèse, nous avons eu recours au centre de calcul intensif de l'Université de Lille 1. Le modèle a été codé en C++, un langage de bas niveau (c'est-à-dire proche du langage machine) permettant d'obtenir des temps de calculs rapides par rapport à l'utilisation de langages de haut niveau ou de logiciels spécifiques. Toutefois, même dans ces conditions, les temps d'exécution restaient relativement importants. A titre d'exemple, dans l'analyse coût-efficacité présentée au chapitre 6, les analyses présentées pour 6 scénarios ont été évalués. Pour chaque scénario, 250 populations ont été simulées (ce qui constitue un nombre relativement modeste de réplications), chacune d'entre elles consistant en 20 communautés de 524 UDI. Chaque jeu de simulations consiste donc à simuler les trajectoires de 16 millions d'individus. Nous avons restreint les analyses de sensibilité aux paramètres clés du modèle : le coût des traitements ; les taux de dépistage, de lien aux soins et de perte de vue, ainsi que l'incidence initiale, les paramètres liés à la réduction des risques et le taux de réinfection. Malgré cela, effectuer l'ensemble des simulations présentées dans cette étude a nécessité plus d'une semaine de temps de calcul.

Deuxièmement, il est difficile d'obtenir les données nécessaires à l'implémentation de ce type de modèle. Comme expliqué au chapitre 2, le principal intérêt de la modélisation individu-centrée réside dans la possibilité de prendre en compte les caractéristiques individuelles, et donc l'hétérogénéité de la population, ainsi que le réseau social. Les sources d'hétérogénéité sont nombreuses lorsqu'on s'intéresse à la problématique de la transmission du VHC chez les UDI. Par exemple, le taux de mortalité varie selon l'âge et le sexe de l'usager (Lopez et al. 2004). Autre exemple : les coinfections VIH/VHC et la consommation d'alcool accélèrent la progression de la maladie vers la cirrhose (Thein et al. 2008). Prendre en compte une telle hétérogénéité nécessiterait d'avoir des données individuelles et statistiques sur ces caractéristiques. De plus, les recommandations pour ce type de modèle sont d'utiliser des paramètres provenant de méta-analyses (Caro et al. 2012). Hors, particulièrement en ce qui concerne les UDI, une population difficile d'accès, ce type de données est difficile à obtenir. Les données relatives à la cascade de soins, comme le taux de dépistage ou de lien aux soins ont été estimés le plus souvent en utilisant des données non-publiées. Dans le cadre de la modélisation de la population UDI d'Île-de-France, ces données provenaient de l'enquête ANRS-Coquelicot (Jauffret-Roustide et al. 2006; Jauffret-Roustide et al. 2009), une enquête de prévalence conduite dans cinq grandes villes française (Lille, Strasbourg, Paris, Bordeaux et Marseille) (Vaissade et al. 2009). Dans le cadre de la modélisation de la population UDI de Montréal, les estimations ont été majoritairement effectuées à partir de données locales du réseau SurvUDI, un réseau de surveillance épidémiologique chez les UDI de Montréal (Leclerc et al. 2011), et du registre des maladies à déclaration obligatoire du Québec, l'hépatite C étant une maladie à déclaration obligatoire dans cette province. Les paramètres ont de plus parfois été estimés indirectement à partir de données provenant de ces enquêtes. C'est le cas notamment du taux de dépistage des UDI en France, qui a été estimé à partir de la date de dernier test connu chez les UDI non-infectés par le VHC dans l'enquête ANRS-Coquelicot (Jauffret-Roustide et al. 2006; Jauffret-Roustide et al. 2009)(voir chapitre 3). Le taux de lien aux soins a également été estimé à partir de l'évolution de la proportion d'individus liés aux soins entre 2006 et 2011 par calcul bayésien approché.

Les données nécessaires à la construction d'un modèle de réseau sont elles aussi difficiles à obtenir. Au Québec, une enquête portant sur les réseaux sociaux des UDI a permis d'utiliser des données locales (De 2007). Ces données sont toutefois individuelles : les participants ont été recrutés indépendamment dans les structures de réduction des risques à Montréal. Cet échantillonnage aléatoire a permis de recueillir des données individu-centrées sur le réseau des UDI, comme le nombre de partenaires d'injection des participants. Grâce à ces données, nous avons pu estimer à 12 le nombre moyen de partenaires d'injections (ou degré moyen) sur l'ensemble de la vie des individus. Ce paramètre est suffisant pour construire un modèle du type graphe aléatoire d'Erdős–Rényi, où chaque couple d'individu est relié avec une probabilité fixe , d étant le degré moyen et N la taille de la population (Erdős et al. 1959). Ce type de modèle reste toutefois très mélangeant, car il ne prend pas en compte l'attachement préférentiel dû à la répartition géographique des individus, le regroupement par affinité ou la transitivité des relations sociales. Ces phénomènes conduisent à l'apparition de certains motifs

dans le réseau comme des triangles ou des groupes d'individus fortement connectés. Mais l'observation de ce type de motifs et de leur densité dans le réseau social n'est pas possible avec des données centrées uniquement sur les individus, et nécessite des méthodes d'échantillonnage particulières pour obtenir les liens entre ces individus.

En Australie, une étude a été menée entre juillet 2005 et janvier 2006 chez les UDI de Melbourne afin de recueillir des données sur le réseau social des UDI (Rolls et al. 2011). Il s'agissait d'une étude par *Chain-Referral Sampling* (Biernacki et al. 1981). Ce type d'étude se déroule de la manière suivante : on commence par recruter un certain nombre d'individus (individus sources) dans la population pour participer à l'étude. A la fin de l'étude les participants sont invités à donner une liste de membres de leurs réseaux (dans le cas de l'étude de Melbourne, ce réseau est défini comme l'ensemble des partenaires d'injection dans les 3 derniers mois). Les enquêteurs peuvent alors retrouver ces membres afin de les recruter à leurs tours dans l'étude. Ce processus se répète jusqu'à recrutement du nombre d'individus requis.

Initialement développé pour permettre le recrutement de populations cachées dans des enquêtes épidémiologiques, ce type d'étude permet également de recueillir des données structurelles sur le réseau social de la population. Ces données peuvent ensuite être utilisées afin de modéliser le réseau social par un graphe aléatoire. En France, de telles données ne sont pas disponibles. Pour l'étude coût-efficacité présentée au chapitre 6, nous avons utilisé les données de l'étude de Melbourne pour construire un modèle de type « modèle de ménage » (Becker et al. 1995). Dans ce type de modèle, chaque individu appartient à un petit groupe (ménage) au sein duquel les individus ont une probabilité de connexion élevée. A l'inverse, deux individus appartenant à des groupes différents ont une probabilité faible d'être liés entre eux. Les paramètres du modèle (probabilité d'appartenance à chaque type de ménage et probabilités de connexions des individus) ont été estimés par calcul bayésien approché à partir du nombre d'occurrence de certains motifs dans l'étude de Melbourne (le nombre d'individus isolés, de couples isolés, d'arêtes et de triangles dans le graphe), et le diamètre du graphe, i.e. la plus grand distance possible entre deux individus.

8.2.3 Problèmes d'ordre méthodologique

L'utilisation de modèles individu-centrés pose également des problèmes d'ordre méthodologique. La transposition de certaines méthodes classiquement utilisées dans le cadre des modèles compartimentaux peut poser problème. Dans cette thèse, nous avons notamment abordé les problèmes liés à l'analyse de sensibilité probabiliste.

L'objectif de l'analyse de sensibilité est l'étude de l'impact de variations dans l'estimation des paramètres du modèle sur les résultats obtenus lors des simulations. L'analyse de sensibilité permet notamment d'estimer l'impact des incertitudes portant sur l'estimation des paramètres du modèle sur les résultats obtenus. Ces incertitudes peuvent avoir plusieurs sources. Les estimations des paramètres sont généralement effectuées à partir des résultats d'enquêtes épidémiologiques, à partir d'un échantillon de

la population, et donc ces estimations sont associées à un intervalle d'incertitude. Plusieurs études peuvent reporter différentes estimations, ou au contraire l'absence de données peut conduire à émettre une hypothèse à propos de la valeur du paramètre, hypothèse dont il faut évaluer l'impact sur les résultats.

L'une des méthodes rencontrée est l'utilisation de graphique de type « Tornado ». Il s'agit ici de définir une borne haute et une borne basse pour chaque paramètre, puis de simuler les trajectoires de l'épidémie pour chaque valeur haute et chaque valeur basse, paramètre par paramètre. L'amplitude des variations obtenues sur les sorties du modèle par rapport aux résultats obtenus avec les paramètres de référence est représenté pour chaque paramètre, lesquels sont classés par amplitude de variation décroissante. C'est la méthode que nous avons utilisée pour les études présentées au chapitre 3.

Une autre méthode consiste à calculer les indices de Sobol (Sobol 2001). Notons $X = (X^1, \dots, X^p)$ l'ensemble des paramètres du modèle, vus comme des variables aléatoires dont la distribution a été choisie pour refléter l'incertitude sur les valeurs des paramètres, et $Y = f(X)$ la valeur mesurée à l'issue des simulations du modèle. L'indice de Sobol d'ordre 1 pour le paramètre $i \in \{1, \dots, p\}$ est défini par : $S_i = \frac{Var(\mathbb{E}[Y|X_i])}{Var(Y)}$. Cet indice correspond donc à la part de la variance de Y expliquée par la variable X_i.

Comme le Tornado, les indices de Sobol permettent donc de quantifier l'impact de l'incertitude liée à un paramètre sur les résultats du modèle. Toutefois, à la différence du Tornado, les indices de sobol représentent une mesure de la variance, là où l'utilisation du Tornado ne permet qu'une mesure ponctuelle des valeurs aux bornes de l'intervalle d'incertitude, ce qui peut notamment poser problème lorsque Y n'a pas un comportement monotone par rapport au paramètre considéré.

Le calcul de ces indices n'a toutefois pas été beaucoup étudié dans le cadre de modèles stochastiques, c'est-à-dire lorsque pour des entrées X fixées, la valeur de Y peut malgré tout fluctuer. En effet, dans un tel cadre, l'aléa dû à la nature stochastique du modèle peut participer à la variance de Y, et perturber les estimations par des méthodes de Monte-Carlo classiquement utilisé pour le calcul des indices de Sobol (Saltelli et al. 2004). De plus, la nature stochastique du modèle entraîne des temps de simulation considérablement plus longs. On peut toutefois citer l'approche de Marrel *et al.* par méta-modèles (Marrel et al. 2012), c'est-à-dire en construisant, par régression, un modèle représentant le comportement moyen de Y afin de se ramener au cadre déterministe pour l'estimation de ces indices.

Au chapitre 7, nous proposons deux estimateurs alternatifs, non-paramétriques, pour calculer ces indices : l'un basé sur l'estimateur de Nadaraya-Watson de l'espérance conditionnelle $\mathbb{E}[Y|X_i]$ (Nadaraya 1964), l'autre basé sur la décomposition dans une base d'ondelettes de cette même espérance (Mallat 1989). Les résultats obtenus sur un exemple test classique en analyse de sensibilité, la fonction d'Ishigami sont prometteurs : la comparaison avec les résultats numériques obtenus par des estimateurs de Monte-Carlo classiques montre un biais plus important, mais un écart quadratique moyen moins élevé pour un nombre de simulations fixé.

8.3 Prolongements possibles

8.3.1 L'élimination du VHC : autres pistes de recherche

Les travaux présentés dans cette thèse démontrent que même sous l'hypothèse d'une amélioration importante de l'ensemble de la cascade de soins de l'hépatite C chronique garantissant un accès le plus large possible au traitement, une élimination du VHC de la population UDI en Île-de-France, définie comme l'atteinte d'une incidence nulle dans la population, est hautement improbable à moyen terme (10 ans). Nous l'avons évaluée, dans le chapitre 5, à 1.8%, avec pour hypothèse une amélioration de l'ensemble de la cascade de soins et un traitement délivré exactement selon les recommandations, sans possibilité de refus du patient ou de report pour causes médicales (troubles psychiatriques, comorbidités, etc.). L'élimination de la maladie en utilisant ce type de stratégie uniquement semble donc peu vraisemblable à moyen terme. Cette stratégie purement médicale a été complétée au chapitre 6 par l'inclusion d'interventions préventives, en améliorant l'accès au matériel stérile et à la substitution. Toutefois, comme nous l'avons évoqué précédemment, l'impact de cet ajout a été très limité et n'avait qu'une influence très faible sur le nombre d'infections, même en diminuant le délai de mise en place.

Ces résultats suggèrent que pour éliminer le VHC, des approches originales sont nécessaires. Premièrement, nous nous sommes focalisés sur l'amélioration des politiques de réduction des risques actuelles : accès au matériel d'injection stérile et aux traitements de substitution aux opiacés. D'autres mesures sont envisageables. L'introduction de salles de consommation à moindres risques, évoquées en introduction de cette thèse, est une possibilité. Ces structures expérimentées dans d'autres pays proposent d'accueillir les UDI afin de leur permettre la pratique de l'injection dans de bonnes conditions d'hygiène et en présence de personnel médical. Un méta-analyse regroupant des études sur le partage de seringues chez les UDI fréquentant des salles de consommation à moindre risque a conclu à une diminution de la probabilité de partage de seringue de 69% (Milloy et al. 2009). De plus, ces structures favorisent également l'accès aux traitements de substitution et favorise l'arrêt des injections (DeBeck et al. 2011), ce qui contribuerait également à diminuer le risque d'infection par le VHC dans la population en réduisant la période de temps pendant laquelle l'individu est susceptible d'être infecté. Une étude de modélisation, publiée en 2008 et portant sur la population d'UDI de Vancouver, et prenant en compte les infections par le VHC et le VHI et les coûts associés, a conclu que l'introduction de ces structures dans cette population permettrait d'économiser jusqu'à 18 millions de dollars canadiens pour 1175 années de vies gagnées 10 ans après leur introduction, pour 7 000 UDI au total dans la population (Bayoumi et al. 2008). Ce type de structure devrait ouvrir à la fin de l'année 2015 à Paris à titre expérimental et pour une durée de 6 ans (Assemblée Nationale 2014).

Une autre possibilité serait l'éducation à l'injection. Une étude cas-témoin a été menée dans 17 villes françaises entre 2011 et 2013. L'intervention consistait à mettre en place des sessions d'éducation à l'injection où des membres d'associations pouvaient observer la pratique de l'injection chez les usagers afin d'identifier leurs pratiques à risques et de les conseiller sur des pratiques d'injection sûres (Roux et

al. 2015). Cette étude a mis en évidence une diminution significative des pratiques à risques grâce à ce type d'interventions, de 44% initialement à 25% au bout de 6 mois. En complément avec les mesures de réduction des risques actuelles, cette mesure pourrait donc permettre d'atteindre un niveau de partage de matériel suffisamment faible pour avoir un impact sur le risque infectieux.

Hors réduction des risques, d'autres interventions pourraient être étudiées grâce au modèle. La recherche active d'individus infectés par l'utilisation du réseau social, par une stratégie de « contact tracing », au lieu d'un traitement initié de manière indépendante, est une possibilité. Cette méthode consiste à rechercher les individus infectés parmi les contacts (ici, les partenaires d'injection) des individus déjà diagnostiqués afin de maximiser les chances de détection de nouveaux cas (Eames et al. 2003). Une étude de modélisation portant sur une étude de modélisation à Melbourne (Rolls et al. 2013) a démontré qu'une stratégie consistant à rechercher et traiter systématiquement les contacts infectés des UDI initiant un traitement (contacts primaires) avec un nombre de traitement annuels limités, permettrait d'optimiser l'impact du traitement sur la transmission par rapport à un traitement distribués aléatoirement dans le population. A titre d'exemple, avec cette stratégie, l'incidence après 3 années de simulation obtenue en traitant 47/1000 UDI chaque année était identique à celle obtenue en traitant 35/1000 UDI annuellement. Etudier le coût-efficacité de stratégies de ce type pourrait constituer un prolongement de cette thèse.

8.3.2 Extensions du modèle et méthodologies

D'un point de vue méthodologique, plusieurs extensions du modèle sont envisageables. La principale d'entre elles concerne la modélisation du réseau de partenaires d'injection. Premièrement, les paramètres du modèle le plus abouti que nous avons utilisé, c'est-à-dire le modèle de ménages utilisé aux chapitres 5 et 6, n'ont pas pu être estimés à partir de données recueillies dans une population d'UDI en France. Pour évaluer une stratégie de type « contact tracing » mentionnée précédemment, il serait important d'avoir des données locales. Dans le cadre de ce travail de thèse, j'ai participé à la mise en place d'une enquête sur les réseaux sociaux d'UDI en Île-de-France, dirigée par Marie Jauffret-Roustide. Cette étude recrutera les UDI dans un CARUUD en Île-de-France par *Respondent-Drive Sampling* (Heckathorn, 1997). Dans ce type d'échantillonnage, similaire à ce qui a été effectué dans la population d'UDI de Melbourne, un ensemble d'individus sources est choisi dans la population d'étude (ici, les injecteurs actifs dans le dernier mois) pour participer à l'enquête. A la fin du questionnaire, comportant des questions sur leurs caractéristiques sociodémographiques et leurs habitudes d'injections, des coupons leurs sont distribués (ici, 3 coupons) afin qu'ils le remettent à leurs partenaires d'injection dans le dernier mois. Ces partenaires peuvent alors, à leur tour, venir participer à l'étude sur présentation du coupon. Le recueil des données pour cette étude est en cours.

Un problème intéressant est l'analyse de ce type de données de réseau pour la construction d'un modèle de graphe aléatoire. En effet, ce type d'échantillonnage est particulier, car il entraîne une censure du nombre de contacts (limité par le nombre de coupons distribués à chaque utilisateur) et ne permet de cartographier que partiellement le réseau, la part du réseau étudié étant dépendante du choix des

individus sources. Dans le cadre de modèles statistiques, des méthodes ont par contre été mises au point. Les modèles de graphes aléatoires exponentiels (ou ERGM) en sont un exemple (Holland et al. 1981). Dans ce type de modèle, utilisé par Rolls *et al.* pour la modélisation du réseau des partenaires d'injection des UDI de Melbourne (Rolls et al. 2013), on suppose que la structure du graphe est expliquée par un ensemble de statistiques (diamètre du graphe, occurrence d'un motif, etc.). L'idée est alors d'attribuer à l'ensemble des graphes de taille n (la taille de la population) une mesure de probabilité selon une famille exponentielle dépendant de ces statistiques, de la forme :

Avec Y le graphe aléatoire, y le graph observé, $s(y)$ un ensemble de statistiques, θ les paramètres du modèle et $c(\theta)$ une constante de renormalisation. L'inférence de θ spécifiquement à partir de données issues d'enquête de type *Respondent-Driven Sampling* a été étudiée (Pattison et al. 2013). Ce type de modèle se focalise sur les aspects statistiques, et peut échouer à reproduire certaines caractéristiques structurelles du réseau. L'utilisation de modèles probabilistes pourrait donc constituer une alternative. Le choix d'un modèle probabiliste pour représenter ce réseau, ainsi que l'inférence des paramètres, constituent un champ de recherche ouvert.

Enfin, dans toutes nos analyses, le réseau a été supposé statique en l'absence de données sur la dynamique des réseaux, c'est-à-dire la prise en compte des changements de partenaire d'injection qui se produisent au cours du temps. Cette dynamique pourrait avoir un impact sur la transmission du VHC n'a pas été beaucoup étudié, certains auteurs considérant même que le taux de changement de partenaire est suffisamment élevé pour considérer la population comme totalement mélangée (Hahn et al. 2009). Des enquêtes de terrain sont toutefois nécessaires pour recueillir des données sur ce phénomène.

9 Conclusion

Au cours de ce travail, nous sommes arrivés à deux conclusions principales à propos de l'épidémie de VHC chez les UDI en France.

Premièrement, chez les utilisateurs de drogues injectables, où la prévention de la transmission est l'un des objectifs du traitement, celui-ci doit être initié dès que possible, indépendamment de la sévérité de la fibrose hépatique, c'est-à-dire dès F0. Ceci permettrait d'avoir un impact très fort sur la transmission du VHC dans la population, en traitant les individus infectés avant qu'ils ne soient susceptibles de transmettre la maladie. Cette mesure entraînerait toutefois un coût important à supporter pour le système de santé, tout en ayant un impact modéré sur la mortalité associé à l'hépatite C dans cette population (i.e. coût-efficacité modérée). Afin d'arriver à diminuer fortement le nombre de complications associées à la maladie et d'être efficient, il est nécessaire d'optimiser la cascade de soins de l'hépatite C, en améliorant le dépistage, mais surtout les liens avec le système de soins et l'adhérence aux traitements. Une telle stratégie deviendrait alors coût-efficace.

Deuxièmement, ces mesures purement médicales ne seront pas suffisantes, au moins à moyen terme, pour éliminer l'hépatite C dans les populations d'UDI en France. L'accès au matériel stérile et traitements de substitution aux opiacés doit être maintenu à un haut niveau afin d'optimiser une stratégie de TasP, mais même une amélioration importante de l'accès à ces interventions ne permettrait pas d'éliminer le VHC. Pour cela, la recherche d'interventions alternatives, comme les salles de consommation à moindre risque, l'éducation à l'injection ou la prévention de l'initiation à l'injection, sont à privilégier.

L'utilisation de modèles individu-centrés permet donc de déterminer des axes prioritaires pour améliorer la santé des populations, en étudiant à la fois leur efficacité et leur efficience. Dans le cas d'une maladie comme l'hépatite C chronique, les conséquences sur la santé ne sont observables que sur le long terme. l'étude de l'impact de recommandations de traitement ou d'étude interventionnelles par des enquêtes épidémiologiques classiques est donc particulièrement difficile. La modélisation permet de synthétiser les connaissances actuelles sur le sujet afin d'orienter la prise de décision sur une base rationnelle, Toutefois, la construction et l'utilisation de ce type de modèles nécessite des données provenant de plusieurs disciplines (épidémiologie, sociologie, médecine) qui sont, dans le cas de population difficile d'accès comme les UDI, difficiles à obtenir. De plus, certaines méthodes restent encore à développer, notamment en ce qui concerne l'inférence des paramètres, la recherche d'une modélisation pertinente du réseau social, et l'analyse de sensibilité.

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