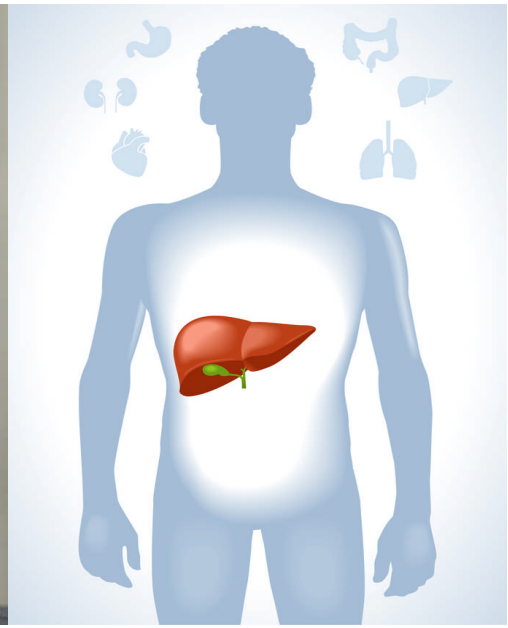
KCE REPORTS 173B

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

HÉPATITE C: DÉPISTAGE ET PRÉVENTION



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HEALTH TECHNOLOGY ASSESSMENT

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HÉPATITE C: DÉPISTAGE ET PRÉVENTION

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PRÉFACE

Voilà plus de 20 ans que le virus de l'hépatite C a été découvert et que les premiers tests sont disponibles. Ce virus s'installe généralement de manière chronique, avec peu de symptômes. Après de nombreuses années ou décennies d'infection asymptomatique, une maladie du foie, éventuellement sévère, peut parfois se développer.

Grâce à l'utilisation de tests plus sensibles, la propagation du virus via les produits sanguins s'est presque complètement arrêtée. L'approche des autres voies de propagation du virus, telles que l'usage de drogues injectables, a par contre été beaucoup moins fructueuse.

La détection de l'infection a du sens, notamment en raison du fait que des médicaments permettant d'éradiquer le virus sont disponibles. Par ailleurs, ces médicaments évoluent rapidement, entraînant qu'un nombre de plus en plus élevé de personnes peuvent être traitées avec succès. Cependant, vu la durée de traitement et les effets secondaires actuels, moins de la moitié des patients atteints d'hépatite C chronique commencent un traitement. Le fait que la plupart des nouvelles infections concernent les usagers de drogues injectables exige également que le traitement tienne compte de la situation psychosociale souvent difficile et de la grande mobilité de ces personnes.

La question suivante était posée au KCE: Y a-t-il, dans notre pays, beaucoup de personnes atteintes d'hépatite C chronique non diagnostiquées et le dépistage de l'hépatite C dans la population générale est-il utile et coût-efficace? Y a-t-il des groupes à risque spécifiques pour lesquels le dépistage ou une approche différente seraient plus judicieux?

Ce rapport se limite essentiellement à l'analyse de la littérature et à une description de la situation dans certains pays. Le potentiel du concept de traitement comme moyen de prévention de l'infection est également exploré en utilisant un modèle mathématique.

Nous espérons que vous apprécierez la lecture de ce rapport.

Jean-Pierre CLOSON
Directeur Général Adjoint

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RÉSUMÉ

INTRODUCTION

Le virus de l'hépatite C (VHC) se propage par le sang. L'infection devient chronique dans 75% des cas, souvent sans symptômes. Après de nombreuses années, une fibrose hépatique, une cirrhose ou un cancer du foie peuvent parfois se développer, particulièrement en association avec l'utilisation d'alcool ou de cannabis. Il n'existe actuellement aucun vaccin préventif.

Depuis la moitié des années 90, la propagation du virus via des produits sanguins s'est presque complètement arrêtée grâce à l'introduction de tests sensibles. L'approche des autres voies d'infection, tels que l'usage de drogues injectables (qui représentent plus de 80% des nouvelles infections) a été moins fructueuse. De nouvelles infections sont également observées après intervention médicale et chez les hommes porteur du VIH et ayant des relations sexuelles avec d'autres hommes. Les infections chroniques sont également plus observées chez les immigrés de première génération provenant de pays avec une prévalence plus élevée du VHC.

Des injections d'interféron pégylé alpha associées à de la ribavirine par voie orale pendant 6 mois permettent d'éradiquer le virus dans 80% des cas pour les infections de génotype 2/3. Pour les infections de génotype 1, le taux de réponse virale a récemment augmenté de 45% à 70% après l'ajout d'un inhibiteur de protéase (telaprevir ou beceprevir). Les effets secondaires (anémie, dépression) sont fréquents.

Une importante partie de la population belge a déjà été testée pour le VHC: 2,76 millions de personnes durant la période 2002-2009. Environ 2000 nouveaux cas d'hépatite C chronique ont été diagnostiqués chaque année, dont moins de la moitié ont commencé un traitement.

MÉTHODES ET OBJECTIFS

Nous avons analysé, à l'aide d'une revue systématique de la littérature, l'efficacité et le rapport coût-efficacité des programmes de dépistage des infections par le VHC dans la population générale ou dans des groupes cibles, de même que des programmes de prévention de l'infection par le VHC chez les usagers de drogues injectables (UDIs). Nous avons également eu l'opportunité d'utiliser un modèle mathématique dynamique analysant l'efficacité du traitement des UDIs actifs pour prévenir la transmission du VHC dans ce groupe.

Enfin, nous avons comparé les plans d'action et les recommandations pratiques à l'égard du dépistage et de la prévention de l'hépatite C en France, aux Pays-Bas, en Allemagne, au Royaume-Uni et aux Etats-Unis.

RÉSULTATS

Les programmes de dépistage de l'hépatite C

Les évaluations économiques

Dépistage de la population générale

Alors que les études du Japon et du Royaume-Uni concluent en faveur du dépistage, l'étude américaine, plus récente, ne recommande pas le dépistage de l'hépatite C dans la population générale. Des études en provenance du Japon ne peuvent cependant pas être transposées facilement à la situation belge car elles utilisent un taux de progression vers le cancer du foie plus élevé. Une très récente publication des Etats-Unis, parue lors de la finalisation de ce rapport, soutient le dépistage de cohortes nées durant la période 1945-1965. Cependant, ces résultats ne peuvent pas non plus être facilement transposés au contexte belge car plus de la moitié de ce groupe a déjà été testée pour le VHC en Belgique.

Dépistage des groupes cibles

De nombreuses études ont porté sur les usagers de drogues injectables. Des études du Royaume-Uni, de l'Italie et des Etats-Unis concluent en faveur du dépistage du VHC chez les UDIs. L'évaluation du Royaume-Uni ne devient toutefois plus favorable au dépistage de ce groupe si les coûts et les effets sont actualisés à un taux équivalent, comme conseillé dans leurs nouvelles directives. De plus, la modélisation des effets à long terme du traitement ne prend pas en compte l'impact potentiel de cofacteurs sur la progression de la maladie.

Recommandations de bonne pratique

Selon les recommandations de bonne pratique examinées, l'information de la population sur les facteurs de risque du VHC et l'offre de tests aux groupes à risque sont considérés comme bonne pratique clinique. Cependant, la définition des groupes à risque, basée sur des avis d'experts, est légèrement différente selon le pays étudié.

Il est peu probable que le volume des tests d'anticorps anti-VHC actuellement effectués en Belgique (plus de 673 000 tests chaque année) ne cible que les groupes à risque énumérés ci-dessous. Beaucoup de gynécologues, par exemple, testent en routine les femmes enceintes pour les anticorps anti-VHC.

Selon l'Association Belge pour l'Etude du Foie (BASL), les groupes à risque pour lesquels le dépistage de l'hépatite C est approprié sont:

- **Les personnes qui, à la suite d'événements médicaux en Belgique avant 01/07/1990 (date de début des tests anti-VHC du sang et de ses dérivés) ont eu: une transfusion sanguine, une intervention chirurgicale majeure (cardiaque, vasculaire, digestive, pulmonaire, gynéco-obstétrique, orthopédique, ...), un séjour en unité de soins intensifs, y compris les soins intensifs néonataux, un accouchement difficile, une hémorragie digestive, une transplantation de tissus, de cellules ou d'organes**
- **Les patients dialysés**
- **Les anciens utilisateurs de drogues par voie intraveineuse ou intranasale**
- **Les enfants nés de mères séropositives au VHC**
- **Les partenaires sexuels et les membres du ménage de patients infectés par le VHC**

- **Les personnes qui ont eu des tatouages, piercing, ou de l'acupuncture sans utilisation d'équipements à usage unique ou personnel**
- **Les personnes qui ont reçu des soins médicaux dans des pays à forte prévalence du VHC (Asie du Sud Est, Moyen Orient, Afrique, Amérique du Sud)**
- **Les personnes présentant une élévation inexpliquée des transaminases**
- **Les patients séropositifs au VIH ou au VHB**
- **Les personnes ayant une asthénie inexpliquée**
- **Les personnes ayant des antécédents d'ictère inexpliqué**

Dans tous les pays étudiés, le fait d'être un UDI n'est plus un critère d'exclusion au traitement de l'hépatite C. Cependant, la population des UDIs est très mobile, ce qui entrave le suivi d'un traitement de longue durée.

Les programmes de prévention de transmission du VHC chez les UDI

Les résultats de la revue de la littérature

Les programmes d'échange de seringues (PES) et de traitements substitutifs aux opiacés (TSO) sont maintenant disponibles dans tous les pays de l'UE.

La revue de la littérature a montré que ces programmes (PES et OST) ont un impact évident sur la transmission du VIH. Des études ayant un niveau de preuve faible suggèrent aussi que la combinaison des programmes PES et OST pourrait également réduire la transmission du VHC. Ces programmes sont considérés comme coût-efficace principalement en raison de leur effet sur la transmission du VIH.

Modèle mathématique sur le traitement comme moyen de prévention

L'objectif est de réduire la transmission du virus en traitant les individus à risque. La prévalence de base du VHC, la participation au traitement et le taux de réponse chez les UDI actifs ne sont actuellement pas suffisamment documentés en Belgique pour pouvoir tirer des conclusions de notre modèle. Les paramètres des essais sur le terrain actuellement en cours à l'étranger seront également utiles pour améliorer le modèle.

En 2015-2017, des associations de médicaments antiviraux hautement efficaces et mieux tolérées (sans interféron) devraient être disponibles. Si cela se concrétise, ces associations thérapeutiques seront susceptibles d'accroître la participation au traitement. Pour éviter le développement de résistance aux médicaments, l'importance d'une bonne observance au traitement va par contre augmenter. A condition de pouvoir contrôler les problèmes de résistance aux médicaments, cette évolution pourrait aussi améliorer les résultats du modèle sur le traitement des UDIs pour prévenir la transmission du VHC.

SYNTHÈSE

1. INTRODUCTION

1.1. L'hépatite C, le virus et la maladie

Tant les voies de transmission les plus courantes que les options thérapeutiques de l'hépatite C évoluent rapidement. Il a fallut attendre 1989 pour découvrir le virus de l'hépatite C (VHC), un virus à ARN responsable des cas d'hépatite dits « non-A non-B ». Peu de temps après (vers la moitié des années 90), des tests de dépistage des anticorps contre le virus ont été introduits pour enrayer la transmission du VHC via les produits sanguins, les transfusions ou les transplantations. Cet effort a été suivi par les diagnostics moléculaires, visant à permettre une détection et une quantification plus sensibles du virus ARN VHC, ainsi qu'à déterminer le génotype et le sous-type du VHC.

Le sang joue un rôle central dans la transmission du VHC, entraînant notamment un risque de transmission via des aiguilles ou du matériel contaminé dans un environnement médical ou non-médical.

Les nouvelles infections par le VHC sont souvent asymptomatiques. Environ un quart de toutes les nouvelles infections guérissent spontanément, généralement dans les 6 mois. On a montré que des variations du génome humain à proximité de la région de l'interleukine 28B sont prédictives de l'éradication du virus, en particulier dans les infections de génotype 1. Les sujets qui restent infectés (définis comme ayant un ARN VHC détectable) sont exposés à un risque accru de développer une pathologie hépatique des années ou même des décennies plus tard (fibrose, cirrhose, cancer du foie).

La plupart des modèles analysant le rapport coût-efficacité du traitement de l'hépatite C font l'hypothèse qu'après l'éradication du virus, la progression vers des maladies hépatiques devient identique à celle de la population générale. Cette hypothèse n'est probablement pas correcte. Malgré une réponse au traitement de l'hépatite C, des cofacteurs de risque de progression vers des maladies hépatiques peuvent toujours être présents (notamment la consommation d'alcool ou de cannabis). Un taux de progression plus élevé vers des maladies du foie par rapport à celui de

la population générale a récemment été confirmé par des données de suivi à long terme de patients ayant éradiqué le virus après traitement.

1.2. Epidémiologie de l'hépatite C en Belgique

Les voies de transmission

Dans les années 90, les patients ayant reçu des **produits sanguins ou une transplantation** avant la mise en place du système de dépistage des produits sanguins (vers la moitié des années 90) représentaient le principal groupe de patients atteints d'hépatite C chronique en Belgique. Entre 1991 et 2002, un nombre croissant de patients atteints d'hépatite C chronique était identifié chaque année en Belgique, souvent contaminés par le VHC de génotype 1. Le nombre de nouveaux cas identifiés s'est stabilisé autour de 2000 par an.

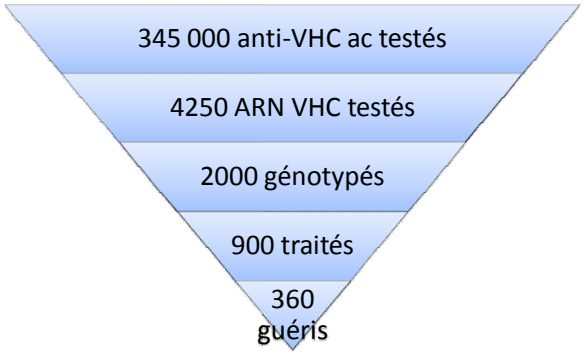
Au fil du temps, une grande partie des patients infectés par des produits sanguins avant 1991 ont été identifiés (ou sont décédés). La principale voie d'infection pour les nouveaux cas identifiés est alors devenue **l'utilisation de drogues injectables**. C'est surtout le partage d'aiguilles et d'autre matériel contaminé qui est associé à un risque élevé de transmission. Les usagers de drogues injectables (UDIs) sont typiquement contaminés par un VHC de sous-type 3a et de plus en plus par un VHC de sous-type 1a. Plus de 80% de l'ensemble des nouvelles infections par le VHC en Europe occidentale concernent désormais des UDIs. L'infection se produit généralement au cours de la première année (ou des premières années) d'usage de drogues injectables.

Un autre groupe à risque identifié au cours de la dernière décennie concerne les hommes séropositifs au virus de l'immunodéficience humaine ayant des rapports sexuels avec d'autres hommes (**VIH + HSH**). Des infections par un VHC de type 1 ou 4 ont également été observées chez des sujets masculins atteints de syphilis clinique et/ou de lymphogranulomatose vénérienne. Les **procédures médicales** continuent à représenter environ 10% de toutes les nouvelles infections par le VHC. Chez les femmes infectées, la **transmission de la mère à l'enfant** peut se produire à la naissance dans 3 à 5% des cas, surtout en cas de coïnfection par le VIH et une charge virale du VHC élevée. Enfin, de nouvelles infections par le VHC sont également détectées chez des immigrants de première génération provenant de pays à forte prévalence du VHC.

Prévalence

Selon une étude effectuée en 1993-1994, la séroprévalence du VHC en Belgique a été estimées entre 0.87 et 1%. Une étude plus récente, publiée en 2007, a trouvé une séroprévalence dans la salive pour seulement 0.12% de l'ensemble de la population en Flandre. En chiffres absolus, un tel pourcentage indiquerait qu'il y aurait probablement entre 10 000 et 75 000 patients chroniquement infectés en Belgique.

Figure 1: Sujets testés pour le VHC par rapport à ceux qui sont traités pour une hépatite C chronique par an en Belgique (2002-2009)



Ac: anticorps. Le nombre réel de patients traités peut être 10 à 20% plus élevés que dans la Figure 1 car, outre les patients couverts par l'assurance soins de santé obligatoire, d'autres patients bénéficient d'un remboursement de leur traitement par le CPAS, les programmes médicaux d'urgence ou le Ministère de la Justice. Ces données sont exclues des statistiques de l'INAMI/Pharmanet.

L'analyses des données de l'échantillon permanent de la population indique qu'une quart de la population belge (2.76 millions d'individus) a été testée pour des anticorps anti-VHC durant la période 2002-2009. Les données suggèrent que la plupart des femmes ont été testées pour les anticorps anti-VHC à chaque grossesse. Les données montrent aussi que 29% de la cohorte de naissance 1945-1965 a été testée au moins une fois durant la période 2002-2009. Nous pouvons donc raisonnablement

supposer que plus de 50% de cette cohorte de naissance a été testée au moins une fois pour des anticorps anti-VHC durant la période 1991-2011. Le nombre de tests réalisés et de traitements remboursés par l'institut national d'assurance maladie-invalidité (INAMI) montre que plus de 2000 patients positifs pour le VHC ARN sont identifiés chaque année en Belgique (Figure 1), dont moins de la moitié entame un traitement. Le nombre de patients génotypés et traités chaque année a subi un léger fléchissement après 2002.

1.3. Traitements

Des traitements par injection d'interféron alpha (IFN) à large spectre antiviral ont été développés. Des formules à action prolongée (pégylation, PegIFN) et l'adjonction de ribavirine (RBV) par voie orale ont amélioré l'efficacité des traitements. Le critère d'évaluation de l'efficacité est une réponse virologique soutenue (RVS), définie comme un ARN du VHC indétectable 6 mois après la fin du traitement. Avec l'association pegIFN et RBV, jusqu'à 80% des infections de génotype 2/3 (après 6 mois de traitement) et 45% des infections de génotype 1 (après 12 mois de traitement) affichaient une RVS dans les essais cliniques randomisés. L'adjonction d'un inhibiteur de la protéase (telaprevir ou bocepravir) au pegIFN/RBV a encore amélioré le taux de RVS, passant de 45% à 70% chez les patients infectés par un VHC de génotype 1, tandis que la durée du traitement a pu être raccourcie.

Malheureusement, les effets indésirables sont plus nombreux avec ce traitement combiné et dépassent ceux du traitment standard pegIFN/RBV. La fatigue et la dépression qui peuvent survenir chez les patients souffrant d'hépatite C chronique non traitée empirent fréquemment sous traitement par pegIFN/RBV. Ces effets secondaires et une situation psycho-sociale difficile des patients peuvent constituer un obstacle à la participation au traitement.

En 2011, les premiers cas d'élimination du VHC après un traitement constitué de l'association de deux antiviraux à action directe (AAD) sans pegIFN/RBV ont été présentés. En se basant sur ces données, les experts prévoient que des associations thérapeutiques mieux tolérées et plus efficaces seront disponibles à l'horizon 2015-2017, à condition bien sûr d'être en mesure de maîtriser les problèmes de résistance aux médicaments.

Table 1: Evolution des voies d'infection du VHC et du traitement

		Past	Today	Future ?
Route of infection		Blood products (G1,5) > IDU	IDU (G1a,3a) > HIV+ MSM (G1,4)	IDU (G1a>G3a) > HIV+ MSM (G1,4)
Treat-ment	Regimen	(peg)IFN + ribavirin G1,4:48 weeks G2,3:24 weeks	G1:pegIFN + ribavirin + telaprevir/ boceprevir: < 48 weeks	DAA combination, treatment as prevention?
	Respons rate (short term)	G1,4:45% SVR G2,3:80% SVR	G1:70% SVR	All G:> 80% SVR? Resistance?
	Side-effects	depression,anemia	+rash,+dysgeusia	few
	Uptake	low	low	high

IDU: usagers de drogues injectables (UDIs). G: génotype. HIV: virus de l'immunodéficience humaine (VIH). MSM: hommes ayant des relations sexuelles avec d'autres hommes (HSH). DAA: antiviraux à action directe (AAD). SVR: réponse virale soutenue (RVS).

2. OBJECTIFS ET MÉTHODES

Les objectifs du projet étaient les suivants :

- Documenter l'efficacité et le rapport coûts-efficacité des programmes de dépistage de l'hépatite C au sein de la population générale ou de groupes à risque spécifiques (excluant le dépistage des produits sanguins)
- Documenter l'efficacité et le rapport coûts-efficacité des programmes de prévention de la transmission de l'hépatite C chez les usagers de drogues injectables (UDIs)
- Décrire les recommandations pratiques et les plans d'action relatifs au dépistage et à la prévention de l'hépatite C réalisés à l'étranger (principalement dans les pays limitrophes)

Pour répondre aux deux premières questions, nous avons réalisé une revue systématique de la littérature. Pour évaluer l'efficacité des programmes, nous avons d'abord cherché des essais cliniques randomisés. Ensuite, comme les études sur les programmes de dépistage et de prévention exigent une foule d'informations émanant d'un vaste éventail de sources pour informer correctement les décideurs, nous avons également cherché des études de modélisation de l'efficacité de ces programmes. Pour évaluer le rapport coût-efficacité, nous avons cherché des évaluations économiques complètes comparant à la fois les coûts et les effets d'au moins deux interventions.

Nous avons également eu la possibilité d'utiliser un modèle mathématique dynamique portant sur l'efficacité du traitement des UDIs dans le but de prévenir la transmission du VHC. Ce modèle a été développé par N. Martin, co-auteur de ce rapport. Sur base de ce modèle, nous avons investigué l'efficacité théorique du traitement des UDIs actifs pour prévenir l'infection avec des paramètres basés autant que possible sur des données belges. Le résultat final était la prévalence du VHC. Les paramètres ont été obtenus à partir de la littérature ou d'avis d'experts belges en hépatite C et/ou en prise en charge des UDIs. Plusieurs hypothèses ont dû être formulées durant cette analyse. Les modèles antérieurs indiquaient que les résultats étaient surtout sensibles aux taux de RVS et de sortie des UDIs (incluant la cessation de la prise de drogues et le taux de mortalité des UDIs). Leur impact sur le résultat a dès lors été testé dans une analyse de sensibilité univariée de même que dans une analyse du pire et du meilleur scénario. Plusieurs scénarii sur la prévalence chronique de base du VHC (25%, 45%, et 65%), de même que sur les taux de traitement (5, 10, 20, et 40 par 1000 UDI annuellement) ont également été testés. En outre, un scénario sur un traitement hautement efficace et bien toléré a été modélisé, reflétant une vision optimiste du futur sur l'association de plusieurs agents antiviraux à action directe (AAD).

La description des plans d'action et des recommandations pratiques dans les autres pays s'est basée sur les sites internet d'instituts HTA ainsi que sur des contacts avec des institutions nationales officielles. Nous avons sélectionné la France, les Pays-Bas et l'Allemagne en raison de leur proximité géographique avec la Belgique. En outre, nous avons retenu les Etats-Unis et le Royaume-Uni (RU, y compris l'Ecosse) parce que ces pays avaient gradé le niveau de preuve de leurs recommandations.

3. RESULTATS

3.1. Revue de la littérature

Le nombre d'études primaires identifiées par la revue de la littérature est présenté dans la table 2. Seuls quelques rares RCT ont été identifiés. En conséquence, les recommandations reposent essentiellement sur les résultats d'études de modélisation de l'efficacité et du rapport coût-efficacité des programmes.

Table 2: Résultats de la revue de la littérature

Design	Dépistage	Mesures de prévention globales visant à réduire les conséquences liées à l'utilisation de drogues injectables***	Traitement des UDIs
Essais cliniques randomisés	0	4	2
Etudes de modélisation de l'efficacité	1*	4	3
Evaluations économiques	6**	4	3

**L'impact du dépistage n'a été testé que lors de l'analyse de sensibilité et peu de détails ont pu être obtenus, empêchant l'analyse de cette étude. ** Des groupes de population multiples, notamment la population en général et les UDIs ont parfois été étudiés dans une même évaluation économique. ***Ces mesures incluent notamment les programmes d'échange de seringues et les traitements de substitution aux opiacés.*

3.2. Les programmes de dépistage de l'hépatite C

3.2.1. Les évaluations économiques

Le dépistage du VHC dans la population générale

Diverses évaluations économiques ont estimé le rapport coût-efficacité du dépistage de l'ensemble de la population au Japon, au Royaume-Uni (RU) et aux USA. Si les études pour le Japon et le RU concluent en faveur du dépistage, en revanche, l'étude réalisée aux Etats-Unis ne recommande pas le dépistage du VHC dans la population générale. Alors que le présent rapport était en cours de finalisation, une seconde étude a été publiée pour les Etats-Unis, soutenant le dépistage des cohortes de naissance 1945-1965. Cependant, les auteurs ont utilisé une séroprévalence du VHC de 3.6% au sein de cette population et une proportion de 25% de personnes déjà testées. En Belgique, les estimations de séroprévalence sont inférieures (probablement comprises entre 0.1 et 1%) et la proportion de personnes déjà testées est, quant à elle, très probablement supérieure à 50%. En conséquence, ces résultats ne peuvent pas être transposés à la situation belge.

Le dépistage ciblé

Au RU, le dépistage du VHC parmi les **détenus** n'est pas considéré comme coût-efficace au seuil de £30 000 par année de vie en bonne santé si les coûts et les effets sont actualisés de manière égale, conformément aux dernières recommandations de NICE.

Les évaluations économiques réalisées au RU, en Italie et aux Etats-Unis concluent en faveur du dépistage des **UDIs** pour le VHC. Néanmoins, si des taux d'actualisation égaux avaient été utilisés dans l'étude réalisée au RU, comme recommandé dans leurs récentes directives, le dépistage n'aurait plus été considéré comme coût-efficace (au seuil du RU).

Dans le cas des patients bénéficiant de **services de prise en charge de la toxicomanie et de l'alcoolisme**, une évaluation économique appliquée au RU a conclu que le dépistage de ces patients est probablement coût-efficace par rapport à l'absence de dépistage (au seuil du RU). Cette étude n'a cependant pas testé l'impact de l'utilisation de taux d'actualisation égaux.

Une évaluation économique réalisée au Japon chez des patients présentant un **niveau élevé d'alanine aminotransférases**, ayant subi une **chirurgie** lourde ou ayant eu une **transfusion sanguine**, a conclu que le dépistage de ces patients était coût-efficace par rapport à l'absence de dépistage. Dans une étude italienne par contre, le dépistage des patients ayant subi une chirurgie n'était pas considéré comme coût-efficace. Une étude américaine sur le dépistage des **femmes enceintes** et de leurs enfants est parvenue à la conclusion que cette stratégie n'était pas coût-efficace par rapport à l'absence de dépistage. Pour les autres groupes à risque, aucune évaluation économique n'a été identifiée.

Discussion

Les plupart des études identifiées n'ont pas effectué d'analyse de sensibilité probabiliste pour traiter l'incertitude des paramètres. En général,

les taux de progression de la maladie variaient considérablement d'un modèle à l'autre. La modélisation de l'effet du traitement à long terme n'a pas tenu compte de l'impact potentiel de cofacteurs sur la progression de la maladie. La récente recommandation (il y a 5 ans) au RU d'appliquer des taux d'actualisation identiques à la place de taux différents aux coût et effets s'est révélée critique pour les résultats des études réalisées dans ce pays. De plus, les conclusions tirées pour des pays autres que la Belgique ne peuvent pas être transposés aisément à la situation belge. Par exemple, le taux d'évolution vers le cancer du foie est supérieur au Japon.

3.2.2. Recommandations de bonne pratique

Selon notre revue des recommandations de bonne pratique internationales, l'information de la population quant aux facteurs de risque du VHC et le fait de proposer un test de dépistage pour les groupes à risque sont considérées comme bonne pratique clinique. La définition, sur base d'avis d'expert, des groupes à risque dans les pays étudiés varie toutefois légèrement.

Groupes à risque pour lesquels le dépistage de l'hépatite C est recommandé selon la « Belgian Association for the Study of the Liver » (BASL):

- **Les sujets ayant subi, en Belgique avant le 01.07.1990 (date à laquelle a débuté le dépistage anti-VHC dans le sang et les dérivés sanguins), les épisodes médicaux suivants: transfusion sanguine, procédures chirurgicales lourdes (cardiaques, vasculaires, digestives, pulmonaires, gynécologiques, obstétriques, orthopédiques, etc.), séjour dans une unité de soins intensifs, y compris les soins intensifs néonataux, accouchement difficile, hémorragies digestives, greffe de tissu, de cellule ou d'organe**
- **Patients dialysés**
- **Les anciens toxicomanes par voie intraveineuse ou intranasale**
- **Les enfants nés de mères séropositives pour le VHC**
- **Les partenaires sexuels et les membres du foyer de patients ayant une infection VHC**
- **Les individus qui se sont fait tatouer, poser un piercing ou ayant suivi un traitement d'acupuncture sans utiliser d'aiguille à usage unique ou leur matériel personnel**
- **Les personnes ayant reçu des soins médicaux dans des pays à haute prévalence du VHC (Asie du Sud-est, Moyen-Orient, Afrique, Amérique du Sud)**
- **Les sujets présentant une hausse inexpliquée des transaminases**
- **Les patients séropositifs pour le VIH ou le VHB**
- **Les personnes souffrant d'asthénie inexpliquée**
- **Les patients ayant des antécédents d'ictère non élucidé**

Il est peu probable que le nombre élevé de tests des anticorps anti-VHC actuellement réalisés en Belgique (plus de 673 000 tests par an) ne cible que ces groupes à risque. Par exemple, beaucoup de gynécologues testent en routine toutes leurs patientes enceintes pour les anticorps anti-VHC.

Dans tous les pays étudiés, le fait d'être un UDI n'est plus un critère d'exclusion au traitement de l'hépatite C. Selon les recommandations de la BASL, une approche individuelle est toutefois recommandée. La population des UDIs tend à être assez mobile, rendant le suivi du traitement difficile. La décision de tester et traiter les UDIs ne devrait pas être prise sans la mise en place d'un système de soutien social et psychologique. Ce système de soutien devrait être flexible et mobile pour assurer le suivi de ces patients durant toute la période de traitement.

Le dépistage peut être justifié pour des raisons de surveillance épidémiologique. Cependant, cela doit se dérouler dans le contexte de protocoles de recherche scientifiquement valides.

L'assurance belge des soins de santé rembourse actuellement jusqu'à 4 tests ARN VHC par patient et par cycle de traitement. Aucun test n'est par contre couvert pour le contrôle des réinfections dans les groupes à risque. Ce problème n'a pas été étudié dans ce rapport mais a été soulevé par les experts du terrain. Les groupes à risque comme les UDIs et les VIH+ HSH restent exposés à un risque de réinfection après avoir obtenu une RVS (ou une élimination spontanée du virus). La surveillance des réinfections ne

peut cependant pas être effectuée en utilisant les tests d'anticorps anti-VHC puisque ceux-ci restent positifs (ou ne sont pas fiables en cas d'immunodéficience avancée). En conséquence, des tests réguliers (par exemple, annuels) peuvent être indiqués chez les sujets faisant l'objet d'une suspicion de réinfection. Ni le test ARN VHC ni le test antigène core du VHC (moins onéreux et plus facile à utiliser, mais légèrement moins sensible) pour la détection de réinfections n'ont cependant été évalués de manière critique dans le présent rapport.

3.3. Programmes de prévention de la transmission du VHC parmi les UDI

3.3.1. Les évaluations économiques

Des programmes d'échange d'aiguilles et de seringues (PES) ainsi que des programmes de traitement de substitution aux opiacés (TSO) sont désormais présents dans tous les pays de l'UE.

La revue de la littérature a montré que les PES et TSO ont un impact manifeste sur la transmission du VIH. Des études de faible niveau de preuve laissent également entendre que la combinaison de ces programmes réduit aussi la transmission du VHC. Ces programmes sont considérés comme coût-efficace, principalement en raison de leur effet sur la transmission du VIH.

3.3.2. Le modèle sur le traitement en tant que prévention

Le traitement en tant que prévention de la transmission du VHC chez les UDIs constitue un concept de recherche relativement nouveau. L'objectif est de réduire la transmission du virus en traitant les individus à risque. Notre modèle est basé sur l'hypothèse non testée que la probabilité de transmettre le VHC est indépendante de la volonté de l'UDI à se soumettre à un test ou à être traité.

Certains paramètres clés devraient être mieux documentés en Belgique avant de pouvoir tirer des conclusions de ce modèle:

- la prévalence de base de l'hépatite C chronique chez les UDIs,
- la proportion des UDIs actifs pouvant être traités chaque année,
- le taux de réponse au traitement parmi les UDIs actifs et les UDIs qui ne se trouvent pas sous TSO (insuffisamment documenté puisque les études sur le traitement des UDIs enrôlent souvent des patients triés sur le volet sous TSO et soignés dans des centres d'expertise).

Les paramètres des essais sur le terrain actuellement en cours à l'étranger seront également utiles pour améliorer le modèle.

Pour 2015-2017, on escompte l'arrivée d'associations hautement efficaces et mieux tolérées d'antiviraux (sans interféron). Si cela se concrétise, de telles associations thérapeutiques seront susceptibles d'accroître la participation au traitement. Cependant, l'observance du traitement peut devenir encore plus importante pour éviter le développement d'une résistance aux médicaments. A condition que l'on puisse maîtriser les problèmes de résistance médicamenteuse, cette évolution pourrait également améliorer les résultats de l'étude du traitement des UDIs pour prévenir la transmission du VHC.

RECOMMANDATIONS[a]

- **Sur base des études publiées de l'efficacité ou du rapport coût-efficacité, le dépistage du VHC dans la population générale n'est actuellement pas recommandé.**
- **Sur base des études publiées de l'efficacité ou du rapport coût-efficacité, le dépistage du VHC chez les usagers de drogues injectables pourrait être envisagé. Toutefois, la décision de tester et de traiter ne doit pas être prise sans qu'un soutien social et psychologique ne soit mis en place. Un tel système de soutien, flexible et mobile, devrait viser à améliorer la sécurité des traitements et leur efficacité.**
- **Compte tenu de l'important volume de tests sur les anticorps anti-VHC réalisés en Belgique, il est recommandé de rappeler à la communauté médicale la liste de l'Association Belge pour l'Etude du Foie (BASL) des indications appropriées pour les tests d'anticorps anti-VHC dans la pratique clinique.**

AGENDA DE RECHERCHE

- **Les estimations relatives à la séroprévalence et la prévalence du ARN VHC pour la population générale et les groupes à risque spécifiques (par exemple, les utilisateurs de drogues injectables) étant peu nombreuses, de nouvelles recherches épidémiologiques bien conçues sont indiquées.**
- **Plus de données sur la participation au traitement et sur le taux de réponse chez les usagers actifs de drogues injectables doivent également être collectées pour le contexte belge, et ce afin d'améliorer le modèle théorique relatif au traitement des UDIs en tant que prévention de la transmission du VHC.**
- **Les usagers de drogues injectables et les sujets homosexuels porteurs du VIH sont susceptibles de rester exposés à un risque de réinfection par le VHC après s'être débarassés d'une infection antérieure par le VHC. Actuellement, aucun test ne fait l'objet d'un remboursement pour cette indication. Il convient encore d'identifier le test le plus approprié et le plus coût-efficace dans cette indication.**

[a] Le KCE reste seul responsable des recommandations faites aux autorités publiques

SCIENTIFIC REPORT

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ALT	Alanine aminotransferase
CUA	Cost-utility analysis
CDSR	Cochrane database of systematic reviews
CEA	Cost-effectiveness analysis
CI	Confidence interval
CRD	Centre for reviews and dissemination
DAA	Directly acting antivirals
DARE	Database of abstracts of reviews of effects
EVR	Early virological response
HCC	Hepatocellular carcinoma
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IDU	Injecting drug user, a new proposed terminology is People who inject drugs (PWID)
INAHTA	International network of agencies for health technology assessment
IWS	Individual with surgery
QoL	Quality of life
LYG	Life-year gained
NHS EED	National health service economic evaluation database

NPV	Net present value
NSP	Needle and syringe program. Specific NSP programs requiring to exchange used needles for an equal number of new needles, also called “syringe-exchange” programs (SEP) are gathered under the term NSP in this report.
MMT	Methadone maintenance therapy
MSM	Men who have sex with men
OST	Opioid substitution treatment, often this is MMT
PCR	Polymerase chain reaction
PPP	Purchasing power parities
QALY	Quality adjusted life year
SVR	Sustained virological response

1. BACKGROUND AND STUDY OBJECTIVES

1.1. Hepatitis C, the virus and the disease

1.1.1. The virus

Hepatitis C is caused by the hepatitis C virus (HCV), a virus of the Flaviridae family.[1] Until its etiologic agent was described in 1989, hepatitis C was formerly defined as non-A, non-B hepatitis.[2] The 9.6 kb single-strand ribonucleic acid (RNA) genome codes for proteins such as core, envelope 1 and 2, protease and RNA-dependent RNA polymerase. The presence of the virus can be detected and quantified based on its antigens, for example the core antigen, or even more sensitive, based on its RNA. Both target amplification (such as polymerase chain reaction (PCR)) and signal amplification techniques (such as branched deoxyribonucleic acid (DNA) assay) are available to detect and quantify the RNA genome. Using population sequencing, reverse hybridization of PCR amplicons, or restriction fragment length polymorphism, the strains of HCV can be classified into 6 genotypes (1-6) and a large number of subtypes.[3, 4] The effectiveness and cost-effectiveness of the molecular tests for HCV was reviewed and included in the annex to the KCE report no 20 on molecular diagnosis in Belgium.[5] Screening for HCV infection was not considered in that review.

1.1.2. Transmission of the virus

HCV is mainly transmitted using blood. There is no preventive vaccine available against hepatitis C.

Transfusion, blood products and transplantation

Before the screening of blood for HCV was introduced in 1990, blood transfusions and organ transplants formed a main source of infections (often HCV genotype 1b). This has been reduced nearly 100%. Also clotting factor concentrates prepared from plasma pools were a source of infection before inactivation procedures were introduced.

Injection drug use

Nowadays, in the Western world, about 80 to 90% of new infections with HCV (often subtypes 1a and 3a) are seen in injection/intravenous drug users (IDU).[4, 6] Transmission occurs mostly via shared needles and other drug injection paraphernalia. The **cumulative incidence of HCV infection after the first year of injecting drug use has been estimated at 27.6%.**[7] Overall at least 50% of the IDU population in Western Europe is chronically infected with HCV.[8]

Intranasal transmission

Another less frequent route of infection is intranasal transmission using contaminated drug sniffing implements such as straws, used to snort cocaine, heroin, and other powdered drugs.[9]

Sexual transmision

Sex with an HCV-infected person is typically an inefficient means of transmission. However, outbreaks of apparently sexually transmitted hepatitis C virus (HCV) infection, often genotype 1 or 4, among human immunodeficiency virus (HIV) positive gay and bisexual men have been reported more frequently after the year 2002, especially after having contracted clinical syphilis and/or lymphogranuloma venereum rectitis.[10-12] No significant overlap with the IDU population, and risk of transmission, seems to exist.

Tattooing

Non-sterile injection practices as used sometimes for tattooing have been reported as a possible route of infection, but a recent study in the Netherlands showed this is no longer a route of HCV infection.[13]

Nosocomial transmission

Nosocomial transmissions through medical acts (e.g.hemodialysis, endoscopy, colonoscopy) or needlestick accidents still occur.[14]

Childbirth

The overall risk of vertical transmission of HCV is 3 to 5%, with a high rate of spontaneous clearance (25-50%). HIV-coinfection and a high viral load are associated with higher vertical transmission rates. Elective caesarean section and withholding breastfeeding do not reduce vertical

transmission.[4, 15] The currently available treatments cannot be used in pregnant women nor in infants.

Unknown route

In many patients the route of HCV infection cannot be well documented.

The importance of migration

First-generation non-Western migrants are more likely to test positive for HCV.[16]

1.1.3. The immune response

With the exception of (few) patients who do not have a functional humoral immune system (can occur e.g. in case of HIV infection), antibodies will be formed against HCV antigens and these will become detectable on average 2 to 8 weeks after the infection. Acute infections with HCV may be associated with jaundice but often remain undetected. Infections with HCV become chronic (defined as persistence of HCV RNA for > 6 months) in about 74% of cases.[3] Spontaneous clearance can be seen even after 12 months from time to time. The host genetic make-up was found to be predictive of spontaneous (and interferon-based treatment induced) clearance of HCV infection. In particular, single nucleotide polymorphisms in the human genome near the interleukin-28B region have been shown to be predictive of clearance, especially in genotype 1 infections (IL28B locus, encoding for the antiviral cytokine interferon lambda).[17-21]

Antibodies can be detected using cheap and easy to use enzyme immunoassays (EIAs) that were optimized for sensitivity. Antibodies will remain detectable lifelong if the infection becomes chronic, but will also remain detectable for longer periods in those who succeed to clear the virus (negative HCV RNA test). In case of a positive EIA test and a negative HCV RNA test it can be impossible to discriminate a false positive EIA test from a cleared HCV infection. No tests are available to measure the cellular immune response to HCV in a clinical routine setting.

HCV re-infection after having cleared HCV is possible in individuals with continued high risk behaviour. Follow-up monitoring for re-infection cannot be performed using anti-HCV antibody tests as these tests remain positive after cure (or not reliable in case of advanced immune suppression). The HCV-RNA test or maybe the HCV core antigen test (cheaper and easier to use, but slightly less sensitive[22, 23]) could be options that need further evaluation in this indication.

1.1.4. A high worldwide prevalence and burden of disease

Hepatitis C is still a neglected disease in many countries, hampering the quantification of the burden of disease.[24] Based on seroprevalence data (using EIA) it has been estimated that currently 160 to 200 million people worldwide are infected with the hepatitis C virus, corresponding to a global seroprevalence of approximately 3%.[25, 26] The prognosis for those chronically infected is highly variable, with many never experiencing any adverse long-term effects at all.[27] The onset of liver disease is insidious, with most patients remaining largely asymptomatic for the first two or three decades after infection. A large proportion of infected people are unaware of their infection (non-diagnosed cases) but may have non-specific symptoms like fatigue. HCV-related mental health problems are also seen. Extrahepatic manifestations of the disease include cryoglobulinaemia and membranous glomerulonephritis. After 20 years of chronic infection, about 15 to 20% of the patients will develop serious liver complications (compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma), resulting in morbidity and mortality. The proportion of patients with advanced liver disease is higher when the duration of infection is longer and when co-factors are present. Continued use of alcohol or cannabis in patients with chronic hepatitis C accelerates the progression to liver fibrosis.[28] Smoking may worsen liver inflammation. Coffee use may decrease the fibrosis progression. Transition to cirrhosis is accelerated after the age of 45 years. Diabetes mellitus, and co-infection with HIV or HBV are also co-factors. Hepatitis C is reported as the main underlying cause of liver transplantation in many countries. The severity of the liver inflammation and the liver fibrosis stage is usually established via liver biopsy. Mild chronic hepatitis C is characterised by no fibrosis or a low fibrosis score (F0/F1 Metavir). Elastography (Fibroscan) is a non-invasive technique that allows to identify subjects without significant liver fibrosis but it does not allow accurate discrimination between advanced (F3/F4 Metavir) and moderate levels of fibrosis (F2 Metavir).

1.2. Treatment of chronic hepatitis C

1.2.1. Treatment and its effect on short term and long term outcomes

Detection of patients with hepatitis C is important because the virus can be cleared with treatment. The proportion of patients who could clear HCV with injections of interferon alpha (IFN) monotherapy was low. More patients successfully cleared the virus when IFN was combined with ribavirin (RBV). The efficacy of this combination treatment was further enhanced when IFN was provided as a pegylated formulation (Peg-IFN), which results in a longer duration of action after a single injection. Combination therapy of Peg-IFN with RBV is currently considered first choice for patients with moderate to severe chronic hepatitis C. Patients should preferably completely abstain from alcohol consumption during treatment.[29] Slight improvements in quality of life have been reported in patients with a sustained virological response (SVR) compared with non-SVR patients. Comparisons of SVR versus non-SVR patients show a better long term prognosis in SVR patients.[30] However, such responder analyses are not a valid method to estimate the effect size of an intervention. Patients who are treated are expected to have a reduced incidence of cirrhosis and HCC and a lower mortality, compared with a similar group of untreated subjects. No RCTs have demonstrated an effect for hard endpoints. This key expectation could also not yet be confirmed in a matched-cohort analysis (using propensity score).[31]

The response to treatment using (Peg)IFN-alpha is associated with single nucleotide polymorphisms in the human genome near the interleukin-28B region and the HCV genotype. Depending on the HCV genotype, treatment duration is 48 (genotype 1, 4, 5 and 6) or 24 weeks (genotypes 2 and 3).[32] Specific guidance to stop treatment early is based on intermediate HCV-RNA measurements (e.g. early virological response, EVR, at week 12).[29] In clinical trials, treated patients can expect a sustained virological response, (SVR i.e. the absence of detectable HCV RNA in plasma 6 months after the end of treatment) in 46 to 52% (genotype 1) or in 78 to 80% (genotypes 2-3).[32] Both pegylated interferon alpha and ribavirin are associated with adverse events (mostly anaemia for ribavirin and fatigue, muscle pain or depressive symptoms for interferon-alpha in over half of the treated patients[33]), compromising the tolerance and compliance with the treatment. Neutropenia may also occur.

1.2.2. Peg-IFN/RBV cost-effective compared to IFN/RBV

According to a recent review,[34] the findings of the published economic evaluations of pegylated versus non-pegylated interferon for chronic hepatitis C were rather consistent. On average, combining pegylated interferon with ribavirin was cost-effective compared to the combination non-pegylated interferon plus ribavirin. The incremental cost-effectiveness ratio (ICER) of using pegylated interferon plus ribavirin in patients with genotypes 2 and 3 was lower (i.e. better) than that for patients with other genotypes. Treating patients with “mild” chronic hepatitis C (i.e. patients with minimal to mild fibrosis and mild inflammation) was associated with higher ICERs than treating patients with “moderate” chronic hepatitis C (i.e. patients with elevated alanine aminotransferase).

Likewise, Shepherd et al.[35] report that in all studies investigated, pegylated interferon alfa-2b plus ribavirin was associated with favourable ICERs when compared with non-pegylated interferon plus ribavirin. Tailored treatment according to bodyweight dosing and circumscribed treatment for different genotypes improves ICERs further.[36]

In the study by Shepherd, the primary outcome modelled is SVR. The benefits of treatment are assumed to result only from changing patients’ virological status, in that an SVR is regarded as a cure. Patients achieving an SVR enter the remission health state where they face no risk of progressive liver disease and are subjected only to general population mortality risks. Moreover an SVR is associated with an increase in health related quality of life, hence a higher utility value. Patients who do not respond to treatment follow the pattern of disease progression as described by the natural history model. The optimistic assumption used in the model is that patients showing SVR become identical to the general population for all variables defining liver disease progression. These co-factors include smoking (associated with liver inflammation), alcohol and cannabis use (both associated with liver fibrosis progression[28]). In active IDUs and ex-IDUs on stable opioid substitution treatment (OST) these co-factors may remain present after successful treatment of HCV, resulting in a remaining increased risk of liver disease when compared with the general population. The model might therefore overestimate the treatment

effect and its cost-effectiveness when applied to populations such as IDUs. A recent paper confirmed excess liver-related morbidity of chronic hepatitis C patients, who achieve a sustained viral response.[37]

1.2.3. Advances in treatment

Two directly acting antivirals (DAAs) telaprevir and boceprevir were FDA and EMA approved in 2011. Both are protease inhibitors for use in combination with PegIFN plus ribavirin. They increase SVR rates for genotype 1 patients from about 50% to about 70% in clinical trials, with somewhat higher SVR rates for subtype 1b infections compared with 1a. Accurate subtyping of genotype 1 therefore becomes important, also for the monitoring of possible antiviral resistance to DAA drugs.[29] The effect of IL28B seems to be less important when DAAs are used. Subtype 3a infections are not an indication for these two agents. Both agents tend to worsen the anemia, associated with ribavirin treatment. The addition of telaprevir can reduce the treatment duration to 24 weeks in many patients. However it frequently causes anorectal itching or pain and sometimes a severe rash. It needs to be taken with 20g of fat. Boceprevir treatment may cause dysgeusia.

Many other direct-acting antivirals (DAAs) are in clinical development.[21] In a more distant future, combinations of well tolerated antivirals without interferon alfa could drastically change the patient acceptance of hepatitis C treatment. On April 2, 2011 at the EASL conference in Berlin, Prof Anna Lok presented the first 4 cases of virological response using an interferon/ribavirin free combination of DAAs (BMS790052+BMS650032). Experts expect such well-tolerated DAA combination treatments to reach the market in 2015-2017.[38] If realized, treatment uptake could increase dramatically.

1.2.4. A low real-life treatment uptake

It should be noted that many patients with chronic hepatitis C are not eligible for most phase 3 trials evaluating new antiviral treatments, because of co-infection, co-morbidities or expected non-adherence. Therefore the SVRs observed in RCTs cannot be extrapolated as such to all subjects identified as HCV positive in screening programs. SVRs may thus heavily depend on the patients selection criteria used in clinical practice.

Community-based studies in HCV antibody-positive individuals report rates of HCV treatment (ribavirin + (peg)interferon) uptake as low as 1.1% in Australia[39] and 33% in Denmark.[40] A US community-based study reports treatment discontinuation rates of 68% (prior to 48 weeks) for genotype 1 and of 34% and 41% (prior to 24 weeks) for genotypes 2 and 3, respectively.[41] Consequently, data from routine medical practice report lower rates of sustained virologic response compared with RCTs: up to 20%, 52% and 43% for genotypes 1, 2 and 3, respectively.[41] Somewhat higher SVRs of 44% (genotype 1) and 72% (genotype 2/3) were reported more recently for a cohort treated in Denmark. Younger age was significant predictor of response.[42] In an analysis of treated patients in the Benelux, ex-IDUs, both those on OST or not, showed similar compliance and response to treatment with interferon and ribavirin compared with other patients.[43]

1.2.5. Treatment of chronic hepatitis C in injection drug users

Injection drug users (IDUs) are a heterogeneous population with various social backgrounds and consisting of opioid users (the largest subgroup), stimulants or a mix of both types of drugs. The average frequency of injecting and the associated risks of HCV transmission likely differ between subgroups. However, this is not well-documented. In some countries it has been estimated that up to half of the opioid users enter opioid substitution treatment (OST) programs. Access to the other IDUs is often limited to needle and syringe programs (NSP) or through outreach workers. In IDUs, death from overdose (1% to 2% per year) is much more important in the short term compared with liver-related complications. Many IDUs have co-morbidities and excessive alcohol use that may need to be controlled first before the patient is ready to cope with the result of an HCV test and possibly start HCV infection treatment.[44]

Until 2001 international guidelines did not support the treatment of IDUs for hepatitis C. All EU countries now have OST/NSP in place. More recently, revised guidelines support the treatment of IDUs who fulfil specific criteria. The 2011 practice guidelines of the European Association for Study of the Liver (EASL) recommend an individualised approach after evaluation and close monitoring by an experienced multidisciplinary team of hepatologists and addictologists.[29] Despite this change in approach, treatment uptake has remained quite low. Physicians are concerned about the risk of

reinfection, the high rates of concomitant alcohol abuse, the high frequency of concomitant mental health issues. Reported SVR rates in IDUs in general are similar to non-IDU chronic hepatitis C patients.[6] Most published studies were conducted in patients on OST. Very few published data are available for treating active IDU (opioid and non-opioid IDU).

Individuals using NSP or OST should be provided with information on hepatitis C, the transmission of hepatitis C among IDUs and the possibility of being tested and treated. There is a consensus that OST should first be optimized before treatment of HCV is started, as side-effects overlap. Psychoeducation (in group), starting 2 weeks before IFN for at least 5 weekly sessions improved treatment results.[45] In selected individuals, preventive antidepressant therapy may be added to IFN-based treatment.[29]

The concept of hepatitis C treatment as prevention of HCV transmission is discussed separately.

1.3. Hepatitis C in Belgium

1.3.1. Chronic hepatitis C, cirrhosis, HCC, and liver transplantation in Belgium

In Belgium, up to 30% of patients waiting for a liver transplant are infected with HCV. Forty percent (40%) of end-stage cirrhosis is due to hepatitis C. In southern Belgium, 44% of 57 HCC cases were associated with HCV infection.[46] Among 131 new diagnoses of HCC in 14 Belgian centres in 2003 (HepCar Registry database), cirrhosis was present in 120 patients (92%). The aetiology of the underlying liver disease was: HCV (41%, n=54), HBV (17%, n=22), alcoholic liver disease (30%, n=39) and miscellaneous (12%, n=16).[47]

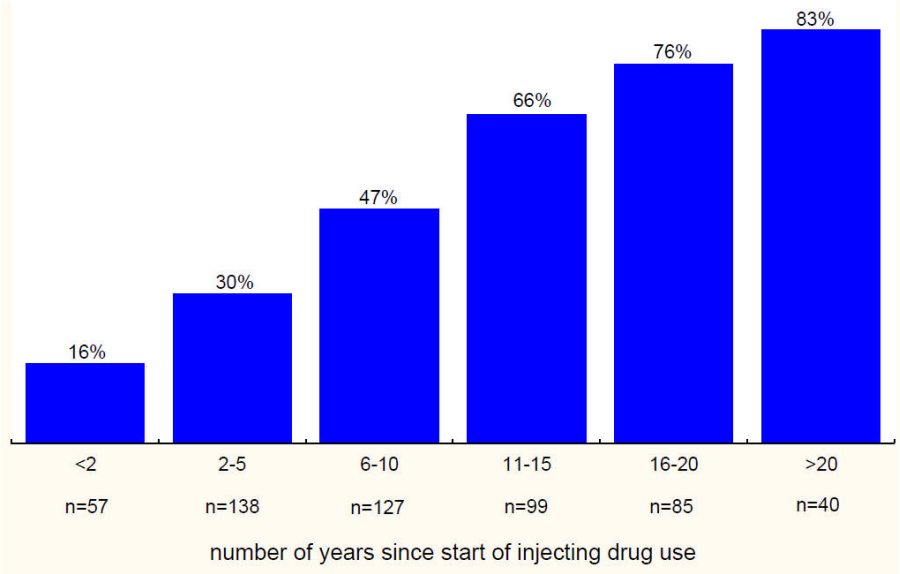
1.3.2. Seroprevalence data suggest a growing concentration of HCV infection in risk groups

Screening for HCV of the blood products in Belgium was introduced July 1, 1990. (KCE report 134, www.kce.fgov.be).[48] The seroprevalence of HCV (positive EIA test result) in Belgium has been estimated at **0.87%-1%** of the population (or extrapolated to Belgium, about 93 000-107 000 individuals).[49-52] These data are all based on a single seroprevalence study dating back to 1993-94 and performed on hospital residual blood samples of the Flemish population.[49] A more recent study in the Flanders region reports a lower HCV prevalence rate of only **0.12%** (or extrapolated to Belgium 12 500 individuals, range 9000 to 40 000), based on saliva testing.[53] Study participation in the latter survey was about a third and was based on the reply to a regular mail. It is clear that homeless, institutionalized or encarcerated individuals may not be reached using this approach. Consequently, only a subset of IDUs may thus have been reached, leading to an underestimation of the overall seroprevalence of hepatitis C. The data suggest however that hepatitis C prevalence is quite low in the mainstream population in Flandres, and consequently population wide screening may not be very effective. In comparison, in France, between 1994 and 2004, the anti-HCV prevalence for adults aged 20-59 years may have decreased from 1.05 (95% confidence interval 0.75-1.34) to 0.71 (0.52-0.97).[54]

The prevalence of hepatitis C antibodies in Belgian prisons has been estimated at 7.5 % in 2006.[55] About 76% of imprisoned drug injectors seeking healthcare tested positive for anti-HCV antibodies according to a 2004 report for Belgium.[56]

In 2004-2005, blood samples were collected from injecting drug users at treatment centers all over Belgium. A seroprevalence rate (anti-HCV antibody positive) of 50% (286 / 569) was reported for ever injection drug users and 61% (205 / 335) for those sharing their injection equipment. Sharing of sniffing equipment could not be determined as transmission route. Only 17% of the HCV positive drug users had ever received medical treatment for it.[56] The mean age was 33 in a random subsample of 147 testing positive for anti-HCV antibodies that was analysed for HCV-RNA. In 98 subjects (67%) the samples tested positive for HCV-RNA.[57]

Figure 1.1: Anti-HCV seroprevalence by number of years since start of injecting drug use, Belgium, 2004-2005.



Source: Plasschaert et al, 2004[56]

The 2011 systematic review published in the Lancet[8] reports for Belgium a hepatitis C seroprevalence in people who inject drugs of 55%. This is the unweighted mean of two percentages (27% and 82.7%) reported for the year 2008 (http://www.emcdda.europa.eu/publications/country-overviews/be) and needs to be interpreted with caution. The 27% seropositivity (17 out of 63) was seen in a subset of the 166 IDUs being treated in 2008 in a residential care setting (De Sleutel) where the physician judged HCV testing to be appropriate after discussion with the individual. It is important to note that De Sleutel provides residential care to IDUs and therefore serves a somewhat different IDU population compared with low threshold services (e.g. Free Clinic Antwerp) where the aim is harm reduction. The **82.7%** was the **proportion of IDUs testing positive for anti-HCV antibodies at The Free Clinic Antwerp** in 2008.

Based on the limited data available there seems to be no clear trend in seroprevalence rates over the last 10 years for HCV in IDUs in Belgium. The proportion of IDUs testing positive for anti-HCV antibodies at De Sleutel remained around a third of the IDUs tested per year in the period 1994 to 2010. However, in the small **subgroup of IDUs aged over 34 years tested at the Sleutel the seroprevalence remained at around 66%** for the same period (data kindly provided by G Lombaert, De Sleutel). From 2001 to 2004 about 79% of the IDUs tested positive at the Free Clinic Antwerp (on average 264 IDUs were tested per year), which is similar to the 82.7% reported for 2008.

For the French speaking community a **67%** seroprevalence rate was reported for IDUs willing to be tested and treated.[56] Data for 2010 from project Lama, Brussels, show that among 494 IDUs under follow-up, 281 individuals had been tested for anti-HCV antibodies, and 150 tested positive (**53%**). HCV-RNA testing had been performed in 72, often in the context of possible treatment. Most recent data show a negative HCV-RNA test in 36 individuals, consisting of 18 subjects with a spontaneous clearance (25%), 10 with SVR and 8 with EVR (personal communication Jerry Wérenne).

In Luxemburg (not the Belgian province), a recent multicenter study found a seroprevalence in IDU of 81% for HCV (218/268, 95%CI=[77; 86]), 29% for HBV, 2.5% for HIV and 57% for HAV and in non-injecting drug users 19% for HCV, 9% for HBV, 5% for HIV-1 and 66% for HAV. Prisoners showed the highest rates for all infections. Age, imprisonment and setting of recruitment were statistically associated with HCV seropositivity.[58]

1.3.3. Belgian guidelines for management of hepatitis C

The Belgian Association for the Study of the Liver, has published two practice guidelines for the treatment of hepatitis C: one general[59] and one specific for treating injection drug users.[60]

According to the BASL, screening for hepatitis C is appropriate in the following risk groups:

- Persons who had following medical events in Belgium before 01.07.1990, starting date of anti-HCV testing of blood and blood derivatives:
  - o blood transfusion

  - major surgical procedures (cardiac, vascular, digestive, pulmonary, gynaeco-obstetric, orthopaedic,…)
  - stay in intensive care unit including neonatal intensive care
  - difficult parturition
  - digestive bleeding
  - tissue, cell or organ transplantation
- Dialysis patients
- Persons who were drugs users by intravenous or intranasal route
- Children from mothers seropositive for HCV
- Sexual partners and household members of patients with HCV
- Persons who had tattoos, piercing, acupuncture without use of single use or personal equipment
- Persons who had medical care in countries with high prevalence of HCV (South East Asia, Middle East, Africa, South America)
- Persons with unexplained elevations of transaminases
- Patients seropositive for HIV or HBV
- Persons with unexplained asthenia
- Persons with history of unexplained jaundice

1.3.4. A high volume of opportunistic testing for anti-HCV antibodies in Belgium

Based on the RIZIV/INAMI data of reimbursed acts, the annual number of anti-HCV antibody tests in Belgium increased steadily to reach **672 798 tests in 2008** (data for 2009 are still incomplete). This corresponds for 2009 to a direct cost at 25% of about 1.3 million euro, or at 100% of 5.2 million euro. This corresponds to about 8 euro per test. Many anti-HCV antibody tests are done routinely (e.g. pre-op, pregnancy) and are not targeted.

Table 1.1 : Annual number of anti-HCV antibody tests in Belgium

Année	Code	Cases	Expenses
1995	551154_551165	154496	455 944 .53 €
1996	551154_551165	261908	786 115 .64 €
1997	551154_551165	308021	888 404 .77 €
1998	551154_551165	362006	1 081 690 .01 €
1999	551154_551165	393408	1 198 746 .60 €
2000	551154_551165	464529	974 984 .30 €
2001	551154_551165	504250	837 981 .13 €
2002	551154_551165	526696	882 223 .39 €
2003	551154_551165	564895	977 214 .66 €
2004	551154_551165	650584	1 138 487 .45 €
2005	551154_551165	644627	1 128 085 .93 €
2006	551154_551165	649092	1 148 356.03 €
2007	551154_551165	646760	1 177 019.44 €
2008	551154_551165	672798	1 244 619.86 €
2009	551154_551165	673817	1 300 000.00 e

In Belgium, registered inhabitants in principle have a compulsory health insurance provided by one of the seven national sickness funds and funded by social security contributions withhold on wages and earned incomes. For all sickness funds Health care reimbursement data of their members are joined into a large database at the IMA (Intermutualistisch Agentschap). From this population a sample of 1/40 was selected among subjects aged 65 or younger (random selection stratified for age and sex) and a sample of 1/20 among subjects of 66 years and older (random selection stratified for age and sex). This sample contains about 300 000 individuals and was started in 2002. The database was updated every year since and is referred to as “permanente steekproef or échantillon permanent” (PS/EP). For all the individuals in the sample also demographic and socio-economic information is updated, in addition to the detailed information on health care expenditures.

Based on the permanent population sample of reimbursed activities for Belgium it can be estimated that about **2.76 million different subjects** (a quarter of the total population) have been tested for anti-HCV in Belgium during the 2002-2009 period. This includes 590 000 subjects born before 1945, 820 000 subjects born 1945-1965 and 1 353 000 subjects born after 1965. The number of women tested was similar to the number of men except for individuals born after 1965 where nearly twice as many women were tested. In contrast to men, most women born after 1965 had multiple tests over the 8 year period. The number of excess tests in women (over men) was similar to the expected number of pregnancies over this period, suggesting repeat testing at each pregnancy of most if not all women.

For the birth cohort 1945-1965, 29% of the subjects were tested at least once for HCV in the 2002-2009 period. As additional subjects from this birth cohort were likely tested in 1991-2001 or in 2010-2011, it is reasonable to assume that over half of this birth cohort has been tested for anti-HCV antibodies (situation end of 2011).

The 2002-2009 statistics show that 2.76 million subjects were tested over an 8 year period. This corresponds to about 345 000 different subjects each year. One should take into account this is an the underestimation as it only considers individuals who are registered at one of the seven national sickness funds. We thus miss part of the tests performed in some at risk groups and the tests performed for blood donation.

The number of patients in Belgium for whom a qualitative HCV molecular test (to confirm positive serology) was reimbursed by RIZIV/INAMI in the period 2002-2007 was 25 560, or on average about 4250 subjects per year. These data suggest **a positivity rate of 1.23% (4250/345 000) of individuals tested with an EAI anti-HCV test**. This seems to be in agreement with preliminary data collected by the Institute of Public Health of mainly hospital-based laboratories showing a rate of positive anti-HCV tests for 2008 between 1% and 6% with some outliers on either side[a].

[a] data kindly provided by G. Muyldermans, WIV

1.3.5. Number of chronic hepatitis C patients considered for treatment each year.

Different sources of information were used to estimate the number of new cases of chronic hepatitis C identified each year in Belgium.

Hepatitis C is an infection that must be notified to the health authorities in Belgium. The health inspectors from the communities collect this information. From contacts with these sources, about **1000 new cases** of hepatitis C were reported annually the last years. Underreporting is a problem. Since 2009 hepatitis C must no longer be notified in Flanders.

The HCV genotyping test is performed when a HCV-RNA positive patient is considered for treatment. The summary statistics of the centres for molecular diagnosis in Belgium show that **2018 patients had a HCV genotyping test during the year 2003** (Feb 1, 2003 to Jan 31, 2004). This is about half of the 4250 subjects tested each year for HCV-RNA after a positive antibody test. If we assume that most subjects testing positive for HCV-RNA will have an HCV genotyping test, about 50% will have a negative HCV-RNA test result. These subjects either have a false positive serology result or could clear the virus spontaneously. The fraction of the total population undergoing HCV genotyping in Belgium in 2003 was in line with the number of HCV genotyping tests in France (population about 6x higher), where this number increased to 11 605 in 2003. The HCV seroprevalence in France is probably similar to Belgium.

In Belgium, the HCV genotyping test has meanwhile been introduced into the nomenclature of reimbursed activities (RIZIV/INAMI). **For 2009 a total of 1613 genotyping tests were reimbursed** (maximum one test per patient). Together with a decreasing number of treatments initiated (see below) these data suggest a decrease in the number of new patients identified and considered for treatment, despite the steady increase in the volume of anti-HCV tests.

1.3.6. Number of chronic hepatitis C patients treated each year

Reimbursed prescriptions of treatment for hepatitis C are another source of data. In Belgium, antiviral treatment for hepatitis C is fully reimbursed in patients with elevated liver enzymes (ALT). The need for a Metavir fibrosis stage of F2 or greater was removed as a criterium for reimbursement AND pegylated interferon replaced non-pegylated interferon. The numbers of

treated subjects were obtained from Farmanet and population sample data. “Ribavirin (Copegus® or Rebetol®)” is specific for the treatment of hepatitis C patients. The number of **ongoing treatments decreased from 1605 patients in 2005 to 1111 patients in 2008**, confirming the decrease seen in the number of genotyping tests. According to the data from the population sample 5440 patients received reimbursement for ribavirin in the period 2002-2007, or on average **900 patients starting treatment per year**. These numbers are to be increased with patients participating in clinical trials and patients without regular social security with treatment costs covered by CPAS-OCMW, the Ministry of Justice, or by "medical need" programs not included in the Farmanet statistics.

1.3.7. Relation between number of patients identified, genotyped, treated and SVR.

In 2004, hepatologists genotyped about two thirds of newly consulting patients with hepatitis C and started treatment in about two thirds of those genotyped (2018 genotyped in 2003 decreasing to 1613 in 2009). It has been reported that of all patients seen in Belgium by a hepatologist for treatment of hepatitis C 16% will finally be cleared of the infection. This proportion of **16% is based on 40% of newly consulting patients starting treatment and a 40% overall SVR rate**.[61] This suggests about 360 patients per year cleared their HCV infection after treatment.

1.3.8. Changes in epidemiology of hepatitis C after 1992

The estimates presented are in part based on a report by Gerard,[62] who studied a total of 1726 patients testing HCV-RNA positive during the 1992-2002 period at the Center for Molecular Diagnosis (CMD) in Liège, Belgium. In addition, a pilot observational study[63] was performed in 2004 in 9 Belgian hepatology centres (not including UZ Gasthuisberg, Clin. Univ. Saint-Luc or UZ Ghent) including 318 newly consulting patients with hepatitis C. Of these patients 50% had been diagnosed during the previous 12 months, and 212 (66%) were genotyped. In 47% of all patients (or 70% 47/66 of patients genotyped) treatment was planned.

In the CMD of Liege, the number of identified subjects per year doubled between 1992 and 2002.[62] **The increase was mainly due to subjects who reported injection drug use as risk factor** (mainly subtype 3a and increasingly subtype 1a), whereas the yearly number of subjects identified with a blood transfusion prior to 1990 (mainly genotype 1b, also genotype 5) remained about stable. In 2004 post-transfusion hepatitis C patients represented 24% of newly consulting patients in 9 hepatology centres, whereas more patients (27%) had IDU as risk factor.[63] **Most of the new infections with HCV today in Belgium are believed to occur through injecting drug use, and often during the first year(s) of drug use.**

As the spread of HCV subtype 3a seems to have reached a steady state in IDUs, it is expected that subtype 1a infections will become the most frequent subtype.[64, 65] A smaller group (8.7%[62] and 11%[63]) of subjects reported an invasive medical procedure as risk factor. This transmission route seems to favour genotype 2 infections.[66] Genotype 4 was dominant in patients with undefined mode of infection and has also been seen more frequently in tattooed drug users.[65] De Maeght et al.[63] report that the circumstances of HCV detection were fortuitous in most subjects seen by the hepatologists (65%). Hepatologists report that new HCV infections in Belgium are also increasingly seen in HIV-infected gay and bisexual men after having contracted clinical syphilis and/or lymphogranuloma venereum rectitis[10] The annual incidence of HCV infection in an Antwerp population of HIV-infected MSM rose steadily from 0.2% in 2001 to 1.51% in 2008, and then peaked to 2.9% in 2009. For 60 episodes (87%), another STI (mainly syphilis and lymphogranuloma venereum) had been diagnosed within the six months before the diagnosis of HCV infection. All but one patients with available genotyping (n=54) were found to be infected with the difficult to-treat HCV genotypes 1 or 4.[12]

1.3.9. Belgian initiatives for prevention and care in IDUs

Injection drug use is currently the primary risk factor for HCV infection in Belgium. Prevention measures of injection drug use and prevention of transmission in (starting) injection drug users are essential[67] Starting opioid injection users in Belgium are 20 years old on average.[68]

In Belgium, a large patchwork of treatment settings exists, also with regard to the specific methods of treatment used. Different types of statutory regulations and financial rules co-exist. Often several authorities are involved at the same time and this leads sometimes to a lack of clarity in terms of the division of competencies.[69]

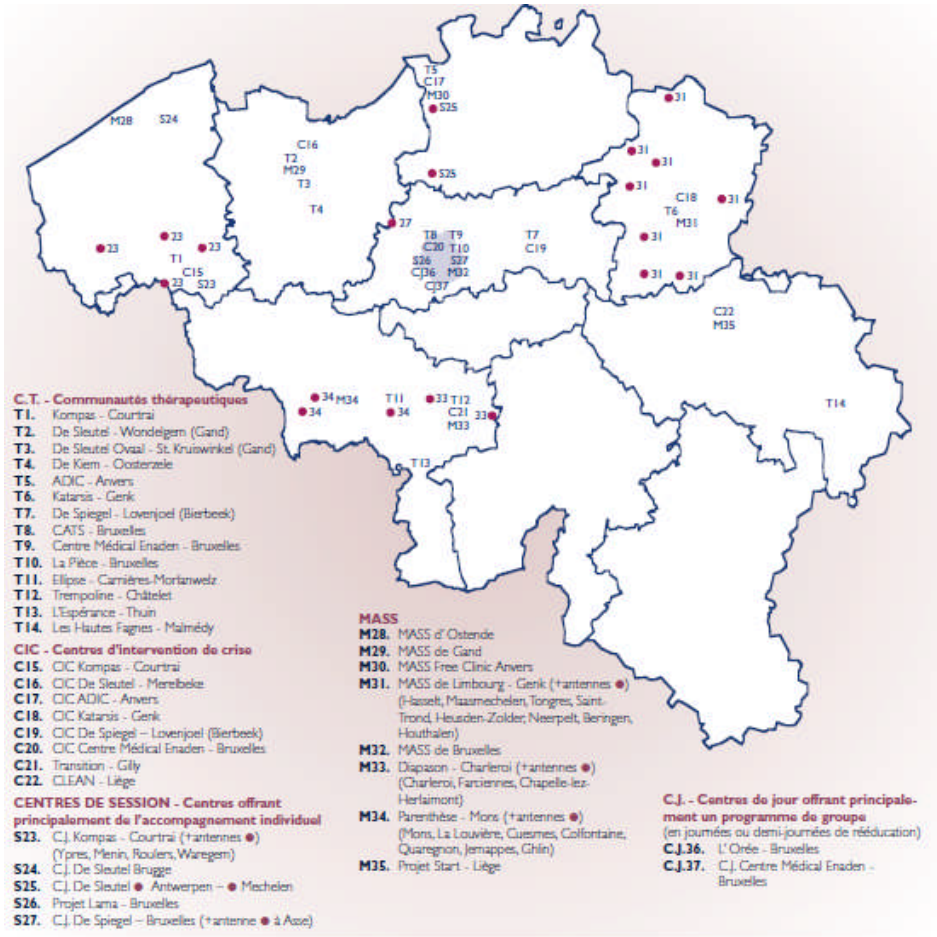
Several early initiatives have been created, following growing awareness of drug use related harm in Belgium, e.g. Free Clinic in 1973, De Sleutel in

1974, Projet Lama in 1983, albeit rooted in distinct approaches towards drug dependence. In 1995, a Federal Action Plan resulted in the creation of a large variety of specialized treatment centres for (mainly illegal) drug addiction. A number of these centres have gradually entered into a so-called 'revalidation agreement' with the National Institute for Invalidity and Health Insurance (RIZIV/INAMI) and consequently fall under the authority of the federal policy level. These centres are often referred to as the 'specialised substance abuse treatment centres with RIZIV/INAMI convention'.

The treatment options financed using these RIZIV/INAMI conventions include residential care (for acute crisis situations, as well as therapeutic communities) and ambulatory care services. These consist of ambulatory day-care centres and centres for medical and social care of drug addicts (Medisch-sociale opvangcentra voor verslaafden, MSOC's; Maisons d'accueil socio-sanitaire pour usagers de drogues, MASS, created in 1997). The total annual RIZIV/INAMI budget for these conventions currently amounts to €44.3 million (data provided by INAMI/RIZIV). Vaccination of non-infected IDUs against hepatitis B is however not covered under these conventions.

The location of the centres (in 2000) for drug addiction management and financed by INAMI/RIZIV convention is given below (annual report 2000 RIZIV/INAMI). According to figure 1.2, there seems to be a lack of centres in the provinces of Namur and Luxemburg. Meanwhile a few more centres were added, e.g. in Namur.

Figure 1.2: Centres for drug addiction management financed by INAMI/RIZIV convention.



Source: Annual report 2000 (INAMI/RIZIV)

Situation in 2000: in the Walloon Region many specialized treatment centres receive an optional grant from the Walloon Region government.

In addition, relatively smaller amounts are provided by agreements on safety and prevention between the Ministry of Internal Affairs and the cities. This budget is spent for activities aimed to manage medical and social problems associated with drug abuse (eg outreach workers).

Needle and syringe programs (NSP) are organised and financed by the communities in Belgium.[69] The five MSOCs in the five provinces in Flandres have an integrated needle and syringe program (Spuitenruil), financed by the Flemish Community using a convenant.[70] Sterile syringes and related injection equipment are spread among users. For the whole Flemish Community, 598 731 syringes were distributed (Windelinckx 2008). In some provincies also pharmacies provide syringes to IDU but absence of financing remains an issue. Also some organized outreach workers are partner of NSP (Spuitenruil). In the French Community the needle exchange program is under the coordination of the NGO Modus Vivendi.[69] It is available in 5 cities (Brussels, Charleroi, Liege, Dinant and Arlon) and proposes sterile syringes and all related injection equipment to drug users in determined places (needle exchange desks) or through mobile structures (street educators, mobile desks in recreational settings or events). In 2007, the amount of distributed syringes through NSP in the French Community was around 319 707.

Because of the unique expertise (eg for IDU related wound care) IDUs coming from all social classes make use of the MSOC services. For many IDUs with social integration problems the MSOC in practice will provide most of the medical services generally offered by GPs.

A second group of service providers are specialized substance abuse units in psychiatric or general hospitals. These treatment centres follow the same general regulations as other hospitals and are therefore mostly subject to federal legislation. Communities have however certain competencies on the matter (e.g. quality assurance).[69]

A third group consists of Centres for Mental Health Care, some of which specialized in the treatment of drug problems. The Communities of Belgium are responsible for these centres but due to historical and pragmatic reasons, in the French-speaking part of Belgium the responsibility has been transferred from the French Community to the Walloon Region (COCOF for the Brussels Region).[69]

Also the general practitioners or psychiatrists provide medical care to IDUs.

1.3.10. Opioid substitution therapy in Belgium

Methadon and other substitution treatments have been prescribed in Belgium since the mid-1970s, by a small number of private physicians in Brussels.[71] According to Picard,[72] about 500 drug users were on maintenance treatment in the early 1980s. A total of 270 000 prescriptions of methadone were made in 2010.[73]

In 2008, 13 737 individuals received methadone sirop or capsules (typically delivered for a period of one week), an increase with 828 (6%) over 2007. Of these subjects 3365 resided in Flandres, 8171 in the Walloon region and 2201 in Brussels.[74] The cities with large number of methadone users other than Brussels are Liège (1249), Charleroi (1024), Antwerp (427) and Ghent (377).

In the Flemish Community, most methadone (maintenance) programmes are being provided by low threshold drug services, offering a pluridisciplinairy approach to a wide variety of drug users seeking help. Also the outpatient treatment centers of De Sleutel provide substitution therapy, although always within a global medical-psychological-social approach, combining substitution with counseling and guiding activities. In smaller towns and rural areas, if existing at all, methadone is being prescribed by GPs under the supervision of drug services.

In the French Community, a broad range of services (low threshold services, GPs, outpatient specialized units, mental health facilities) offer access to methadone. SSMG- ALTO (Walloon region) and RAT (Réseau d'Aide aux Toxicomanes, in Brussels) are networks of primary care general practitioners giving care to drug users in the French speaking part of Belgium.

General practitioners account for the majority of methadone prescriptions in Brussels and the French speaking community whereas in Flandres this is about a third.[68] The MSOCs in Flandres provide services to about 3000 to 3500 persons per year and methadone prescriptions for about 2500 individuals each year[b].

[b] www.free-clinic.be

In the different settings where IDUs are seen, screening for hepatitis C and referral for management is possible and may be offered, but this is currently not done in a standard way. Belgian guidelines have been proposed to individualise start of treatment in cases of mild hepatitis C.[75] Guidelines have also been published for the treatment of hepatitis C patients after substance abuse.[60] Treatment of ex-IDUs on OST or not and with similar proportions of genotype 1 and 3 resulted in similar SVR rates as obtained in other patient groups.[43] No evaluation of the treatment of active IDUs as prevention has been conducted.

1.3.11. Summary of situation in Belgium

- No recent anti-HCV seroprevalence data are available for Belgium, but in Flandres the prevalence may be low (0.12%) in the mainstream population.
- Over 25% of the total population has been tested for anti-HCV since 2002 and probably about 1.23% of these individuals were tested for HCV-RNA after a positive anti-HCV antibody test. About half of these patients were genotyped, indicating a positive HCV-RNA test result and an interest to know the HCV genotype.
- Based on data sources that changed over time, the number of HCV-RNA positive subjects detected during the first decade of HCV testing (1992-2002) increased to over 2000 subjects per year but this trend seems to be reversed during the period 2003-2009.
- This more recent decreasing trend is reflected in the number of ongoing treatments: 1605 patients in 2005 versus 1111 patients in 2008. About 900 patients started treatment each year (2002 to 2007) and probably 360 patients per year cleared the infection because of the treatment.
- In Western Europe, 80 to 90% of new HCV infections are now seen in IDUs. Among IDUs in Belgium, the proportion of genotype 3a infections decreases while the frequency of genotype 1a infections increases. Also HIV-infected gay and bisexual men are at increased risk of HCV infection.
- Experienced multidisciplinary teams of hepatologists and addictologists are not yet standard practise when IDUs are tested for HCV and considered for treatment in Belgium.

1.4. Screening for hepatitis C

1.4.1. Terminology and objectives

Screening is the examination or the application of a test to asymptomatic people in order to distinguish people likely to have a disease from those unlikely. The aim is to detect disease or risk factors for disease in an early stage (pre-symptomatic or preclinical stage) to enable earlier intervention. Persons with positive or suspicious findings must then be referred to their physicians for diagnosis and necessary treatment.[76] Several types of screening exist. Mass/population screening relates to the large-scale screening of whole population groups while selective/case-finding screening concerns the screening of selected high-risk groups in the population.[76]

A further distinction is to be made between screening programs and opportunistic screening activities. Opportunistic screening usually occurs when a person who is presenting to the health system for another reason is asked a question or offered a test in order to detect the presence or confirm the absence of a specific condition. A population-based screening program is one in which screening is systematically offered by invitation to a defined, identifiable population; this requires a means of identifying and inviting the target population, for example through a population register.[77]

Even if screening has the advantage of enabling early intervention, potential harms should also be taken into account. These harms mainly concern unnecessary investigation, treatment of false positive results (a very low risk with current HCV-RNA tests) and a false sense of security caused by false negative results, which may even delay final diagnosis.[77]

In contrast with other countries (e.g. in France[78]), Belgium has no formally organised strategy to screen specific populations for hepatitis C (except HCV screening of blood/organ products, introduced on July 1, 1990)[48] and the question of establishing an HCV screening program is raised. Well established criteria exist to determine if a screening program should be carried out. These criteria were adapted in 2009 by the UK national Screening Committee and are summarized in Table 1.2.

Table 1.2 : Criteria for efficient screening programs[79, 80]

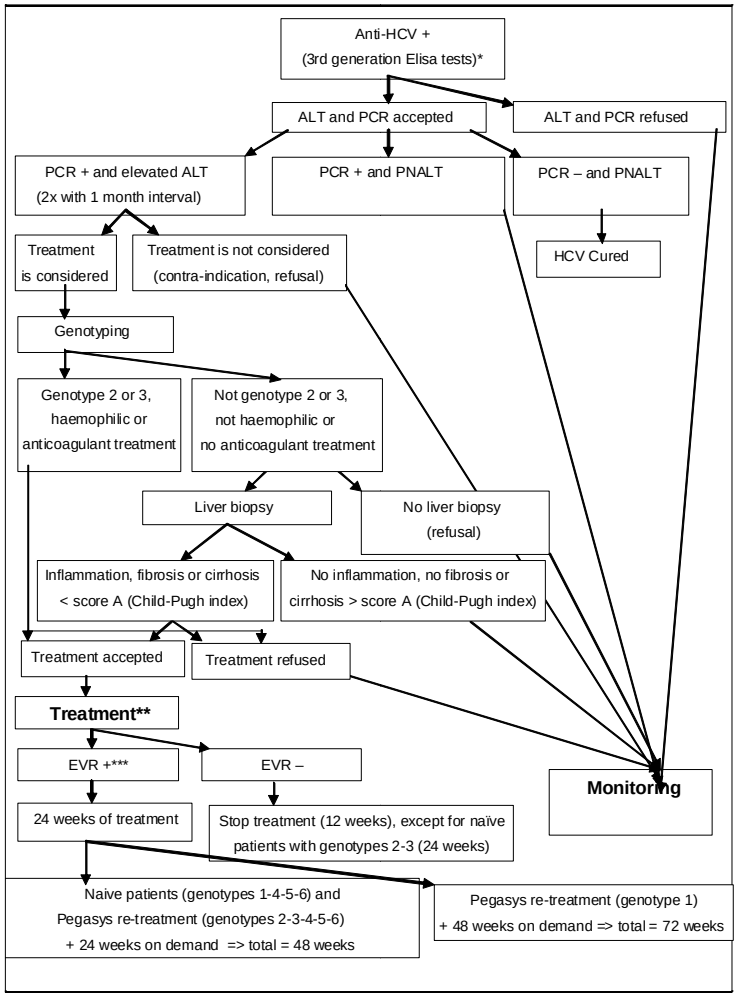
Condition	Important public health problem Natural history and epidemiology well understood
Screening test	Simple, safe, precise and acceptable to the general population Existence of a precise diagnostic process following a positive test (algorithm)
Treatment	Lead to better outcomes than treatment provided at the point of clinical diagnosis
Program	Provide value for money

Source: Karnon 2007; National screening committee 2011[76, 77]

1.4.2. Screening tests and diagnostic process

Screening for hepatitis C infection can be done using the detection of antigen, HCV-RNA or anti-HCV antibodies. The setting will define the test that is most appropriate for screening. For screening of the blood supply, detection of HCV-RNA is more sensitive as the test is already positive when no antibodies are detectable yet. For screening of other populations for chronic infection, the EIA anti-HCV antibody tests are the least expensive and have a high sensitivity. Detection of anti-HCV antibodies as used in seroprevalence surveys does however not distinguish between ongoing and cleared infections and false-positive results. Therefore confirmation of infection is necessary.

Figure 1.3: Algorithm for HCV diagnostic and treatment according to Belgian reimbursement criteria



*Legend to figure 1.3: *In some persons (blood donors, immunosuppressive patients), the PCR test is performed directly. **No EVR test for genotypes 2 and 3 ***HCV-RNA negative for re-treatments and under 1% of baseline value for naive patients. ALT = Alanine aminotransferase ; HCV = hepatitis C virus; PCR = Polymerase chain reaction; PNALT = Persistently Normal ALT*

1.5. Study objectives

1. To document, based on a literature review, the effectiveness and cost-effectiveness of screening for hepatitis C in the general population or in specific target groups (excluding screening of the blood supply).
2. To document, based on a literature review, the effectiveness and cost-effectiveness of prevention programs for hepatitis C in injection drug users.
3. To describe action plans abroad (mainly surrounding countries) with regard to hepatitis C screening and prevention.

We also had the opportunity to study a dynamic mathematical model on the effectiveness of treating IDUs to prevent HCV transmission. This opportunity allowed us to also investigate the theoretical effectiveness of treating active IDUs as prevention program based as much as possible on Belgian data.

2. SCREENING FOR HEPATITIS C

2.1. Review of the effectiveness literature

As described in section 1.4.1, there must be evidence from high quality RCTs that the screening program is effective in reducing mortality and morbidity. Randomized clinical trials analyzing the impact of screening on morbidity and mortality will therefore be searched. Moreover, because the effectiveness of screening requires a lot of information from a wide range of sources to correctly inform decision makers,[79] modelling studies will also be searched.

2.1.1. Methods

2.1.1.1. Literature search strategy

The research question for the current review is:

- What is the evidence, based on RCT and/or modelling studies, on the effectiveness of screening for HCV infection (in terms of reducing mortality or morbidity) compared to no screening?

Electronic databases were consulted up to July 2011. For RCTs, Medline, EMBASE, CINAHL, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Cochrane Central Register of Controlled Trials (CCRCT), Cochrane Methodology Register (CMR), Health Technology Assessment Database (HTAD), and NHS Economic Evaluation Database (NHS EED) were investigated.

For modelling studies, Medline, EMBASE, CDSR, DARE, HTAD, and NHS EED were investigated.

No restriction on the time period was imposed. Reference lists of the selected studies were checked for additional relevant citations. The websites of the HTA institutes listed on the INAHTA websites (see appendix 1.1.1) were also consulted to retrieve HTA reports on this topic.

The keywords used and the results are detailed in appendix 1.1.2. The main search terms were:

- Hepatitis C;
- Mass screening; and
- Randomized controlled trials (for RCTs) or Models (for modelling studies)

2.1.1.2. Selection criteria

All retrieved references were assessed against pre-defined selection criteria (in terms of population, intervention, outcome, and design – Table 2.1) in a two-step procedure: initial assessment of the title, abstract and keywords; followed by full-text assessment of the selected references. Only studies reporting long-term effectiveness data were retained. The flow chart of this selection is presented in appendix 1.1.2.

Table 2.1 : HCV screening effectiveness - Selection criteria

	Inclusion criteria	Exclusion criteria
Population	General population	Blood donors
Intervention	Screening strategies for HCV infections	No screening (e.g. HCV treatments, HCV diagnostics,
Outcome	Long term outcomes in terms of reducing mortality or morbidity	Other outcomes
Design	RCT, meta analysis or systematic reviews of RCT	Other designs

2.1.1.3. Quantity of research available

RCT

After excluding 58 duplicates, 160 unique citations were identified from the databases. Hand searching allowed us to identify 1 additional citation. Of this total of 161 references, 154 did not meet the inclusion criteria based on title and abstract evaluation. Among the 7 citations retained for full-text assessment, 4 studies had an inappropriate design (see Table 2.2 for the detail of the studies excluded).

Table 2.2 : HCV screening effectiveness – RCTs. Studies excluded after full-text assessment

Exclusion criteria	Studies
Population	0
Intervention	0
Outcome	0
Design	Ho 2008, Templeton 2006, Vogel 2011, Whang 2007[81-84]

Finally, no RCT was identified. Three reviews that included a search for RCTs were identified. However none of these reviews could identify an RCT. [85-87] (See appendix 1.1.2).

Modelling studies

After excluding 32 duplicates, 277 unique citations were identified from the databases. Of this total, 245 did not meet the inclusion criteria based on title and abstract evaluation. Among the 32 citations retained for full-text assessment, 27 studies had an inappropriate design and 4 did not meet the intervention criteria (see Table 2.3 for the detail of the studies excluded). Most of the studies were excluded on the "design" criteria because they were cost-effectiveness studies (not only effectiveness). These studies were investigated in section 2.2 related to the cost-effectiveness of screening. Finally, 1 study was retained. [88]

Table 2.3 : HCV screening effectiveness – Modelling studies. Studies excluded after full-text assessment

Exclusion criteria	Studies
Population	0
Intervention	Ho 2008; Kershenobich 2011; Mather 1995; Rein 2011[81, 89-91]
Outcome	0
Design	Benet 2007; Chapko 2005; Coon 2006; D'Souza 2003; Fischer 2000; Helsper 2009; Honeycutt 2007; Jhaveri 2006; Jusot 2001; Kirkizlar 2010; Lapane 1998; Loubiere 2003; Loubiere 1999; Nakamura 2008; Pereira 2001; Pereira 2000; Plunkett 2005; Rotily 1997; Saab 2001; Singer 2001; Sroczynski 2009; Stein 2003; Stein 2004; Sutton 2006; Sypsa 2001; Tramarin 2008[86, 92-116]

2.1.2. Review of randomized controlled trials

Three systematic reviews of RCTs were identified, [85-87] but none of them found RCTs. In addition to RCT, one of these reviews also searched for observational studies but they did not find anything.

The most recent review (2009) tried to identify all long-term clinical trials, meta-analysis and health technology assessment reports evaluating the long-term effectiveness of screening for HCV infection. In the absence of long-term clinical studies, they based their analysis on modelling studies only (i.e. 5 cost-effectiveness studies). In these studies, the life years gained due to screening varied from 0.0004 to 0.066 and the quality-adjusted life-year (QALY) gained varied from no gain to 0.072 QALYs. [87, 100, 108, 117, 118] The quality of these studies was not assessed in the review.

2.1.3. Modelling studies

In this section, only modelling studies on the effectiveness of screening for HCV infection were assessed. One modelling study was identified, [88] in which the impact of screening was only assessed in the sensitivity analysis.

They constructed a Markov model to predict the 2006-2025 HCV mortality. The impact of alcohol, current screening and antiviral therapy was taken into account. Based on French prevalence studies, they assumed that 5% of individuals were aware of their HCV infection in 1991 and that this

proportion increased linearly to 24% in 1994 and to 56% in 2004. By assuming a constant progress in screening similar to that observed between 1994 and 2004, they predicted that the French government objective of 75% of HCV infected patients aware of their infection would be reached in 2014.[88] In their base-case model, the expected cumulated HCV-related mortality between 2006 and 2025 was estimated at 59 000 deaths. The impact of screening was partially analysed in the sensitivity analysis. If efforts in screening were done and if 75% of HCV infected patients were aware of their infection in 2010 (instead of 2014), they estimated that 950 people could be saved (95% CI 900-1000).[88]

2.2. Review of the cost-effectiveness literature

2.2.1. Introduction

Screening for infection with the hepatitis C virus (HCV) outside the blood transfusion setting is typically performed using the detection of antibodies to the virus. Such antibodies appear during an acute HCV infection and remain present also in those subjects who are able to clear the virus and do not develop chronic hepatitis C. The proportion of HCV infections that clear spontaneously was estimated at 26%. HCV can also be cleared after antiviral treatment. This is one reason why a positive antibody test always requires confirmation of ongoing infection, using the detection of HCV antigen or more frequently HCV-RNA. In addition, some subjects will show a false positive result with the antibody test, and in the context of screening this proportion will be higher compared to a clinical setting.

Before determining recommendations on the screening for HCV infections, information on its cost-effectiveness is needed to determine whether screening offers 'value for money' (see section 1.4.1). In this chapter we review the literature on full economic evaluations about screening for HCV infections.

2.2.2. Methods

2.2.2.1. Literature search strategy

The research questions for the current review are:

- What is the evidence, based on full economic evaluations, on the efficiency of screening for HCV infection?
- For which population is screening for HCV infection cost-effective?

To answer these questions, electronic databases were consulted up to mid September 2010. The HTA database, the CDSR and the websites of HTA institutes listed on the INAHTA websites (see appendix 1.1.1) were consulted to retrieve HTA reports on this topic. The NHS EED, DARE, Medline, EMBASE, and Econlit databases were searched to retrieve full economic evaluations (i.e. studies comparing at least two alternative treatments in terms of costs and outcomes - appendix 1.2.1) and reviews of full economic evaluations. No restriction on the time period was imposed. Reference lists of the selected studies were checked for additional relevant citations.

The keywords used and the results are detailed in appendix 1.2.2. The main search terms were:

- Hepatitis C;
- Mass screening; and
- Cost or economic.

2.2.2.2. Selection criteria

All retrieved references were assessed against pre-defined selection criteria (in terms of population, intervention, outcome, design and language – Table 2.4) in a two-step procedure: initial assessment of the title, abstract and keywords; followed by full-text assessment of the selected references. When no abstract was available and the citation was unclear or ambiguous, the citation was assessed on the basis of keywords and full-text assessments. Because of insufficient details to assess the quality of the study, conference abstracts were excluded. Moreover, as clinical and economic consequences of screening occur over a long time horizon, only studies reporting long-term cost-effectiveness in terms of cost per life-year gained (cost/LYG) or cost per quality-adjusted life-year gained (cost/QALY) were retained. Studies only reporting cost per case detected or studies that did not report sufficient data to derive incremental cost-effectiveness ratio (ICER) were therefore excluded. Combination therapy with pegylated interferon (PegIFN) and ribavirin is now the standard treatment for patients with moderate chronic hepatitis C in Belgium.[59] Consequently, cost-effectiveness studies assessing the impact of HCV screening followed by a less-effective treatment (e.g. interferon therapy) have also been excluded.

The flow chart of this selection is presented in appendix 1.2.3.

Table 2.4 : HCV screening cost-effectiveness - Selection criteria

	Inclusion criteria	Exclusion criteria
Population	General population	Blood donors, healthcare workers exposed to HCV
Intervention	Screening strategies for HCV infections and treatment with PegIFN and ribavirin	HCV vaccine, HCV treatments, HCV diagnostics, HCV prevalence, screening strategies for HCV infections followed by a treatment less effective than PegIFN and ribavirin (e.g. Interferon)
Outcome	Long term outcomes in terms of cost/LYG or cost/QALY	Others: e.g. cost per HCV case detected
Design	Full economic evaluations (primary or secondary studies)	Non full economic evaluation (see appendix 1.2.1)
Language	English, French, Spanish, German or Dutch	Other

2.2.2.3. Data extraction and quality assessment strategies

The selected full economic evaluations were critically assessed and summarized in data extraction sheets (see appendix 1.2.4). The quality of these studies was assessed narratively.

2.2.2.4. Conversion in Euro 2009

Original costs were converted to 2009 costs for each country using Consumer Price Indices available on the OECD website.[119] Then the Purchasing Power Parities (PPP) index was applied to obtain comparable costs in Euro across the different countries. These PPP index were obtained from the website of Eurostat.[120] The PPPs used correspond to 2009 Euro for the 27 member states of the European Union. If no costing year was mentioned in the study, an interval of two years before the publication date was chosen. The original cost figures (i.e. before conversion) are presented in appendix 1.2.4.

2.2.2.5. Quantity of research available

After excluding 253 duplicates, 599 unique citations were identified from the databases. Hand searching allowed us to identify 8 additional citations. Of this total of 607 references, 529 did not meet the inclusion criteria based on title and abstract evaluation. Among the 78 citations retained for full-text assessment, 3 studies reported the same results as other already published studies, 28 studies had an inappropriate design, 17 did not meet the outcome criteria, 3 did not meet the population criteria, and 17 did not meet the intervention criteria. Among the latter, 7 studies were excluded because the treatment given to the patients was not the combination therapy with PegIFN and ribavirin (see Table 2.5 for the detail of the studies excluded).

Table 2.5 : HCV screening cost-effectiveness - Studies excluded after full-text assessment

Exclusion criteria	Studies
Population	Deuffic-Burban 2009; Nguyen 2000; Pereira 2000[107, 121, 122]
Intervention	
No screening	Alzahrani 2005; Bruguera 2006; Contreras-Navarro 2007; Dal Molin 2003; Kim 2008; McHutchison 2005; Mizui 1994; Sterling 2005; Udeagu Pratt 2002; Wozny 1997[123-132]
Less effective treatment	Jusot 2001; Leal 1998; Leal 1999; Loubiere 2003; Pereira 2001; Singer 2001[100, 103, 106, 111, 118, 133]
Outcome	Batra 2001; Chapko 2005; Desenclos 1997; Gordon 1999; Honeycutt 2007; Josset 2004; Josset 2004; Kaur 1996; Lapane 1998; Leikin 1994; Loubiere 1999; Monnet 2000; Rotily 1997; Saab 2001; Seme 2007; Somsouk 2008; Sutton 2006[93, 98, 102, 104, 109, 110, 114, 134-143]
Design	Anonymous 1997; Anonymous 2003; Barnett 2005; Boutwell 2005; Calonge 2004; Fabrizi 1997; Fabrizi 2001; Ferguson 2005; Hagedorn 2007; Hill 2005; Jullien-Depradeux 2002; Jusot 2002; Klein 2008; Loubiere 2002; McCaughan 2007; Rosenberg 1999; Sypsa 2001; Thomas 2010; Toledo 2005; Trepo 1997; Williams 2005; Yoho 2003; Zaller 2007; ANAES 2001; Centers for disease control and prevention 1998; Chou 2004; Gezondheidsraad 2004; U. S. Preventive Services Task Force 2004[115, 144-170]
Duplicate	Coon 2006; Stein 2003; Stein 2004[94, 112, 113]

Finally, 11 studies were retained, i.e. 6 economic evaluations[101, 105, 108, 116, 117, 171] and 5 reviews of economic evaluations[86, 87, 172-174] (See appendix 1.2.3). The review of Stein et al. 2002[87] also included and economic evaluation. However, the treatment assessed in the base case of this study

was a combination of interferon and ribavirin. The impact of using Peg-IFN and ribavirin was only tested in the sensitivity analysis. Moreover, the study of Castelnuovo et al.[117] was an update of the economic evaluation of Stein et al.[87] Therefore, only the review of the literature performed by Stein et al[87] was investigated and not the economic evaluation.

2.2.3. Reviews of economic evaluations

Five reviews of economic evaluations were identified.[86, 87, 172-174] Among those, the review of Stein et al.[70] was the only one that fully described the method used to identify the studies and that assessed the quality of the selected studies. Only this study was therefore detailed in the current report. Stein et al. identified 6 economic evaluations of screening for HCV infection[102, 109, 133, 135, 139, 175] and concluded that they all had methodological limitations and/or were of limited relevance to the UK populations of concern. It should be noted that none of these studies were selected in our review. The study of Ishizuka et al[175] was excluded because it was written in Japanese. Moreover, in the six studies reviewed by Stein,[102, 109, 133, 135, 139, 175] patients were treated by a less-effective treatment (interferon therapy) than the current standard and five of them[102, 109, 135, 139, 175] only reported a cost per case detected. Therefore, they did not correspond to the inclusion criteria of our review.

2.2.4. Primary economic evaluations

Table 2.6 gives an overview of the characteristics of the 6 primary economic evaluations identified. Five studies were static Markov model-based economic evaluations[105, 108, 116, 117, 171] and one study was a dynamic model-based economic evaluation.[101]

Table 2.6 : General characteristics of the economic evaluations

Author	Year*	Country	Analysis		Time horizon	Discount rate	Costing perspective: cost items included
			CEA	CUA			
Kirkizlar et al.[101]	2010	USA	-	X	65 years	Cost: 3% Outcome: 3%	Direct medical costs
Nakamura et al.[105]	2008	Japan	X	-	30 years	Cost: 3% Outcome: 3%	Direct medical costs
Tramarin et al.[116]	2008	Italy	-	X	Lifetime	Cost: 3% Outcome: 3%	Seems to be direct medical costs (not clearly described)
Sutton et al.[171]	2008	UK	-	X	80 years	Cost: 3.5% Outcome: 3.5%	Direct medical costs
Castelnuovo et al.[117]	2006	UK	X	X	Lifetime	Cost: 6% Outcome: 1.5%	Direct medical costs
Plunkett et al.[108]	2004	USA	-	X	Lifetime	Cost: 3% Outcome: 3%	Direct medical costs

*CEA: cost-effectiveness analysis; CUA: cost-utility analysis; UK: United Kingdom; USA: United States of America.*Publication year.*

2.2.4.1. Analytical technique

The majority of the studies reported their results in terms of cost-utility ratios (with outcomes expressed as quality-adjusted life years gained – QALY).[101, 108, 116, 171] One study was a cost-effectiveness analysis (with outcomes expressed as life-years gained – LYG)[105] and one study was both a cost-effectiveness and a cost-utility analysis.[117] Because a

screening strategy may lead to early detection of the infection and therefore may have an impact on the quality of life, performing a CEA only is less relevant.

2.2.4.2. Perspective

All studies adopted a health care payer's perspective, with direct medical costs. One study reported they adopted a societal perspective but the critical analysis showed that the perspective seems to be that of the health care payers.[116]

Although HCV affects people in the workforce age, indirect productivity costs were never considered.

2.2.4.3. Time horizon and discount rate

The time horizon of the economic evaluations spanned from 30 years to a lifetime. Given the chronic nature of hepatitis C and the relatively slow progression of the disease, this time horizon appears long enough to capture significant clinical endpoints. One problem with such long time horizons, however, is the difficulty to find valid long-term data to populate the model.

Most studies discounted their costs and outcomes with the same discount rate, being 3% or 3.5%. Castelnuovo et al.[117] used different discount rates (6% for costs and 1.5% for outcomes). This UK study followed the old NHS guidelines (current guidelines: 3.5% for both costs and outcomes) and their sensitivity analysis showed that this choice had an important impact on the results. If the current NHS guidelines were followed, conclusions would have been different (not anymore cost-effective at a threshold of £30 000/QALY according to the univariate sensitivity analysis performed for the general case (i.e. former IDUs)).

2.2.4.4. Population

The characteristics of the population studied are described in Table 2.7. Target population was injecting drug users (IDU) in 3 studies,[101, 116, 117] prisoners in 2 studies,[117, 171] patients in drug and alcohol services in one study,[117] other population at risk in 2 studies (high aminotransferase level, "major" surgery, blood transfusion),[105, 116] pregnant women and their child in 1 study,[108] and the general population in 3 studies.[101, 105, 117]

A recent pilot observational study estimated that less than 30% of Belgian HCV infected patients had a genotype 2 or 3.[63] Moreover, a higher proportion of genotypes 2-3 can be expected for IDUs.[173] The genotype's distribution assumed in the selected studies is therefore appropriate to the Belgian settings.

One exception is the study of Nakamura et al.[105] that focused on Asiatic population living in Japan. This population is expected to have a higher incidence of hepatocellular carcinoma than in our country and is therefore not appropriate to the Belgian setting.

It should also be noted that, because of a different objective compared to other studies, the studies of Kirkizlar et al.[101] and Tramarin et al.[116] assumed that all patients were healthy at presentation in the model. The aim of the first study was to determine the best timing and frequency of screening tests. The second study aimed at assessing the impact of early detection of acute HCV infection through regular testing of healthy patients (e.g every six months for IDUs).

Table 2.7 : Population characteristics

Author	Population/Setting	Average age at presentation (years)	Liver disease stage at presentation (For HCV infected)	Genotypes (For HCV infected)
Kirkizlar et al.[101]	General population	15	Healthy at presentation. When HCV infected, no specification of liver disease stage	Not specified (from the SVR rate source: Genotypes 2 or 3: 29% - Other genotypes: 71%)[176]
	IDUs			
Nakamura et al.[105]	General population aged 40-70 years	40-49	Chronic hepatitis (without specification of liver disease stage)	Genotypes 2 or 3: 30% Genotype 1: 70%
		50-59		
	High risk group over 40 years: having a high aminotransferase level (not defined), having undergone a major operation (not defined) or having received a blood transfusion during childbirth	60-69		
		70 and over		
Tramarin et al.[116]	IDUs	32	Healthy at presentation and acute hepatitis when infected.	Genotypes 2 or 3: 33% Genotype 1 or 4: 67%
	IWSs	42		
Sutton et al.[171]	All new prisoners (including non IDUs, former and current IDUs). However, the screening test was only proposed to former and current IDUs.	Stratification:	Mild: 95.5% / Moderate: 4.5%	Genotypes 2 or 3: 51.6% Genotypes 1, 4 or 5: 48.4%
		15-24 (average 20)	Cirrhosis: 0%	
		25-34 (average 29)	Mild: 91.4% / Moderate: 7.9%	
			Cirrhosis: 0.7%	
		35 and over (average 44)	Mild: 82.9% / Moderate: 15.1%	
			Cirrhosis: 2.0%	
		Total: 15 and over (average 27)	Mild: 90.1% (57% with raised ALT)	
			Moderate: 8.9% (82.5% with raised ALT). Cirrhosis: 1.0%	
Castelnuovo et al.[117]	General case: Former IDUs	37	Mild: 75% Moderate: 13.7% Severe: 5.4% Cirrhosis: 5.9%	Genotypes 2 or 3: 51.6% Genotypes 1, 4 or 5: 48.4%
	In general practice setting: all patient with a history of injecting drug use (former IDUs) = target approach			
	In general practice setting: all patients aged 30-54 years attending for a non-urgent appointment = population approach			
	In prisons: all new prisoners aged 25-39 years			
	In drug and alcohol services: all clients assessed for HBV vaccination			
Plunkett et al.[108]	Asymptomatic, HIV-negative pregnant woman without risk factor for HCV infection (not defined) and their child	30 for the mother20 for the child	Mild chronic hepatitis	Not specified (from the SVR rate sourcee: Genotypes 2 or 3: 29% - Other genotypes: 71%)[176]

HCV: Hepatitis C virus; IDU: Injecting drug users; IWS: Individual with surgery; SVR: sustained viral load

2.2.4.5. Interventions

In Belgium, the following stages are usually considered for the screening and diagnosis of hepatitis C (adapted from the study of Robaeys et al.[60] and from expert opinion):

- Screening test:
  - determination of serum anti-HCV antibodies [e.g. with an ELISA test]
- Diagnostic tests:
  - if the anti-HCV test is positive: determination of HCV RNA [PCR test]
  - if the PCR test is positive: genotyping
  - Liver biopsy can then be performed to obtain information on prognosis (mandatory to obtain reimbursement of treatment in patients who are not genotypes 2 or 3; who do not suffer from haemophilia and who do not receive a concomitant treatment with anticoagulants)

The screening and diagnostic tests used in the economic evaluations are described in Table 2.8. The tests performed in the studies of Kirkizlar et al.[101] and Tramarin et al.[116] do not correspond to the current practice in Belgium because no diagnostic test was taken into account in the model. The screening and diagnostic strategies of Nakamura et al.[105] also slightly differ from the current practice in Belgium (use of an antibody test and no genotyping included in the model).

For HCV infected patients, the disease stage at the beginning of the treatment, the percentage of patients with contra-indications and the treatment acceptation rate, duration and stopping rules are summarized in Table 2.9. Only the studies of Sutton et al.[171], Tramarin et al.[116] and partially that of Nakamura et al.[105] followed current good clinical practice (i.e. 24 weeks of treatment for genotypes 2 and 3; 48 weeks of treatment for other genotypes).

Table 2.8 : Screening and diagnostic tests

Authors	Screening and diagnostic tests
Kirkizlar et al.[101]	Not reported (seems to be the Elisa test according to the source given; no PCR test)
Nakamura et al.[105]	Semi-quantitative HCV antibody test -> If moderate or low titer, HCV core antigen test -> If negative, PCR test
Tramarin et al.[116]	HCV serology test (every 6 months for IDUs and 2 tests at time 0 and after 6 months for IWSs)
Sutton et al.[171]	Enzime immunoassay test (Elisa) -> If positive, PCR test -> If positive, genotyping
Castelnuovo et al.[117]	Enzime immunoassay test (Elisa) -> If positive, PCR test (with repeat Elisa) -> If positive, genotyping -> if genotype 1 or 4, liver biopsy
Plunkett et al.[108]	Enzyme immunoassay test (Third-generation) -> PCR test -> Genotyping

Elisa = Enzyme-Linked Immunosorbent Assay

In the studies of Castelnuovo et al. and Plunkett et al.,[108, 117] a treatment duration of 48 weeks for all genotypes (without stopping rules) was assumed while Kirkizlar et al.[101] gave no detail on treatment duration.

Only three studies took into account that some patients may have contra-indications to the treatment or may refuse to be treated.[108, 117, 171] The probability to be treated in these studies varied between 44% and 70% for the screened population. In a Belgian observational study assessing treatment eligibility, 59% of patients considered for treatment where not treated (among those, 34% had medical contra-indications). The treatment was also interrupted in 16% of patients because of adverse events.[177]

Table 2.9 : Treatment characteristics

Authors	Treatment	Disease state at the beginning of the treatment	Probability of receiving treatment (in %)		Duration	Stopping rules
			Without contra-indication to treatment	Acceptance rate		
Kirkizlar et al.[101]	PegIFN + Ribavirin	Moderate	/	/	Not specified	/
Nakamura et al.[105]	PegIFN + Ribavirin	Chronic hepatitis C (no more details)	/	/	Genotypes 2-3: 24 weeks Genotype 1: If HCV RNA Negative at week 12: 48 weeks; If HCV RNA positive at week 12 and negative at week 24: 72 weeks; If HCV RNA positive at week 12 and positive at week 24: 24 weeks	Genotypes 2-3: /
Tramarin et al.[116]	PegIFN + Ribavirin	Screened population: acute hepatitis C	/	/	Genotypes 2-3: 24 weeks	No stopping rules
		Unscreened population: chronic hepatitis C			Other: 48 weeks	No stopping rules
Sutton et al.[171]	PegIFN + Ribavirin	Mild, moderate or cirrhosis	88%	In prison: 50% In the community (after prison): Genotypes 2-3: 60.5%; Genotypes 1-4: 55%	Genotypes 2-3: 24 weeks Genotypes 1-4: 48 weeks	Genotypes 2-3: / Genotypes 1-4: If no EVR at 12 weeks
Castelnuovo et al.[117]	PegIFN + Ribavirin + advices to reduce alcohol consumption	For genotypes 2-3: mild, moderate, severe or cirrhosis	88%	Genotypes 2-3: 60.5%; Genotypes 1-4: 55%	48 weeks	No stopping rules
		For genotypes 1-4: moderate, severe or cirrhosis (not for mild HCV)				
Plunkett et al.[108]	PegIFN + Ribavirin	Moderate	Screened population: 70% Unscreened population: 20%		48 weeks	No stopping rules

EVR: Early virologic response; PegIFN: Pegylated interferon

2.2.4.6. Outcomes

Estimates of QoL values (utilities) used in the studies are presented in Table 2.10, together with the population from which utilities were derived and the source references.

A high discrepancy between QoL values was found. Methods to estimate utility values were not clear in almost all studies. Only the studies of Castelnuovo et al.[117] and Sutton et al.[171] clearly described their method. In these studies, utility values were obtained from the study of Wright et al.[178] using the EQ-5D, for which UK community preference values were available (time trade-off technique). Unfortunately, differences were found between the parameters used in the model and the values reported in the study of Wright et al.[178] Most importantly, the study of Wright et al.[178] did not make the distinction between diagnosed and undiagnosed patients. It is therefore not clear how they could estimate utilities for undiagnosed patients. Because decrement in quality of life of diagnosed people compared to undiagnosed people may have an impact on the result for HCV screening evaluations, more reliable data are needed.

Table 2.10 : Health-state utilities used in the economic evaluations

Author (Country)	Cured	Categories	Chronic hepatitis C			Cirrhosis		HCC	Waiting list for LT	LT (year 1)	Post LT	Population	Method	Ref.
			Mild*	Moderate*	Severe*	CC*	DC*							
Kirkizlar et al.[101] (USA)	Not reported	Diagnosed	0.98					0.48				Not reported Sources: Experts in hepatology-patients-population (Canada)	Not reported Sources: VAS-TTO-SG-SF-36 HUI-II & -III	Singer 2001[111]-Hornberger 2006[179]
		Undiagnosed	1											
Tramarin et al.[116] (Italy)	1	/	Not reported			Not reported		Not reported				Not reported Sources: patients	Not reported Sources: SF-36	Bonkovsky 2007[180]; Kallman 2007[181]; Wong 2006[182]
Sutton et al.[171] (UK)	see the next states - responder	Non-symptomatic/ Undiagnosed	0.79 (0.024)	0.64 (0.03)	/	0.55 (0.054)	0.45 (0.056)	0.45 (0.056)	/	0.67		UK population	EQ-5D - TTO	Wright et al 2006[178]
		Symptomatic/ Diagnosed	0.75 (0.024)	0.60 (0.03)	/	0.51 (0.054)								
		During treatment	0.65 (0.002)	0.525 (0.003)	/	0.46 (0.005)								
		Treatment responder	0.82 (0.005)	0.69 (0.0065)	/	0.61 (0.006)								
		Treatment non-responder	0.76 (0.003)	0.63 (0.0051)	/	0.55 (0.004)								

Author (Country)	Cured	Categories	Chronic hepatitis C			Cirrhosis		HCC	Waiting list for LT	LT (year 1)	Post LT	Population	Method	Ref.
			Mild*	Moderate*	Severe*	CC*	DC*							
Castelnuovo et al.[117] (UK)	see the next states - responder	Non-symptomatic	0.79 (0.024)	0.68 (0.03)	0.60 (0.03)	0.55 (0.054)	0.45 (0.056)	0.45 (0.056)	0.45 (0.056)	0.45 (0.056)	0.45 (0.056)	UK population	EQ-5D - TTO	Wright et al 2006[178] and Ratcliffe 2002 (for LT)[183]
		Symptomatic	0.75 (0.024)	0.64 (0.030)	0.56 (0.030)	0.51 (0.054)	0.45 (0.056)	0.41 (0.056)						
		During treatment	0.65 (0.002)	0.55 (0.003)	0.50 (0.003)	0.46 (0.005)								
		Treatment responder	0.82 (0.005)	0.72 (0.007)	0.66 (0.006)	0.61 (0.006)								
		Treatment non-responder	0.76 (0.003)	0.65 (0.0042)	0.61 (0.006)	0.55 (0.0038)								
Plunkett et al.[108] (USA)	1	Diagnosed	0.96 (0.96-1.0)	0.92 (0.82-0.98)	/	0.85 (0.50-0.90)	0.60 (0.50-0.88)	0.25 (0.1-0.5)	/	0.86 (0.6-0.9)	0.95 (0.8-0.95)	Not reported Sources: Experts in hepatology-patients	Not reported Sources: VAS-TTO-SG	Buti 2000[184]; Wong 1998[185]; Wong 2000[186]; Wong 2000[187]; Younossi 1999[188]; Singer 2001[111]
		Un-diagnosed	1		/									
		During treatment	/	0.88 (0.82-0.91)	/									

*Numbers under brakets () represent standard error for the Studies of Castelnuovo et al. and Sutton et al. and the range for P lunkett et al. *Because of the small sample size, utility values for these health states were not considered robust enough. CC: compensated cirrhosis; DC: decompensated cirrho sis; EQ-5d: EuroQol instrument 5 dimensions (self-reported generic preference-based instrument); HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HUI: health utility index (self-reported generic preference-based instrument); LT: liver transplant; SF-36: short form (36) health survey; SG: standard gamble; TTO: time trade-off; VAS: visual analogue scale.*

2.2.4.7. Effectiveness / modelling

Screening efficacy

Discrepancies were found among studies on the proportion of HCV infected people detected by screening tests (see Table 2.11). The proportion of HCV infected persons identified by a case-finding strategy (screening) was estimated at 8% for former IDU, 0.4% for the general population, between 0.4% and 1.6% for prisoners, 11% in drug and alcohol services, 0.85% for pregnant women (own calculation) and around 0.81% for other high risk patients. Because of a different design, the study of Kirkizlar et al.[101] and Tramarin et al.[116] were not reported in Table 2.11.

In three studies, screening and diagnostic tests were only performed on people who accepted the test (Castelnuovo et al., Sutton et al., and Plunkett at al.).[108, 117, 171] For example, Castelnuovo et al.[117] analysed the screening of the general population in general practice and assumed that only 10% of the population accepted the test, which has an important impact on the results compared to screening all patients (100% acceptance rate). In a Belgian study trying to estimate the HCV prevalence in the Flemish population, 30.6% of patients accepted the test after an invitation to participate sent by regular mail (which is different from the consultation setting).[53]

Moreover, the study of Castelnuovo et al.[117] and of Sutton et al.[171] took into account the possibility of spontaneous presentation for screening in the non-case finding group (3.8%/year and 3.75%/year respectively); and the possibility of representation for screening in the case finding group (for people who had previously refused the test; 7.7%/year and 7.5%/year respectively). Those assumptions allowed to detect additional HCV infected patients on a 30-year period (see Table 2.12).

The study of Castelnuovo et al.[117] also took into account a selection bias for the screening (i.e. people who accepted the test had a higher risk to be infected and thus the probability of positive results among the tested patients differed from the HCV prevalence in the target population). This selection bias does not seem to be taken into account in other studies (or was not reported). A Belgian study tried to estimate the HCV prevalence in the Flemish population and contacted people by regular mail (thus missing people without formal postal address). This study found a HCV prevalence of 0.12% among the 30.6% of patients who accepted the test.[53] In this study, people who accepted the test were therefore not at higher risk to be HCV infected. The results would thus depend on the way of performing the screening.

Because all these data are expected to have an important impact on the results, more Belgian data are needed.

Table 2.11 : Acceptance rate of screening and diagnostic tests and proportion of HCV infected people

Authors	Population/ setting	Prevalence of HCV infected patients	Elisa test (or other) acceptance rate	Proportion of positive HCV antibody among those tested	PCR acceptance rate	Proportion of positive PCR results among those tested	Percent of HCV infected patients among the population identified by the screening
Nakamura et al.[105]	General population	0.36%	Not taken into account => 100%	Not reported	Not taken into account => 100%	Not reported	0.36%
	High risk group	0.81%					0.81%
Sutton et al.[171]	In prison	10.1%	10.25%	Not reported	92%	Not reported	0.7%
Castelnuovo et al.[117]	General case: Former IDU	49%	49%	49%	39%	82%	7.7%
	General practice: Former IDU	49%	49%	49%	39%	82%	7.7%
	General practice: Population	Not reported	10%	12.5%	39%	82%	0.40%
	Prison with general lecture	31%	8.5%	16%	39%	82%	0.43%
	Prison with specific lecture	31%	12%	42%	39%	82%	1.60%
	Drug and alcohol services	49%	49%	68%	39%	82%	10.60%
Plunkett et al.[108]	Pregnant Women	1%	85%	Not reported	100%	Not reported	Not reported *(0.85%*)*

**:Based on own calculation: (1%*85%); IDU = injecting drug users; IWS = individuals with surgery*

Table 2.12 : Proportion of additional HCV infected patients identified on a 30-year period due to spontaneous presentation or representation.

Authors	Population/setting	Case-finding	Non-case-finding	Cases averted
Sutton et al.[171]	In prison	8.6%	7.8%	0.8%
Castelnuovo et al.[117]	General case: Former IDU	28.4%	25.9%	2.5%
	General practice: Former IDU	28.4%	25.9%	2.5%
	General practice: Population	7.2%	6.6%	0.6%
	Prison with general lecture	9.3%	8.4%	0.9%
	Prison with specific lecture	19.1%	22.6%	-3.5%
	Drug and alcohol services	39.4%	36,00%	3.4%

IDU = injecting drug users

Disease progression and treatment efficacy

The disease progression and treatment effects modelled in the economic evaluations are presented in Table 2.13, Table 2.14, and Table 2.15.

Discrepancies were found concerning annual transition rate parameters (see Table 2.13 and Table 2.14). According to the parameters of the models, patients progressed more quickly (natural evolution) to compensated cirrhosis in the studies of Castelnuovo et al.,[117] Nakamura et al.,[105] and Tramarin et al.[116] compared to other studies (more than 70% after 30 years versus around 10%, based on own calculations, i.e. for each study, the natural evolution of the disease until the state of compensated cirrhosis for a 30-year period was modelled using the parameters reported in the study). This may partially be explained by a younger population in the other studies. In the study of Nakamura et al.,[105] liver transplantation was not considered in the disease progression.In the study of Kirkizlar et al.,[101] decompensated cirrhosis, liver transplant and hepatocellular carcinoma were grouped in one health state, which may be a too simplistic representation of the reality.

However, when performed, univariate sensitivity analyses showed that these parameters only had a small impact on results.

Table 2.13 : Annual transition rates (%) between chronic hepatitis (mild, moderate, and severe) and cirrhosis

			Kirkizlar et al.[101]	Nakamura et al.[105]	Tramarin et al.[116]	Sutton et al.[171]				Castelnuovo et al.[117]				Plunkett et al.[108]	
						0-29	30-39	40-49	>50	20 years past infection + alcohol advice	30 years past infection + alcohol advice	20 years past infection[a]	30 years past infection[a]	Mother	Child
Chronic Hepatitis C to CC	Mild to moderate		See the next table	6.5	Not reported (99% for the lifetime period)	2.1	1.3	2	6.8	6.19	12.08	6.2	12.1	2	3
	Moderate to severe	Moderate to CC				2.2	2.2	2.2	2.2	7.52	14.59	7.54	14.62	2	3
	Severe to CC									8.75	16.87	8.77	16.9		

[a] *Without alcohol advice; CC: compensated cirrhosis*

Table 2.14 : Annual transition rates for long term consequences

	Kirkizlar et al.[101]	Nakamura et al.[105]	Tramarin et al.[116]	Sutton et al.[171]	Castelnuovo et al.[117]	Plunkett et al.[108]
CC to DC	Chronic to DC-HCC-LT: 1.15 with alcohol and 0.25 without	2.9	Not reported	4	5.8	3.9
Chronic to HCC		1.4		/	/	/
CC or DC to HCC		7.3		2.5	2.5	1.5
HCC to LT		/		HCC or DC to LT: 2	HCC or DC to LT: 5	/
DC to LT		/				3.1
LT to DPT		/		/	6.9	/
DC to death	DC-HCC-LT to death: 22.0	15.3		13	49% at 5 years	12.9
HCC to death		19.6		43	91	42.7
LT to death (year 1)		/		15	31.2% at 10 years	21
LT to death (subsequent years)		/		3		5.7

CC: compensated cirrhosis; DC: decompensated cirrhosis; DPT: decompensation post-transplantation; HCC: hepatocellular carcinoma; LT: liver transplant

Discrepancies were also found between studies concerning the SVR rate (see Table 2.15). SVR rates were higher in the studies of Castelnuovo et al.[117] and Sutton et al.[171] However, the univariate sensitivity analysis performed in Castelnuovo et al.[117] showed that SVR rates for genotypes 2-3, genotypes 1-4 and cirrhotic patients should be higher than 54.6%, 30.9% and 27.5%, respectively, for the screening strategy to remain cost-

effective compared to a no screening scenario (at the UK willingness to pay threshold of £30 000/QALY). This parameter has thus little impact on the results.

Table 2.15 : SVR rates

	Kirkizlar et al.[101]	Nakamura et al.[105]	Tramarin et al.[116]	Sutton et al.[171]		Castelnuovo et al.[117]		Plunkett et al.[108]
				Chronic hepatitis C	Cirrhosis	Chronic hepatitis C	Cirrhosis	
Genotypes 2-3	54%	71%	79%	87%	75%	94%	48%	54%
Other genotypes		50%	42%	57%	/	54%	24%	

2.2.4.8. Costs

Table 2.16 and Table 2.17 again show discrepancies between studies for the cost of screening tests and the annual health states disease treatment costs. The studies of Kirkizlar et al.,[101] Tramarin et al.[116] and Nakamura et al.[105] did not consider the cost of PCR test and/or genotyping. The cost of screening and diagnostic in these studies is thus not transferable to our country setting (underestimation). The same remark can be made concerning the estimation of the annual health state disease treatment costs.

Compared to a Belgian study assessing the cost of hepatitis C complications (Wong et al.[189]), the cost of chronic hepatitis C and cirrhosis was higher in all selected studies and the cost of liver transplantation was higher in the study of Plunkett et al.[108] and Tramarin et al.[116] However, when performed, univariate sensitivity analyses showed that these parameters had little impact on the results. Moreover, costs data and results are not easily extrapolable across countries. Cost inputs used by the economic evaluations are therefore not deeply analysed in the present chapter.

Table 2.16 : Cost of screening tests in Euro 2009

Authors	Enzyme immunoassay test (Elisa or other)	Semi-quantitative HCV anti-body test	PCR	Genotyping	Liver biopsy	Cost item included
Kirkizlar et al.[101]	18.3	/	/	/	/	Not reported
Nakamura et al.[105]	7.9	15.9	23.8	/	/	Test*
Tramarin et al.[116]	34.4	/	/	/	/	Test + 1 consultation
Sutton et al.[171]	16.5	/	78.3	129.2	/	Test*
Castelnuovo et al.[117] *	23.4	/	77.0	129.2	342.2	Test*
Plunkett et al.[108]	41.9	/	112.0	132.2	/	Not reported
Belgium (based on NIHDI codes)**	6.7	/	54.3-106.6	106.8	/	Test

** Without cost of counselling, consultation, etc.; Cost of counselling and consultations were taken into account separately and are not reported in this table; **Taken into account a PPP of 1.15356 for Belgium; Elisa: Enzyme-linked immunosorbent assay; HCV: Hepatitis C virus; NIHDI: National Institute for Health and Disability Insurance; PCR: Polymerase chain reaction; PPPs: Purchasing power parities*

Table 2.17 : Annual cost of health states in Euro 2009

Author (Country)	Hepatitis C treatment costs	Categories	Chronic hepatitis C			Cirrhosis		HCC	Waiting list for LT	LT (year 1)	LT subsequent years	Source
			mild	moderate	severe	CC	DC					
Kirkizlar et al.[101]	17 165	Diagnosed	Not reported			19 260 (for DC, HCC and LT) and 38 188 (for secondary infections)						Direct health care cost (fees) Sullivan 2004 - Analy$ource online 2006
		Undiagnosed	Not reported									
Nakamura et al.[105]	24 813 (24 weeks) - 55834 (72 weeks)		1231			1343	12 061	13 894	/	/	/	Direct health care cost (fees) in a university hospital
Tramarin et al.[116]	1576/month (around 18 912 for 48 weeks)		Not reported			4287		Not reported	/	82 097	Not reported	Direct health care cost (fees) Coppola 2000
Sutton et al.[171]	7615 (24 weeks) - 16 402 (48 weeks)	Undiagnosed	0	0	/	0	12 533	11 168	/	40 774 (transplantation) + 14 111 (follow-up)	2066	Direct health care costs (fees) of the UK mild HCV trial (Wright et al 2006)
		Diagnosed	190	985	/	1564						
		Treatment responder	356	985	/	1564						
		Treatment non-responder	162	1003	/	1564						
Castelnuovo et al.[117]	see the next states (during treatment)	Undiagnosed/Diagnosed	190	985	985	1564	12 533	11 168	11 562	37 558 (transplantation) + 12998 – 13 108 (follow-up)	1903	Direct health care costs (fees) of the UK mild HCV trial (Wright et al 2006)
		During treatment	15 701	15 844	15 844	16 406						
		Treatment responder	356	985	985	1564						
		Treatment non-responder	162	1003	985	1564						
Plunkett et al.[108]	12 399	Diagnosed	104	104	/	155	20 973	15 443	/	103 911	20 782	Direct health care costs (fees) Bennett 1997 - Wong 2000
		Undiagnosed	0									
Wong 2002[189]			138			277	8926	11 074	/	55 370	9634	Belgian direct health care cost (fees)

CC: compensated cirrhosis; DC: decompensated cirrhosis; HCC: hepatocellular carcinoma; LT: liver transplant; /: not taken into account in the model

2.2.4.9. Results

A synthesis of the results of the economic evaluations is presented in Table 2.18 and 2.19. Discrepancies among results appear. Moreover, given the numerous concerns exposed in the methodological sections above, the validity of these results can be questioned. The following sections detail the results for each target population.

Table 2.18 : Results of cost-effectiveness analyses

Author	Discount rate	Population	Incremental discounted costs (Euros)	Incremental discounted LYGs	ICER (cost/LYG) (Euros)
Nakamura et al.[105]	Costs and outcomes: 3%	General population: 40-49 years	1 749	2.650	660
		General population: 50-59 years	2 750	2.170	1 267
		General population: 60-69 years	3 722	1.530	2 432
		General population: 70 years and over	4 681	1.240	3 775
		High risk group: 40-49 years	-1 543	2.650	Dominant
		High risk group: 50-59 years	884	2.170	407
		High risk group: 60-69 years	2 729	1.530	1 784
Castelnuovo et al.[117]	Costs: 6% Outcomes: 1.5%	General case: Former IDUs	1 043	0.038	27 449
		In general practice: current or former IDUs	1 042	0.038	27 413
		In general practice : all patients aged 30-54 years	234	0.007	33 375
		In prisons: all new prisoners (25-39 years) with a general lecture	388	0.008	48 442
		In prisons: all new prisoners (25-39 years) with a specific lecture	840	0.023	36 507
		In drug and alcohol services	1 141	0.044	25 923

ICER: Incremental cost-effectiveness ratio (compared to no screening); IDU = injecting drug users; LYG: Life-year gained

Table 2.19 : Results of cost-utility analyses

Author	Discount rate	Population	Incremental discounted costs (€ 2009)	Incremental discounted QALYs	ICER (Cost/QALY) (Euros)
Tramarin et al.[116]	Costs and outcomes: 3%	IDUs	-28 517 956	9036	Dominant
		IWSs	911 475 613	993	917 901
Sutton et al.[171]	Costs and outcomes: 3.5%	All new prisoners: 15-24 years	/	/	55 282
		All new prisoners: 25-34 years	/	/	68 778
		All new prisoners: 35 years and over	/	/	176 486
		All new prisoners: total	378	0.005	75 583
Castelnuovo et al.[117]	Costs: 6% Outcomes: 1.5%	General case: Former IDUs	1 043	0.046	22 675
		In general practice: current or former IDUs	1 042	0.046	22 645
		In general practice : all patients aged 30-54 years	234	0.011	21 238
		In prisons: all new prisoners (25-39 years) with a general lecture	388	0.014	27 681
		In prisons: all new prisoners (25-39 years) with a specific lecture	840	0.037	22 694
		In drug and alcohol services	1 141	0.047	24 269
Castelnuovo et al.[117]	Costs and outcomes: 3.5%	General case: Former IDUs	/	/	45 673
Plunkett et al.[108]	Costs and outcomes: 3%	Pregnant woman and their child (screening vs no screening)	95	-0.00011	Dominated
		Pregnant woman and their child (screening + caesarean vs no screening)	103	0.0001	1 026 100

ICER: Incremental cost-effectiveness ratio; IDU = injecting drug users; IWS = individuals with surgery; QALY: quality-adjusted life-year

Screening of the general population

Castelnuovo et al.[117] concluded that screening the general population in primary care is likely to be a cost-effective strategy at a UK willingness to pay of £30 000/QALY. However, the probabilistic sensitivity analysis showed that results were uncertain and that screening the general population was a dominated strategy in some cases (more costly and less effective than no screening). Moreover, the impact of the discount rate choice was not analyzed.

Nakamura et al.[105] concluded that screening of the general population was a cost-effective strategy compared to no screening. However, uncertainty of parameters was not handled by a probabilistic sensitivity analysis.

Conversely, Kirkizlar et al.[101] assessed different scenario's on alcohol consumption and concluded that the population not consuming alcohol excessively (<50g/day) should not be screened. They also added that if they assumed that 4.9% of the population was heavy drinker (>50g/day) and that 100% of heavy drinkers reduced their consumption after the diagnosis of hepatitis C, two tests should be performed (at 20 and 25 years old). They also analysed a similar scenario where only 50% of heavy drinkers reduced their consumption after HCV diagnosis. In this case, no screening test should be performed. However, in this study, uncertainty of parameters was not handled by a probabilistic sensitivity analysis.

Screening of IDUs

Castelnuovo et al.[117] concluded that screening former IDUs is likely to be a cost-effective strategy at the UK willingness to pay threshold of £30 000/QALY. However, the probabilistic sensitivity analysis showed that results were uncertain and that screening these patients was a dominated strategy in some cases (more costly and less effective than no screening). Moreover, the authors themselves state that with the discount rate recommended in the current NHS guidelines (3.5% for both costs and outcomes), screening former IDUs is no longer cost-effective (£33 235/QALY).

Kirkizlar et al.[101] concluded that yearly screening of IDUs aged between 16 and 35 years was cost-effective ($21 839.4/QALY) compared with no screening. However, as specified above, no probabilistic sensitivity analysis was performed.

Tramarin et al.[116] concluded that screening the IDUs population every 6 months was a dominant strategy compared to no screening (less costly and more effective) but as specified in the methodological section (e.g. section 2.2.4.5 Interventions), parameters used in this study were not always transferable to the Belgian setting. Moreover, no probabilistic sensitivity analysis was performed.

Screening of prisoners

Castelnuovo et al.[117] concluded that prisoners screening is likely to be a cost-effective strategy at a UK willingness to pay of £30 000/QALY. However, the probabilistic sensitivity analysis showed that results were uncertain and that screening these patients was a dominated strategy in some cases (more costly and less effective than no screening). Moreover, the impact of the discount rate choice was not analyzed.

Sutton et al.[171] performed a similar study but used, among other differences, the discount rates advised in the current NHS guidelines. They concluded that screening of prisoners was not a cost-effective strategy. The probabilistic sensitivity analysis showed that results were uncertain and that screening these patients was dominated in some cases (more costly and less effective than no screening).

Screening of patients in drug and alcohol services

Castelnuovo et al.[117] concluded that screening people in drug and alcohol services is likely to be a cost-effective strategy at a UK willingness to pay of £30 000/QALY. However, the probabilistic sensitivity analysis showed that results were uncertain and that screening these patients was a dominated strategy in some cases (more costly and less effective than no screening). Moreover, the impact of the discount rate choice was not analyzed.

Screening of pregnant women

Plunkett et al.[108] concluded that screening pregnant women and their child was not a cost-effective strategy compared to no screening ($1 170 000/QALY). However, uncertainty of the parameters was not handled by a probabilistic sensitivity analysis.

Screening of other populations at risk

Nakamura et al.[105] concluded that screening the populations at risk (risk factors considered: high aminotransferase level (not defined), major

operation (not defined) or blood transfusion) was cost-effective compared to no screening. However, no probabilistic sensitivity analysis was performed.

Tramarin et al.[116] concluded that screening individuals having had surgery was not a cost-effective strategy compared to no screening. However, no probabilistic sensitivity analysis was performed.

2.2.5. Conclusions

Except for IDUs where the three identified studies were in favour of screening, discrepancies among the results appear. Moreover, all studies suffer from major flaws casting doubts on the validity of their conclusions. The limitations of the studies pertained to the following:

- Not enough consideration of the wide uncertainty in the estimates in most studies (Plunkett et al.[108], Kirkizlar et al.[101], Nakamura et al.[105] and Tramarin et al.[116]).
- Non reliable data on quality-of-life scores, especially on the impact of HCV diagnosis due to the screening (either not taken into account or based on assumptions).
- The impact of the discount rate choice was not taken into account in the conclusions (Mostly in Castelnuovo et al.[117])
- Unfair study design (CEA and not CUA), i.e. the impact of screening on the quality of life was not considered (Nakamura et al.[105])
- Discrepancies across the studies in the natural evolution of the disease (transition rates), in the prevalence of HCV infected person, in the costs and in the utility data. More reliable data for each target population are needed.
- Moreover, results are not transferable to our country setting:
- Different population from the Belgian setting (higher incidence of hepatocellular carcinoma in Japan) (Nakamura et al.[105]).
- Discrepancies in the practical choice of screening or diagnostic tests performed compared to current practice in Belgium (Kirkizlar et al.,[101] Tramarin et al.,[116] Nakamura et al.[105])
- Discrepancies in treatment duration compared to current practice in Belgium (Castelnuovo et al.,[117] Plunkett et al.[108], Kirkizlar et al.,[101] Nakamura et al.[105])
- No Belgian cost or utility values

In view of those limitations, no reliable conclusion can be drawn from the current studies. If a model is to be build, adapted to the Belgian setting for each target group (general population and high risk groups), the following variables will be needed. Some of these variables are readily available.

- Belgian epidemiologic data
- Data on screening test and treatment acceptance rate
- Data on the rate of spontaneous presentation or re-presentation for screening
- Data on the compliance to the treatment and its impact on the SVR in real practice
- Quality of life data, especially on the impact of HCV diagnosis due to the screening
- Data on the natural evolution of the disease for each target group, on long term treatment effect and on influence of co-factors such as alcohol use
- Belgian cost data

Pending collection of missing input data, a model-based cost-utility study on HCV screening adapted to the Belgian setting could be performed.

Key points

- **There are discrepancies in the results of the economic evaluations on HCV screening**
- **In view of the limitations of the studies identified, more robust data are needed before drawing any conclusions on the cost-effectiveness of hepatitis C screening in Belgium**

2.3. International comparison

2.3.1. Introduction and methods

The purpose of this chapter was to compare national screening strategies among some countries. France, the Netherlands and Germany were selected because of their geographic proximity with Belgium and their comparable living standard.

To identify if national screening programs are in place in other countries, the websites of HTA institutes listed on the INAHTA website (see appendix 1.1.1) were investigated. This search allowed the selection of two additional countries, i.e. the United States and the UK (including Scotland). Both countries were chosen because they graded the level of evidence of their recommendations.

For these five selected countries, information on screening strategies was obtained from:

- national official websites related to health care
- personal contacts with national official organisms related to health care
- INAHTA websites

For Belgium, the guidelines published by the Belgian association for the study of the liver were used, i.e. the most official source available.

The screening of blood/organ donors was not assessed in this report (out of scope).

2.3.2. Results

Screening strategies for each country are described in appendix 1.3. Methods to produce these recommendations were not always reported and when a method was specified, recommendations were mainly based on literature review (mostly on other recommendations and guidelines) associated with expert opinions (see appendix 1.3). Only the US Preventive Services Task Force (USPSTF)[170] and the German[190] and Scottish guidelines[191] assessed a level of evidence for their recommendations.

The USPSTF concluded that adults who have no risk factors for HCV infection should not be screened. They found no evidence that screening for HCV infection leads to improved long-term health outcomes and only limited evidence that antiviral therapy (long, costly and associated with a high patient dropout rate) improves long-term health outcomes. They added that potential harms of screening include unnecessary biopsies and labeling (limited evidence on the magnitude of these harms). Therefore, they concluded that they found at least fair evidence that the potential harms of HCV screening are likely to exceed the potential benefits. They also found no evidence to determine if adults at high risk should or should not be screened for HCV infection (no evidence that a screening of patient at high risk leads to improved long-term health outcomes).[170]

The UK National Screening Committee is the only one that included cost-effectiveness considerations in their assessment. They concluded that neither a systematic population screening program nor an antenatal screening program for Hepatitis C are recommended.[192, 193]

In all other investigated countries, an HCV screening program for the general population was also not recommended (see Table 2.20).

No information on selective screening programs for high risk groups were found (= screening systematically offered by invitation). Only dialysis patients were often systematically screened as part of their medical treatment. For other risk factors, different recommendations were made between countries: no recommendation, no screening, no evidence for screening, information of the target population and/or test offer, and systematic screening (often as part of their medical treatment) (see Table 2.20).

Finally, most countries formulated general recommendations on the need to inform both the professionals and the population on hepatitis C (risk factors, treatment possibilities, hygiene rules, etc.), with a special focus on people who use illegal drugs.

Fair = “Evidence is sufficient to determine effects on health outcomes, but the strength of evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes”[170]

Table 2.20: HCV screening strategies in other countries

Target population	Belgium[59]	France[166, 194]	Germany[190]	The Netherlands[169, 195]	UK (department of Health)[196]	Scotland[191]	USA (CDC)[167]
General population	No	No	No	No	No	No	No
Recipients of blood or blood products	O (if <7/1990)	O (if < 1988 for stable products or < 1992 for labile products)	O (if < 1992)	O	O (if < 1991 for transfusions and < 1986 for blood products)	O (if < 1991 and < 1987 for blood clotting factor concentrates)	O (if < 1992 and < 1987 for blood clotting factor concentrates)
Recipients of organ transplant	O (if < 7/1990)	O (if < 1992)	O	V	O (if < 1992 or in countries at risk*)	O (if < 1992)	O (if < 1992)
Recipients of tissue transplant	O (if < 7/1990)	O (if < 1992)		O	O (if < 1992 or in countries at risk*)	O (if < 1992)	NE
Recipients of cell transplant	O (if < 7/1990)	O (if < 1992)					
People who were notified they received blood from a donor who later was tested positive for HCV							O
People who had undergone a major medical or surgical treatment (e.g. cardiac surgery, period in intensive care, digestive bleeding etc.)	O (if < 7/1990)	O					
Former IDUs	O	O	O	O	O	O	O
Current IDUs		O (regularly)	O	O	O	O	O
Intranasal cocaine and other noninjecting illegal drug users	O (if former)				No		NE
Current prisoners		O	O				
Former prisoners		O					
HIV infected people	O	O	O		V	O	
HBV infected people	O	O	O				
People with sexually transmitted diseases							NE

Target population	Belgium[59]	France[166, 194]	Germany[190]	The Netherlands[169, 195]	UK (department of Health)[196]	Scotland[191]	USA (CDC)[167]
Children born from HCV-positive mothers	O	O	O		O	O	O
Household members of HCV infected persons (no sexual contact)	O	O	O			O	No
Sexual partners of HCV infected persons	O	O	O		O (if regular)	O	NE
High-risk sexual behaviour (e.g. multiple sexual partners)					No		NE
Immigrants from risked countries*			O	O			
Dialysis patients	O	O	O	V	V	V	O
Haemophiliacs; Polytransfusees; Patients with hypogammaglobulinemia				V			O
People with puncture wounds				V			
People with (a history of) tattoos and other skin-penetrating interventions	O (if non disposable equipment)	O (if non disposable equipment)		O	O (if non disposable equipment)	O (if poor control)	NE
People who have received (medical or dental) care in risked countries*	O	O			O	O	
Persons with unexplained elevated serum aminotransferase levels and/or clinical signs of hepatitis or chronic liver disease	O	O	O		O	O	O
Persons with unexplained asthenia or with history of unexplained jaundice	O						
Pregnant woman					No		No

Target population	Belgium[59]	France[166, 194]	Germany[190]	The Netherlands[169, 195]	UK (department of Health)[196]	Scotland[191]	USA (CDC)[167]
Woman who had difficult parturition	O (if < 7/1990)						
Health care workers		No but O if exposed	V	O if exposed	No but O if exposed	V (if career that requires to perform exposure prone procedure); O (if exposed)	No but O if exposed

NE: No evidence available on the effectiveness of screening; No = Do not test (except if other risk factors); O = provide information and offer a test; V = To be tested systematically (often as part of their medical treatment); Countries at risk = high HCV prevalence or countries with poor infection control. If a risk factor listed in the left column was not mentioned in the identified reports, the cell was left blank.*

3. PREVENTION OF HCV INFECTION IN IDU

3.1. Review of the effectiveness literature

3.1.1. Methods

3.1.1.1. Literature search strategy

The research question for this current review is:

- What is the evidence on the effectiveness of prevention measures to reduce transmission of HCV infection among IDUs?

Electronic databases were consulted up to July 2011. In a first stage, Medline, Embase, CDSR, DARE, HTA databases and the websites of HTA institutes listed on the INAHTA websites (see appendix 1.1.1) were consulted to retrieve HTA reports, systematic reviews and meta-analyses on this topic.

Original studies analysing the impact of primary prevention on the spread of hepatitis C among IDUs were then searched. However, for this population, epidemiological studies are very difficult to carry out (hidden nature, low prevalence in general population, challenge of follow-up and confounding). To obtain an insight into the dynamics of viral transmission among IDU and the consequence of specific interventions in this population, modelling studies are needed. The NHS EED, Medline, Embase, and Econlit databases were therefore searched to retrieve modelling studies on this topic.

No restriction on the time period was imposed. Reference lists of the selected studies were checked for additional relevant citations.

The keywords used and the results are detailed in the appendix 2.1.1. The main search terms were:

- Hepatitis C;
- Primary prevention OR Treatment; and
- IDUs;

3.1.1.2. Selection criteria

All retrieved references were assessed against pre-defined selection criteria (in terms of population, intervention, outcomes, and design – Table 3.1) in a two-step procedure: initial assessment of the title, abstract and keywords; followed by full-text assessment of the selected references.

Because the definition of active IDUs varies in the literature, all kinds of IDUs were retained (current IDUs, IDUs under opiate replacement therapy, no specification). The aim of this section is to analyse the impact of primary prevention measures on the transmission of HCV. Therefore, only studies reporting an impact on HCV incidence or prevalence were included. Studies analysing the impact of needle exchange programs on life expectancy or on HIV incidence/prevalence without including the impact on HCV incidence/prevalence, for example, were excluded.

All primary prevention interventions were retained. As some studies analysed the impact of using treatment to prevent HCV transmission, meta-analyses and systematic reviews on the treatment of IDUs were also retained in order to check the parameters used in these studies.

Table 3.1 : Prevention of hepatitis C in IDUs - Effectiveness studies - Selection criteria

	Inclusion criteria	Exclusion criteria
Population	IDUs	Non IDUs
Intervention	Primary prevention: • Needle or syringe exchange • Opiate replacement therapy • Provision of injecting paraphernalia • Bleach disinfectant • Behavioural interventions • Drug consumption rooms • Treatment used as a way to avoid the development of disease • Expanded harm reduction (where the harm reduction interventions of needle exchange, opiate replacement, etc. was not evaluated independently)	No intervention, secondary prevention (e.g. screening), tertiary prevention (except meta-analysis and systematic reviews on the treatment of IDUs) or quaternary prevention.
Outcome	Incidence rate, prevalence rate, or measures of associations (e.g. rate ratio) with prevalence or incidence.	Other outcomes
Design	Meta analysis or systematic reviews Modelling studies	Other designs

3.1.1.3. Quantity of research available

Systematic reviews, meta-analysis and HTA

After excluding 18 duplicates, 45 unique citations were identified from the databases. Hand searching allowed us to identify 2 additional citations. Of this total of 47 references, 33 did not meet the inclusion criteria based on title and abstract evaluation. Among the 14 citations retained for full-text assessment, one study was a duplicate. Finally, 13 studies satisfied our inclusion criteria, i.e. 6 on primary prevention interventions (see Table 3.2)[197-202] and 7 on the treatment of IDUs.[6, 203-208] The flow chart of this selection is presented in appendix 2.1.1.

Table 3.2 : Systematic reviews or meta-analysis on primary prevention interventions

	Gillies 2010 [197]	Hagan 2011 [198]	Jones 2010 [199]	Palmateer 2010 [200]	Tilson 2006 [201]	Wright 2006 [202]
Needle or syringe exchange		X	X	X	X	X
Opiate substitution therapy		X			X	X
Provision of injecting paraphernalia	X					
Bleach disinfectant		X				X
Behavioural interventions		X			X	X
Treatment*						
Expanded harm reduction**		X				X

**used as a way to avoid the development of disease; **where the harm reduction interventions of needle exchange, opiate replacement, etc. was not evaluated independently*

Modelling studies

After excluding 27 duplicates, 123 unique citations were identified from the databases. Hand searching did not allow us to identify additional citations. Of this total of 123 references, 114 did not meet the inclusion criteria based on title and abstract evaluation. Among the 9 citations retained for full-text assessment, 2 did not fulfil the intervention criteria.[209, 210] Finally, 7 modelling studies were retained: 4 on broad harm reduction interventions,[211-214] and 3 on treatment used as primary prevention.[215-217] The flow chart of this selection is presented in appendix 2.1.1.

3.1.2. Systematic reviews, meta-analyses and HTAs

Intervention studies in injecting drug users (IDU) aim to reduce the injecting drug use itself as well as the prevention of viral infections. The focus in such studies has mainly been on reducing HIV infections. Compared with HIV, the impact of these interventions to reduce HCV infection is less clear.[201] The interventions studied using new HCV seroconversions as an outcome include prevention counseling and other behavioral interventions, opiate-substitution therapy (OST), needle and syringe programs (NSP), syringe disinfection, and interventions that combine OST and NSP.

Two recent systematic reviews of the literature were published in 2010[199] and 2011[198]. Most studies identified by the reviews were observationals. Hagan[198] included 2 RCTs on behavioral interventions, 1 RCT on opiate-replacement therapy, and 1 RCT comparing enhanced versus standard counseling in an OST program. In none of the RCTs a significant reduction of HCV seroconversion was observed. Previous published reviews of the literature had similar conclusion.[200, 202] The only intervention identified in systematic reviews which was associated with a reduction of HCV seroconversion was the combination of OST and NSP.[198, 199] A cohort study of IDU in Amsterdam showed a lower HCV seroconversion rate in those subjects who showed a high adherence to the methadone and NSP programs. A recent pooled analysis of the experience at six UK centres confirms this observation.[218] The level of evidence provided by such observational data remains low however. Ideally, a causal relationship of the intervention with the observed decrease in HCV seroconversion is best studied using an RCT.

One review also assessed the provision of non-needle/syringe drug injecting paraphernalia in prevention of HCV among IDUs but concluded that evidence on this topic was limited.[197]

Two recent reviews of the short-term outcomes of hepatitis C treatment in IDU were published in 2009[6] and 2010.[207] The sustained virological response rate (SVR) after treatment of acute or chronic hepatitis C in IDU depends on the population studied. Overall genotype 1/4 accounted for about 50% of the infections studied.[207] The median completion rate in IDU was found to be 71%.[6] Most studies included IDUs that had a substantial period of abstinence and 96% were enrolled in an OST program.[207] Across these reported studies, the median SVR in chronic hepatitis C in IDU was similar to response rates observed in the RCTs for product registration.[6, 207] Among IDU in an OST program SVR seems to be lower in those who injected at least once during the study period, but only very few subjects were studied who reported a more regular use of drugs. Hellard reported an overall median SVR of 41%.[6] Zanini reported a mean SVR of 52%; SVR was reported to vary from 39% (in studies not excluding active IDU) to 55% (in studies excluding active IDU).[207] Treatment and treatment outcomes in active IDU who are not being followed as part of a OST program has not been well documented. Based on the literature reviewed it was not possible to define a minimum duration of drug abstinence (or participation in a OST program), that was predictive of hepatitis C treatment outcome.

Previous reviews of the short-term outcomes of hepatitis C treatment in IDUs did not allow us to identify additional relevant studies not reported in the reviews of Hellard et al. and Zannini et al.[203-206, 208] The previous reviews were therefore not detailed in this report.

3.1.3. Modelling studies

3.1.3.1. Harm reduction interventions

Study design and model type

All identified publications used a theoretical mathematical model to simulate HCV transmission among IDUs and to evaluate the potential prevention impact of harm reduction interventions on HCV prevalence.[211-214] Two of these studies also assessed the impact on HIV prevalence.[212, 214]

Three of the studies used a dynamic model, allowing for entry of new injectors in the system or leave of the system because of death or cessation of injecting.[211-213] One study used a static model based on the current level of IDUs in the studied population and therefore did not show the potential spread of the epidemic over time.[214]

Population

Target population was active IDU in all studies. No more description was given except in the study of Vickerman et al.[213] where a distinction was made between new IDUs (<1 year) and older IDUs (>1 year) and between IDUs with lower or higher frequency of syringe sharing.

Model structure and parameterization

Each study highlighted the great uncertainty around parameters of their model, especially for behavioural parameters (based mostly on self-reported behaviour). Moreover heterogeneity of risk behaviour was not taken into account (except partially in the model of Vickerman et al.[213]

Important parameters such as the proportion of IDUs who shared syringes varied across the studies (40-54% in the study of Hutchinson et al.[211] and 15-20% in the Study of Kwon et al.[214]). These parameters are dependant of the country setting and of prevention measures implemented. They are therefore not transferable to the Belgian setting.

Outcomes

Because results of these studies were specific to the setting of the country analysed, only general conclusions were reported. A detail of the results can be found in appendix 2.1.2.

Studies showed that current harm reduction interventions were effective in the control of HIV[212, 214] but not in the control of HCV transmission among IDUs.[211-214] Different suggestions to reduce HCV prevalence among IDUs were highlighted:

- Interventions should target all IDUs (and not only high risk IDUs), reach IDUs within 12 months of injecting and be sustained for many years.[213]
- Interventions should especially focus on the reduction of the number of partners, the proportions of IDUs who share syringes, and/or the frequency of syringe sharing.[211-214]

However, even if these interventions would permit to reduce HCV prevalence, thousand of people will continue to be HCV infected and additional measures are needed.

3.1.3.2. Treatment as primary prevention

Study design

Three publications have utilized theoretical mathematical models to evaluate the potential prevention impact of HCV antiviral treatment on HCV prevalence among injecting drug users.[215-217] A comparison of the models can be found in Table 3.3.

Table 3.3 : Summary of the effectiveness models on the treatment of IDUs as prevention of HCV infection

	Zeiler et al. 2010[217]	Martin et al. 2011a[216]		Martin et al. 2011b[215]
Target population	Current IDUs; Current IDUs on/off methadone maintenance therapy	Current IDUs		Current IDUs
Country	Australia	UK		UK
Baseline HCV prevalence	60% acute+chronic	20%, 40%, 60% chronic		20%, 40%, 60% chronic
Baseline treatment rate	1% chronic HCV infections per year	0%		0%
Immunity	Yes, all who spontaneously clear or attain treatment SVR. Waning immunity.	Yes, 25% who spontaneously clear or who attain treatment SVR.		No
Retreatment of nonresponders	Yes	Yes		No
Treatment term	Fixed proportion of chronic infections per year	Fixed proportion of chronic infections per year; fixed number of chronic infections per year		Fixed number of chronic infections per year
Genotype distribution		Mixed genotype	50% genotype 1, 50% genotype 2/3	50% genotype1, 50% genotype 2/3
		Genotype 1	100% genotype 1	
Treatment SVR	50% (stated), 33% effectively modeled, see Vickerman et al.[219]	Mixed genotype	62.5% (45% genotype 1, 80% genotype 2/3)	62.5% (45% genotype 1, 80% genotype 2/3)
		Genotype 1	45%	
Time horizon	Long-term steady-state	Long-term steady-state; 0-100 years		5, 10, 20 years
Treatment rate needed for eventual eradication	60% prevalence: 56.5% annually	Mixed genotype	20% prevalence: 4% annually or 2 per 1000 annually	Not examined
			40% prevalence: 10% annually or 9 per 1000 annually	
			60% prevalence: 25% annually or 29 per 1000 annually	
		All genotype 1	20% prevalence: 5% annually	
			40% prevalence: 13% annually	
			60% prevalence: 34% annually	
Proportion of treatment which should be allocated to those not in methadone maintenance programs	Assuming equal adherence and treating 60% annually: 84%	Not examined		Not examined
	Assuming 44% adherence if not in MMT and treating 60% annually: 50%			

	Zeiler et al. 2010[217]	Martin et al. 2011a[216]	Martin et al. 2011b[215]
Short-term impact	60% acute+chronic prevalence: treating 56.5% annually halves chronic prevalence in 3.3 years and halves acute prevalence in 11.1 years.	40% chronic prevalence: treating 2%, 4%, or 6% annually could reduce chronic prevalence within 20 years by over 15%, 33%, or 50%, respectively.	20% chronic prevalence: annually treating 10 per 1000 IDU results in a 16%, 30%, and 57% reduction in chronic prevalence within 5, 10, and 20 years, respectively. 40% chronic prevalence: treating 10 per 1000 IDUs annually reduces prevalence by 8% after 5 years, and 22% after 20 years. 60% chronic prevalence: treating 10 per 1000 annually reduces prevalence by 9% after 20 years.
Model sensitivity	Baseline prevalence most sensitive to infection rate and exit rate.	Threshold level of treatment needed for eradication most sensitive to infection rate and exit rate.	Prevalence reduction most sensitive to infection rate and exit rate.

Model type

All three models used deterministic systems of ordinary differential equations to model HCV transmission and treatment among current injecting drug users.

Population

Target population was current IDU in all three studies. Zeiler et al.[217] also examined allocating treatment to those enrolled or not enrolled in methadone maintenance therapy (MMT).

Model structure and assumptions

All studies included the potential for reinfection after successful HCV treatment. Discrepancies were found concerning the presence and duration of immunity. Further, differences were found between whether the model considered or neglected the acute HCV stage.

The model used in Zeiler et al.[217] included susceptible IDUs, acute HCV infections, chronic HCV infections, treatment, and immunity. All who spontaneously clear the acute infection, or who succeed treatment enter the partial immune phase. Zeiler et al.[217] assumed IDUs could leave the immune class and re-enter the susceptible class due to waning immunity. Those who fail treatment return to the chronic infection pool and can be retreated. Those on treatment are assumed not to be infectious.

Martin et al. 2011a[216] tracked susceptible IDUs, chronic HCV infections, treatment, and immunity. Due to the relatively short duration of the acute stage and the small proportion that spontaneously clear infection, the number of HCV infections caused by IDU that cleared spontaneously was assumed small, and neglected in the model. In contrast to Zeiler et al. 2010,[217] only 25% of those who spontaneously clear or attain SVR enter an immune stage, which the authors assumed to be permanent (this assumption is probably incorrect, see further). The remaining 75% return to the susceptible stage. Those who fail treatment return to the chronic infection pool and can be retreated. Those on treatment are assumed not to be infectious.[216]

Martin et al. 2011b[215] extended the 2011a model[216] to include a compartment for treatment nonresponders, assuming those who fail treatment cannot be retreated. Further, they conservatively assume no immunity as they acknowledge the concept of sterilising immunity following HCV infection is controversial, and a previous publication (Martin 2011a)[216] indicated the model projections were not sensitive to this stage.

Antiviral treatment term

Discrepancies were found relating to the mathematical formulation of the treatment term. Zeiler et al. 2010[217] implemented treating a fixed proportion

of chronic infections per year. Martin 2011a[216] examined two treatment terms: treating a fixed proportion of chronic infections per year, and also treating a fixed number of chronic infections per year. Martin 2011b[215] only modelled treating a fixed number of chronic IDUs annually. The use of different treatment terms is important in explaining some of the differences in model conclusions. In a model with a fixed proportion treated per year, fewer IDUs are treated over time as the prevalence is driven down. In the fixed number of treatments per year scenario then as the prevalence is reduced, a greater proportion of chronic infected are treated over time.

Model parameterization

Epidemiological parameters

Exit rates (cessation of drug injection or death) of 0.083 (Zeiler et al. 2010)[217] and 0.085 (Martin et al. 2011a[216] and 2011b[215]) per year were used. Infection rates were fit to baseline chronic prevalences. A probability of spontaneous clearance of 0.25 (Zeiler et al. 2010)[217] and 0.26 (Martin et al. 2011a[216] and 2011b[215]) was used.

Substantial discrepancies were found among studies concerning the proportion of those becoming immune, and the duration of immunity. Zeiler at al.[217] assumed 100% of those who spontaneously clear or attain SVR enter the immune phase, with a waning immunity of 0.25 per year. Martin et al. 2011a[216] assumed 25% of those who spontaneously clear or attain SVR enter a permanent immune phase. Martin et al. 2011b[215] assumed 0% transition to immunity, however an uncertainty analysis showed varying the proportion transitioning to immunity from 0 to 50% had little impact on the results.

An acute phase of 6 months was used in Zeiler et al.,[217] and no acute phase was modelled in Martin et al. 2011a[216] and 2011b[215].

In the two-group model, Zeiler et al.[217] assumed an average duration in and out of methadone maintenance therapy of 8 and 12 months, respectively. Zeiler et al.[217] assumed no reduction in HCV risk or transmission while on methadone maintenance therapy.

Sustained viral response rates and treatment duration

Discrepancies were found among studies on the average treatment sustained viral response rate. Zeiler et al.[217] claimed to use a 50% SVR rate, along with a treatment duration of 18 weeks for nonresponders and 36 weeks for responders. However, a commentary by Vickerman et al.[220] noted that the use of differential exit rates by response led to an effective SVR rate of 33%. Martin et al. 2011a[216] and 2011b[215] used treatment success rates of 45% for genotype 1 and 80% for genotype 2. Hence, in their mixed genotype scenario (50% genotype 1, 50% genotype 2), an SVR rate of 62.5% was used, but was varied in the sensitivity analysis.

Baseline prevalence

Zeiler et al.[217] defined baseline prevalence as including acute+chronic infections, and examined a baseline acute+chronic prevalence of 60%. Martin et al. 2011a[216] and 2011b[215] defined baseline prevalence as including chronic infections only, and examined scenarios of 20%, 40%, and 60% baseline chronic prevalence.

Baseline treatment rate

Zeiler at al.[217] modelled a 1% annual baseline treatment rate of chronically infected IDUs, while Martin et al. 2011a[216] and 2011b[215] assumed no treatment at baseline.

Time horizon

Time horizon of the models spanned from 5 years to long-term steady state, this means the model is run until an equilibrium is achieved.

Genotype distribution

Martin et al. 2011a[216] examined two genotype scenarios: a mixed genotype of 50% genotype 1 and 50% genotype 2/3, and also an all genotype 1 scenario. The baseline case in Martin 2011b[215] was a mixed genotype scenario of 50% genotype 1 and 50% genotype 2/3. Zeiler et al.[217] did not specify a genotype distribution.

Outcomes

Treatment rate needed for eradication

Discrepancies were found among studies on the treatment rates needed to eradicate HCV at similar baseline chronic prevalences. Zeiler et al.[217] concluded that annually treating 56.5% chronic infections per year would eradicate HCV at the 60% baseline acute+chronic prevalence scenario. Uncertainty of the necessary treatment rate was not handled by a probabilistic sensitivity analysis. However, a commentary by Vickerman et al[219] notes that the use of differential exit rates from treatment means that

any cohort of IDUs on treatment experience treatment failure at a faster rate than treatment success, resulting in an effective 33% treatment SVR rate, instead of the intended 50%. With this mistake corrected, Vickerman et al[219] predict a required treatment rate for eradication of just under 40% chronic infections per year, instead of the 56.5% claimed by Zeiler et al.[217].

Martin et al. 2011a[216] concluded annually treating 25% infections per year, or 29 per 1000 IDU, would eradicate HCV in the 60% prevalence scenario (using a 62.5% SVR rate). The predicted necessary treatment is lower due to the use of a higher SVR rate (62.5% in Martin et al. 2011a, [216] 50% in Vickerman et al.[219], 33% Zeiler et al.[217]) and also the difference in baseline prevalence (60% acute+chronic prevalence in Zeiler et al.[217] and Vickerman et al.[219], 60% chronic prevalence in Martin et al. 2011a[216] and 2011b[215]). Uncertainty in the necessary treatment rate was handled in a univariate sensitivity analysis, but not a probabilistic sensitivity analysis.

Short-term impact of treatment

Due to the discrepancies in treatment term (proportional vs. fixed), treatment rates, and baseline prevalences examined, a comparison between study results of the short-term impact was impossible. Zeiler et al.[217] found that annually treating 56.5% in the 60% acute+chronic prevalence setting halves chronic prevalence in 3.3 years and halves acute prevalence in 11.1 years.

Martin et al. 2011a[216] concluded that in a 40% chronic prevalence setting, annually treating 2%, 4%, or 6% could reduce chronic prevalence within 20 years by over 15%, 33%, or 50%, respectively.

Martin et al. 2011b[215] used a treatment term where a fixed number of chronic infections are treated annually, and concluded that for an IDU population with 20% chronic prevalence, treating 5, 10, 20, or 40 per 1000 IDU annually results in a 15%, 30%, 62%, or 72% reduction in prevalence, respectively, after 10 years. Annually treating 10 per 1000 IDU results in a 16%, 30%, and 57% reduction in prevalence within 5, 10, and 20 years, respectively. For an IDU population of 40%, expected prevalence reductions are at most halved as compared to the 20% scenario, and quartered for 60% prevalence. At 40% chronic prevalence, treating 10 per 1000 IDUs annually reduces prevalence by 8% after 5 years, and 22% after 20 years. At 60% chronic prevalence, treating 10 per 1000 annually reduces prevalence by 9% after 20 years.

Treatment subpopulation targeting

Zeiler et al.[217] concluded that with an annual treatment rate of 60%, the majority of treatment should be targeted to those not on methadone maintenance therapy, unless adherence in those not enrolled in MMT is less than 44% as compared to those enrolled in MMT. No sensitivity analysis was performed on this result. Vickerman et al.[219] notes that insufficient explanation and detail is given regarding this result. It is not clear whether the finding results from less IDUs being treated when MMT is targeted, possibly because of fewer IDUs being on MMT, or whether less impact is achieved per IDU treated in the MMT population (Vickerman et al.[219]). Attempts to replicate this result have failed (Martin NK, *unpublished work*). Martin et al. 2011a[216] and 2011b[215] did not examine allocation between separate subpopulations.

Sensitivity analyses

Despite using different outcome measures for the sensitivity analysis (baseline chronic prevalence in Zeiler et al.,[217] treatment threshold needed for eradication Martin et al. 2011a[216], relative prevalence reduction Martin et al. 2011b[215]), the models were consistently found to be most sensitive to exit rate and infection rate.

Conclusions

Discrepancies among the results of the mathematical models of antiviral treatment for HCV prevention among injecting drug users appear, with differences in SVR rates resulting in substantial differences in predicted necessary treatment rates for eradication and short-term impact projections. The limitations of the studies pertained to the following:

- No reliable data on the SVR rates for current injectors, especially in comparison to that found in Belgium.
- No reliable data on the presence and duration of immunity for current injectors.
- Discrepancies in the baseline chronic prevalence compared to that found in Belgium.
- Discrepancies between baseline treatment rates compared to that found in Belgium.
- Assumption across the studies that no chronic infections are entering the country from abroad, which may be different to the Belgian setting.

- Lack of incorporation of heterogeneity with respect to HCV risk and treatment accessibility across the population (genotype distribution, age, high/low risk injectors) as well as across an injecting career (times in/out prison or homeless).

In view of those limitations, no specific and reliable conclusion with respect to the Belgian situation can be drawn from the current studies. More projections specifically adapted to the Belgian setting are needed, and can be found in section 3.4.

3.2. Review of the cost-effectiveness literature

3.2.1. Methods

3.2.1.1. Literature search strategy

The research question for this current review is:

- What is the evidence on the cost-effectiveness of primary prevention measures to reduce transmission of HCV infection among IDUs?

In a first stage, the HTA reports and systematic reviews identified in section 3.1. were analysed to collect pertinent reviews of economic evaluations. Full economic evaluations (see appendix 1.2.1) analysing the impact of primary prevention on the spread of hepatitis C among IDUs were then searched. The NHS EED, Medline, Embase, and Econlit databases were consulted up to July 2011. No restriction on the time period was imposed. Reference lists of the selected studies were checked for additional relevant citations.

The keywords used and the results are detailed in appendix 2.2.1. The main search terms were:

- Hepatitis C;
- Primary prevention OR Treatment;
- IDUs; and
- Cost.

3.2.1.2. Selection criteria

All retrieved references were assessed against pre-defined selection criteria (in terms of population, intervention, outcomes, and design –Table 3.4) in a two-step procedure: initial assessment of the title, abstract and keywords; followed by full-text assessment of the selected references.

Table 3.4 : HCV prevention in IDUs – Cost-effectiveness studies - Selection criteria

	Inclusion criteria	Exclusion criteria
Population	IDUs	Non IDUs
Intervention	Primary prevention: • Needle or syringe exchange • Opiate replacement therapy • Provision of injecting paraphernalia • Bleach disinfectant • Behavioural interventions • Drug consumption rooms • Treatment used as a way to avoid the development of disease • Expanded harm reduction (where the harm reduction interventions of needle exchange, opiate replacement, etc. was not evaluated independently)	No intervention, secondary prevention (e.g. screening), tertiary prevention (except meta-analysis and systematic reviews on the treatment of IDUs) or quaternary prevention. Vaccination.
Outcomes	Cost per HCV case avoided, cost/LYG or cost/QALY	Other outcomes
Design	Full economic evaluations	Other designs (see appendix 1.2.1)

All kinds of IDUs were retained (current IDUs, IDUs under opiate replacement therapy, no specification). Studies that did not include the impact on HCV incidence or prevalence were excluded.

Full economic evaluations reporting long-term cost-effectiveness in terms of cost per life-year gained (cost/LYG) or cost per quality-adjusted life-year gained (cost/QALY) were retained. Moreover, because the analysed prevention measures aimed to reduce HCV incidence/prevalence, studies reporting a cost per HCV case avoided were also retained.

One study assessed the impact of a hypothetical vaccine against HCV (effectiveness only based on assumptions). Because no vaccine is currently available for HCV, this study was excluded.

3.2.1.3. Data extraction and quality assessment strategies

The selected full economic evaluations were critically assessed and summarized in data extraction sheets (see appendix 1.2.4). The quality of these studies was then assessed narratively.

3.2.1.4. Quantity of research available

After excluding 59 duplicates, 197 unique citations were identified from the databases. Hand searching allowed us to identify 3 additional citations.[221-223] Of this total of 200 references, 183 did not meet the inclusion criteria based on title and abstract evaluation. Among the 17 citations retained for full-text assessment, 9 did not meet the outcome criteria,[131, 209, 222, 224-229] 1 did not meet the population criteria,[230] and 2 did not meet the intervention criteria.[231, 232] Finally, 5 full economic evaluations were identified: 4 on harm reduction measures[221, 223, 233, 234] and 1 on the treatment of IDUs.[235] An additional study on the treatment of IDUs was found after the timing of our search strategy [accepted for publication in September 2011] and was added.[236] The flow chart of this selection process is presented in appendix 2.2.1.

3.2.2. Overview of the economic evaluations on harm reduction measures

Because of limited evidence on the effectiveness of harm reduction measures on HCV incidence, economic evaluations on this topic were only summarized (no full description as in section on screening).

Vickerman et al.[223] analysed the cost-effectiveness of interventions related to needle and syringe programs (NSP) for IDUs for a 20-year period. They adopted the societal perspective. Three kinds of interventions were investigated, i.e. interventions that improve the coverage of syringe distribution, interventions that increase participation to opiate substitution therapy (OST) and interventions that increase participation in HCV treatment. Two areas were investigated, i.e. Bristol with HCV prevalence among IDUs of 64.9% (57.8-71.4%) and Teesside with HCV prevalence among IDUs of 26.8% (20.7-33.5%). Authors concluded that interventions to increase syringe coverage could be cost-effective (especially in area with low HCV prevalence) if the associated intervention costs were modest and that interventions to increase participation to OST programs were likely to be cost-effective. However, these results were mostly due to their impact on HIV infection. The analysis showed that improving the coverage of syringe distribution and the participation to OST programs had a significant impact on HIV but not on HCV incidence. Moreover, the quality of effectiveness data used was poor and uncertainty of these parameters was not sufficiently handled by a probabilistic sensitivity analysis. As recognized by the authors, more data from RCT are needed. It should also be noted that this study analysed interventions improving current NSP compared to current NSP without these interventions (and not NSP compared to no program).

Health Outcomes International[221] analysed the cost-effectiveness of NSP compared to no program. It was not possible to separate the effects of implementation of NSPs from other prevention measures performed in the studied countries. Because NSP was often associated with other measures such as OST, the impact of NSP is therefore overestimated and the intervention should be considered as harm reduction measures globally. Results were presented in terms of net present value (NPV) of the investment in NSP (present value of the cost of NSP – present value of HCV and HIV treatment costs avoided thanks to NSP). Although different discount rate were used in their analysis (0%; 3% and 5%), only undiscounted resuts on the impact of the intervention on HCV could be retrieved from the study.

During the time frame of the study (20 years), the present value of NSP cost was superior to the present value of HCV treatment costs avoided (NPV: -$132 million). However, if HCV treatment costs over the life of the avoided cases was considered, the NPV of investment in NSP became positive (NPV: $632 million). Taken into account the impact on HIV, the NPV increased to $6876 million over the life of the cases. They also assessed the impact on the quality of life, with an NPV varying from 32 207 QALYs (discount rate of 5%) to 119 992 QALYs (discount rate of 0%) for HCV and from 138 072 QALYs (discount rate of 5%) to 715 245 QALYs (discount rate of 0%) for HIV. However, even if NSP was considered a dominant strategy compared to no intervention, results were again mostly due to the impact on HIV. Moreover, effectiveness data came from an ecological study. The design was therefore of poor quality and resulted in a lot of bias. Uncertainty of the parameters was also not sufficiently handled (or not reported), especially for HCV parameters.

Bayoumi et al[233] assessed the cost-effectiveness of a supervised injection facility compared to other interventions such as needle exchange

programs and methadone maintenance treatment without such supervised facility. Three effects of this facility were taken into account: i.e. a decreased needle sharing (= base case; odds ratio: 0.30); an increased use of safer practices during shared injections (odds ratio: 2.70) and an increased referral to methadone maintenance treatment (MMT) (odds ratio: 1.84). Authors concluded that the supervised injection facility was a dominant strategy (less costly and more effective) compared to other interventions for a 10-year period (Base case: -$37 866 and +1326 LYG). However, the result was again mostly due to the impact on HIV. Indeed, the cost per HIV case averted was estimated to $20 100 (undiscounted) while the cost per HCV case averted was estimated to $444 500 (undiscounted). Moreover, the quality of effectiveness data used was poor and uncertainty of these parameters was not sufficiently handled in the sensitivity analysis.

Pollack et al[234] was the only cost-effectiveness analysis that assessed the impact of NSP for IDUs on HCV incidence without taking into account the impact on HIV incidence. Authors concluded that in terms of HCV incidence and prevalence among IDUs, NSP were not cost-effective (i.e. >$1 000 000 per HCV infection averted within the range of observed HCV prevalence in high-risk populations). However, the quality of effectiveness data used was poor and uncertainty of the model parameters was not sufficiently handled in the sensitivity analysis.

3.2.3. Overview of the economic evaluations on treatment of IDUs

Sheerin et al.[235] assessed the cost-effectiveness of HCV treatment of IDUs on methadone maintenance therapy (MMT) for a lifelong period. They compared four strategies:

- No Methadone maintenance therapy (MMT) and no HCV treatment
- MMT and no HCV treatment
- MMT and HCV treatment with interferon + ribavirin
- MMT and HCV treatment with pegylated interferon + ribavirin

Authors concluded that compared to no MMT and no HCV treatment, MMT alone and MMT combined with HCV treatment were cost-effective strategies (<NZ$50 000/LYG). However, the quality of effectiveness data was poor and the uncertainty of parameters was not sufficiently handled in the sensitivity analysis.

The study of **Vickerman et al**.[223] described in the previous section also assessed the impact of increasing participation rates of IDUs to HCV treatment. They assumed that 52% of treated patients were cured by the treatment (taking into account incomplete compliance). The SVR rate and compliance was not varied according to whether patients were under MMT (45.4% in Bristol and 77.5% in Teesside) or not. They concluded that such kind of intervention is likely to be cost-effective if sufficient patients were treated (10% per year or more compared to <0.9% in Teesside and 2.43% in Bristol without the intervention). At a willingness to pay of £30 000/QALY, an additional cost of £4429 for the intervention would be acceptable in Bristol. However, evidence to support the effectiveness of such intervention was limited and the uncertainty of parameters was not sufficiently handled in the sensitivity analysis. Moreover, they focused on the cost-effectiveness of the intervention to increase participation rates to HCV treatment and not on HCV treatment itself compared to no treatment.

Finally, **Martin et al**.[236] performed a dynamic mathematical model of HCV transmission and disease progression to examine the cost-effectiveness of providing antiviral treatment for IDUs compared to treating ex/non-IDUs or no treatment. Three baseline scenario of chronic hepatitis C prevalence amongst IDUs were analysed, i.e. 20%, 40%, and 60%. With a baseline chronic prevalence setting of 20% and 40%, treating IDUs was the most cost-effective option, with ICERs compared to no treatment of £521/QALY (95%CI: dominant-£1,839) and £2539/QALY (95%CI: £1,262-£4,822) respectively. However, with a baseline prevalence of 60%, treating ex/non-IDUs was slightly more likely to be the most cost-effective option (probability to be cost-effective around 60% for a willingness to pay threshold of £20 000/QALY) and treating IDUs was dominated due to high reinfection. Results are therefore highly dependent of HCV prevalence and a prevalence of 60% may be the more realistic scenario in Belgium. Authors also highlighted the great uncertainty around several parameters such as SVR rate for active IDUs in the community, utility values related to IDUs and ex-IDUs and lifespan. More data for the Belgian setting are needed. The heterogeneity in infection risk and treatment acceptability should also be taken into account.

3.2.4. Conclusions

Positive results of economic evaluations on harm reduction interventions were mostly due to their impact on HIV. Studies reporting a cost per HCV case averted showed that in terms of HCV prevalence and incidence, harm reduction interventions were not cost-effective (>$400 000 per HCV case averted). Concerning the treatment of IDUs, the potential cost-effectiveness will depend on the baseline HCV prevalence. Results of these studies were not detailed in this report because they suffer from major limitations due to the lack of reliable effectiveness data and to the fact that the wide uncertainty in the estimates was not sufficiently handled. More studies assessing interventions on active IDUs not on OST are needed.

Key points

- **The potential cost-effectiveness of harm reduction interventions would mostly be due to their impact on HIV;**
- **More robust data are needed before drawing any conclusion on the cost-effectiveness of harm reduction interventions in term of HCV incidence/prevalence;**
- **More robust data are needed before drawing any conclusion on the cost-effectiveness of treating IDUs as HCV prevention measure for the Belgian setting;**
- **Studies on active IDUs not on OST are needed.**

3.3. International comparison

3.3.1. Introduction and methods

The purpose of this chapter was to compare HCV prevention measures among some selected countries. The same countries as in section 2.3 on screening were chosen, i.e. Belgium, France, the Netherlands, Germany, the United States and UK (including Scotland).

Information was obtained from:

- national official websites related to health care
- personal contacts with national official organisms related to health care
- INAHTA websites

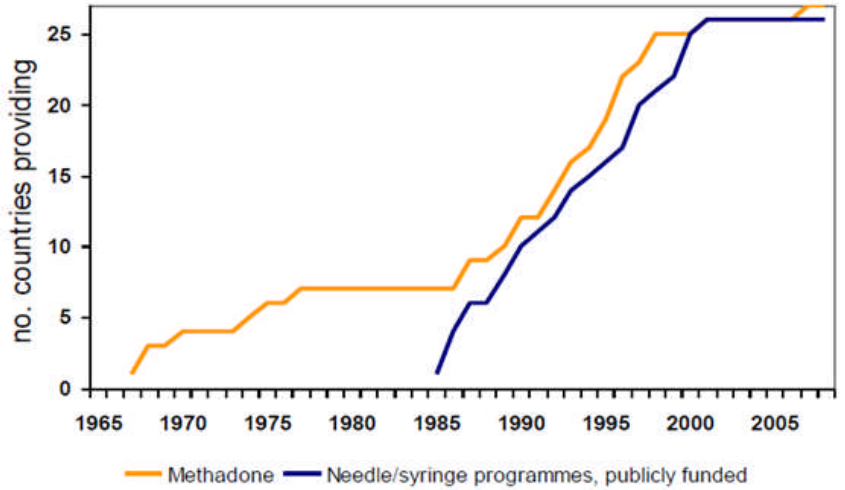
For Belgium, no guidelines on the treatment of IDUs are published by governmental authorities. We therefore used the guidelines published by the Belgian association for the study of the liver, i.e. the most official source.[60]

3.3.2. Results

3.3.2.1. Opioid substitution treatment and needle and syringe programs

Opioid substitution treatment and needle and syringe programs are available in every investigated country. As information, Figure 3.1 shows the evolution of the introduction of these prevention measures in the 27 EU member state.

Figure 3.1: Introduction of opioid substitution treatment and needle and syringe programs in the 27 EU Member States



Source: EMCCDA 2010[237]

3.3.2.2. HCV treatment as prevention

As shown in Table 3.5, IDU is no longer a contra-indication for treatment. An individual estimation of the benefit-risk together with an appropriate

support (multidisciplinary follow-up, participation on OST, etc.) is nevertheless usually advised.

Table 3.5 : Indications for the treatment of IDUs by country

Belgium[60]	• Persons in long-term complete remission (> 12 months), in long-term partial remission (e.g. on agonist therapy and/or in a controlled environment, including occasional drug users), and other persons in remission (e.g. who experimented with substances for a very short period) may be eligible for antiviral treatment. They have to "understand the need for and actively want HCV treatment, be able and willing to maintain close monitoring and take the necessary measures for birth control (contraception)"[60] • Persons with either substance dependence or substance abuse and who are not in remission will usually not be eligible for antiviral treatment (general rule). Treatment could nevertheless be considered in some case but the decision has to be made by a multidisciplinary treatment team together with the patient and be based on individualized risk-benefit assessments. • They have to be educated and informed, drug use counselling and relapse prevention support should be available. If needed, psychiatric services should be easily accessible. • Persons in partial remission or not in remission have to be evaluated by a physician having an expertise in treating substance users and by a psychiatrist and have to agree to be followed up in a multidisciplinary setting. • Patients not in remission "have to be advised and referred to start a substitution therapy. Their social situation needs to be stabilised as well before interferon treatment can be started."[60]
France[238]	• IDU is not a contra-indication for treatment • IDUs should only be treated after a follow-up by a multidisciplinary team. The team should assess the psychological, relational and social stability of the patient. The team should then determine the need for a psychological follow-up and for the use of psychotropic or not. • New recommendations on the treatment of hepatitis C are currently in process (publication date: June 2012).
Germany[190]	• IDU is not a contra-indication for treatment. • Active IDUs should only be treated after an individual estimation of benefit-risk. The treatment decision should take into account both psychiatric and somatic co-morbidity. • Participation in OST is a favourable condition to start treatment.
The Netherlands[169, 195]	• IDU is not a contra-indication for treatment. • The treatment decision should take into account their likely adherence to antiviral treatment but doubt on compliance should not be an exclusion criteria. • Participation in OST is a favourable condition to start treatment. • It is also preferable that they stop injecting or that they control the sterility of the material to avoid transmission.
UK[239, 240]	• IDU is not a contra-indication for treatment. • Treatment is recommended for those who wish to receive therapy and who have appropriate support. Active injectors who are receiving therapy can be given advice on not sharing or reusing injecting equipment and information on how to access needle exchange programs.
Scotland[191]	• IDU is not a contra-indication for treatment. • Participation in drug treatment program is a favourable condition to start treatment. • Each treated patient should be offered integrated multidisciplinary care. • Active drug users should be engaged in efforts to address their healthcare needs and in harm reduction. They should also have a comprehensive assessment of their psychological needs and of their likely adherence to antiviral treatment.
USA (NIH)[241]	• IDU is not a contra-indication for treatment. • IDUs could be linked to drug treatment programs, and to community-based education and support programs to modify risk behaviour. • Treatment of active IDUs who are not in drug treatment programs should be considered on a case-by-case basis •

3.4. Mathematical model on effectiveness

3.4.1. Background

HCV antiviral treatment with peginterferon-alfa and ribavirin is the standard care for chronic HCV, with a 45–80% cure rate in registration trials (sustained viral response, SVR) depending on genotype. In many countries in the European Union, treatment is recommended for all patient groups, including IDUs.[242]

The Belgian Association for the Study of the Liver (BASL, http://www.basl.be), has published two practice guidelines for the treatment of hepatitis C: one general[59] and one specific for treating injecting drug users.[60] Treatment of selected ex-IDUs on OST or not (similar proportions of genotype 1 and 3) has been shown to give similar results as obtained in other patient groups in Belgium.[43]

Currently, few active IDUs have been treated worldwide.[243, 244] This may be due to a reluctance among physicians to treat IDUs because of concerns over non-compliance and re-infection.[245, 246] However, limited information available from clinical studies (over 90% of patients studied were on OST) suggests that current IDUs exhibit similar compliance and response rates to treatment when compared to non- or ex-IDU.[6, 247-249] Furthermore, there are little data on re-infection after successful treatment, except from small-scale studies which report low rates in the first few years.[250-252]

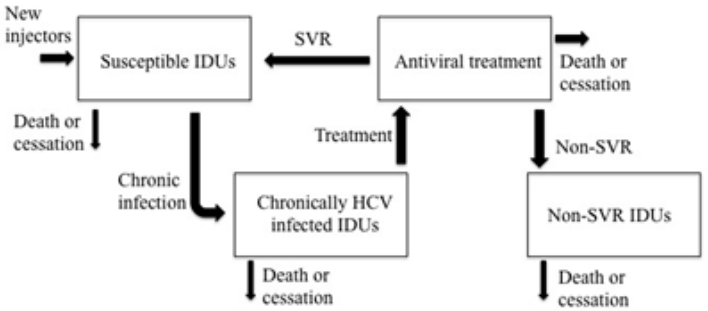
Previous mathematical modelling work suggested HCV antiviral treatment could prevent HCV transmission,[215, 216] however these models were not fit to Belgian specific data. In this section we used Belgium-specific parameters in an attempt to predict the potential impact that increased levels of HCV treatment could have on HCV prevalence in Belgium.

3.4.2. Methods

3.4.2.1. Mathematical Model Structure

A previously published mathematical model of HCV transmission among IDUs was used,[215, 216] describing the transitions between four groups of IDU: susceptible (including those who spontaneously clear acute infection), chronically infected who are naïve to treatment or reinfected (including those in the acute stage who progress to chronic infection), chronically infected who have failed treatment (non-SVR), and currently in treatment. The structure of the model can be found in Figure 3.2.

Figure 3.2: Structure of the dynamic transmission model of HCV transmission among injecting drug users (IDUs).



The set of differential equations describing the transition between the different stages is presented below. In those equations, X represents susceptible IDUs, C_1 represents chronically infected IDUs, T represents IDUs on antiviral treatment, C_2 represents those who do not attain SVR following treatment, N is the total IDU population ($N=X+C_1+T+C_2$), and t is time in years:

$$\frac{dX}{dt} = \theta - \pi(1-\delta)\frac{C_1+C_2}{N}X + \omega\alpha T - \mu X$$
$$\frac{dC_1}{dt} = \pi(1-\delta)\frac{C_1+C_2}{N}X - \Phi - \mu C_1$$
$$\frac{dT}{dt} = \Phi - \omega T - \mu T$$
$$\frac{dC_2}{dt} = \omega(1-\alpha)T - \mu C_2$$

New IDU enter the susceptible pool at a fixed rate ‘θ’, and leave all compartments (due to death or ceasing injection) at a per capita rate ‘μ’. The rate of infection of susceptible IDU is proportional to the number of susceptibles, the fraction of the population chronically infected, and the

infection rate 'π'. Acute infection spontaneously clears in a proportion 'δ'. The remaining infected patients (proportion '1-δ') progress to chronic infection. Due to the relatively short duration of acute stage[253] and the small proportion that spontaneously clear infection, the number of infections caused by IDU with acute HCV who spontaneously clear is likely to be small, and is neglected in this model.

Chronic infected patients who are naive to treatment or reinfected are recruited onto treatment at a fixed rate (Φ chronically infected IDU per 1000 IDU annually) unless the number infected is driven below Φ, whereupon all chronically infected IDU are treated. This fixed treatment number aimed to provide a realistic scenario of potential treatment recruitment. IDU remain in treatment for 1/ω and during this short period are assumed to be non-infectious (due to significantly reduced viral load[254, 255] and access to opiate substitution therapy and sterile equipment while on treatment). A proportion 'α' of those treated are cured (achieve SVR). They become susceptible again. As the concept of sterilising immunity following HCV infection is controversial, we conservatively assume no immunity following spontaneous clearance or SVR. This assumption is conservative as it assumes all injectors are susceptible to reinfection following SVR, and hence the projected impact of treatment as prevention is less than if immunity occurs. Those who are not cured (fraction '1-α') move to the chronically infected non-SVR after treatment compartment. These IDUs cannot be retreated.

In Belgium, the HCV epidemic is approximately at steady-state, so we allowed the model to reach a stable endemic state prior to initiating treatment. We assumed no change in the infection rate or clearance/treatment success rates for those who cleared infection (spontaneously or through treatment).

We projected the relative decrease in chronic infection prevalence after different time periods with varying treatment rates, in three settings ('low', 'moderate', and 'high') with a range of untreated endemic chronic infection prevalences (referred to as 'baseline chronic prevalence').

3.4.2.2. Model Parameterization

The parameters used for the model can be found in Table 3.6. A study of 147 injectors between 2004 and 2005 in Belgium found 47% genotype 1/4 and 51% genotype 2/3.[57] Among a random sample of 50 IDUs in Brussels, 54% of them were genotype 1 or 4, and 46% were genotype 2 or 3 (Chantal de Galocsy, *personal communication*). Therefore, we assume a genotype distribution of 50% genotype 1, and 50% genotype 2 or 3 for all scenarios.

SVR rates among ex- or non-injectors report SVR rates of approximately 45% for genotype 1 and 80% for genotypes 2/3.[239] A recent meta-analysis found that SVR rates among injectors (mainly individuals on OST) are comparable to those in the ex- or non-injecting population,[6] however the studies reported were small and likely subject to selection bias. A publication of SVR rates among injectors in a drug substitution participant in Switzerland found SVR rates of 35-40% in genotype 1, and 66% in genotype 2/3.[256] In Belgium, Chantal de Galocsy found a SVR rate of 59% in genotype 1 and 72% in genotype 2/3 among a random sample of 50 IDUs (*personal communication*). Due to the slightly lower SVR rates reported in Belgium and Switzerland, we assume SVR rates of 35% for genotype 1 and 70% for genotype 2/3.

Due to the difficulty in estimating the average duration of injecting career, there are few studies rigorously examining this issue. Previous models assume a range of injecting durations from 8 to 20 years.[234, 257, 258] A study of heroin injectors in Zurich estimated an average injecting career of 25 years.[259] However, these estimates are all likely subject to considerable bias. For example, unadjusted estimates based on longitudinal surveys (such as in Nordt, et al.[259]) often recruit from treatment or criminal justice sites, and therefore tend to over-represent IDUs with a longer injecting duration. On the other hand, unadjusted estimates based on population surveys tend to under-estimate duration. Using Bayesian Markov chain Monte Carlo methods, Sweeting et al. obtained an unbiased estimate of 11 years average injecting duration from a UK population survey of ex-IDUs.[260] In Brussels, Chantal de Galocsy found an average injecting duration of 4 years (range 0.5 to 10 years) among a random sample of 50 IDUs (*personal communication*) presenting for treatment. Due to the wide uncertainty in this estimate, we assume an average injecting duration of 8 years at baseline, but vary this to 4 years and 20 years in the sensitivity analysis.

For the baseline analysis we assume an IDU death rate (due to overdose, etc) of 1% per year.[261] However, overdose rates may be even higher than

this, and we include a 2% death rate in the "worst case" sensitivity analysis.[262]

HCV prevalence among IDUs is not well characterized across Belgium. As is common in other countries, HCV prevalence appears to be heterogeneous. A recent systematic review reports that 55% IDUs in Belgium are HCV antibody positive.[8] This is the unweighted mean of two percentages (27% and 82.7%) reported for the year 2008 and needs to be interpreted with caution. The 27% seropositivity (17 out of 63) was seen in a subset of the 166 IDUs being treated in 2008 at the residential care "De Sleutel" where the physician judged HCV testing to be appropriate after discussion with the individual. It is important to note that De Sleutel provides residential care to IDUs and therefore serves a somewhat different IDU population compared with low threshold services like MSOCs/MASS (eg Free Clinic Antwerp) where the aim is harm reduction. The 82.7% reported in the systematic review was the proportion of IDUs testing positive for anti-HCV antibodies at The Free Clinic Antwerp in 2008.

Based on the limited data available there seems to be no clear trend in seroprevalence rates over the last 10 years for HCV in IDUs in Belgium. The proportion of IDUs testing positive for anti-HCV antibodies at De Sleutel remained around 33% of the IDUs tested per year in the period 1994 to 2010. However, in the small subgroup of IDUs aged over 34 years tested at De Sleutel, the seroprevalence remained at around 66% for the same period (data kindly provided by G Lombaert, De Sleutel). From 2001 to 2004, about 79% of the IDUs at the Free Clinic Antwerp tested positive for HCV (on average 264 IDUs were tested per year), which is similar to the 82.7% reported for 2008.

For the French speaking community, a 67% seroprevalence rate was reported for IDUs willing to be tested and treated (https://www.wiv-isp.be/reitox/Publications/inf05nl.pdf). In Luxemburg (not the Belgian province), a recent multicenter study found a seroprevalence in IDU of 81% for HCV (218/268, 95%CI=[77; 86]), 29% for HBV, 2.5% for HIV and 57% for HAV and in non-injecting drug users 19% for HCV, 9% for HBV, 5% for HIV-1 and 66% for HAV. Prisoners showed the highest rates for all infections. Age, imprisonment and setting of recruitment were statistically associated with HCV seropositivity.

Overall, it is clear that HCV prevalence is heterogeneous across Belgium, with a range of settings from low (e.g. an average of 33% for IDUs in residential care "De Sleutel") to very high (about 80% for Free Clinic Antwerp) HCV seroprevalences. As roughly one-quarter of acute HCV infections spontaneously clear,[263] we assume chronic prevalence is roughly three-quarters that of seroprevalence. Hence, we model three baseline HCV chronic prevalence scenarios (25%, 45%, and 65%) to capture the range of scenarios found in Belgium.

Table 3.6: Parameters used in the baseline model simulations.

Model parameter definition	Symbol	Value	Units	Source
Average exit rate (cessation or death)	μ	0.135[a]	Per year	(Sweeting et al.[260]; Nordt et al.[259]; Cornish et al.[261]; Chantal de Galocsy, *personal communication*).
Average proportion infections with SVR[b]	α^c	0.525	-	(Witteck, et al.[256]; Micalessi et al.[57]; Hellard et al.[6]; Chantal de Galocsy, *personal communication*)
Average treatment duration	$1/\omega^d$	0.433	Per year	(NICE, "Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C", 2007)
Average proportion of infections that spontaneously clear	δ	0.26	-	(Micallef et al.[263])
Average new injector rate	θ	135	Per 1000 IDUs annually	Given to retain a total population of 1000 IDUs with the exit rate above.
Average infection rate	π	[0,1]	Per year	Varied to produce three baseline prevalences (25%, 45%, 65%).
Average treatment rate	Φ	5-40	Per 1000 IDUs annually	

[a]Based on a cessation rate of 12.5% per year (8 year injecting duration), and an IDU death rate of 1%. [b]SVR: sustained viral response. [c]Weighted 50% genotype 1 and 50% genotype 2/3, assuming 35% genotype 1 SVR and 70% genotype 2/3 SVR. [d]Weighted average of treatment duration for genotype 1 and genotype 2/3 (24 weeks all genotype 2/3, 48 weeks genotype 1 responders (35% SVR), 12 weeks genotype 1 non-responders (65% nonSVR)).

3.4.2.3. Scenarios and sensitivity analysis

Baseline model scenarios

We project the prevalence and relative prevalence reductions for three baseline chronic HCV prevalences: 25%, 45%, and 65%. We examine four treatment rates: 5, 10, 20, and 40 per 1000 IDUs annually, and project the potential impact up to 20 years.

Sensitivity analysis

Previous model uncertainty and sensitivity analyses indicate the model is most sensitive to the IDU exit rate (comprised of cessation and IDU death rates) and SVR. Therefore, a series of univariate sensitivity analyses are performed on the results (prevalence and relative prevalence reductions in 20 years) for the 45% and 65% baseline chronic prevalence scenarios, with all four treatment rates (5, 10, 20, an 40 per 1000 IDUs annually).

'Worst case scenario- high exit rate': In this scenario, we utilize a higher than baseline IDU death rate (2% per year, as compared to 1% in the baseline scenario) and also a shorter average duration of injecting prior to permanent cessation (4 years as compared to 8 years in the baseline scenario). This leads to a higher than baseline exit rate, and reduced prevention impact, thus simulating a worst case scenario.

'Best case scenario- low exit rate': In this scenario, we utilize a longer average duration of injecting (20 years as compared to 8 years), and the baseline IDU death rate (1% per year). This leads to a smaller than baseline exit rate, and increased prevention impact.

Increased SVR: In this scenario, we project the potential impact of future antiviral treatments (such as combinations of new direct-acting antivirals) which will likely increase both SVR rates and decrease treatment durations within the next 5 years. Hence we model SVR rates of 80% for genotype 1 (increased from 35% in the baseline analysis), and 80% for genotype 2 (increased from 70% in the baseline analysis), with an average of 24 weeks treatment duration for all genotypes (reduced from a maximum of 48 weeks in the baseline analysis). In addition, we also model an increased treatment rate of 80 per 1000 IDUs annually, to reflect the potentially higher uptake (and therefore higher treatment rates possible) with well-tolerated, effective, and affordable combinations of direct-acting antivirals.

3.4.3. Baseline results

Figure 3.3 shows how the prevalence (top row) and relative prevalence reductions (bottom row) vary over time for the three baseline chronic prevalence scenarios and four treatment rates.

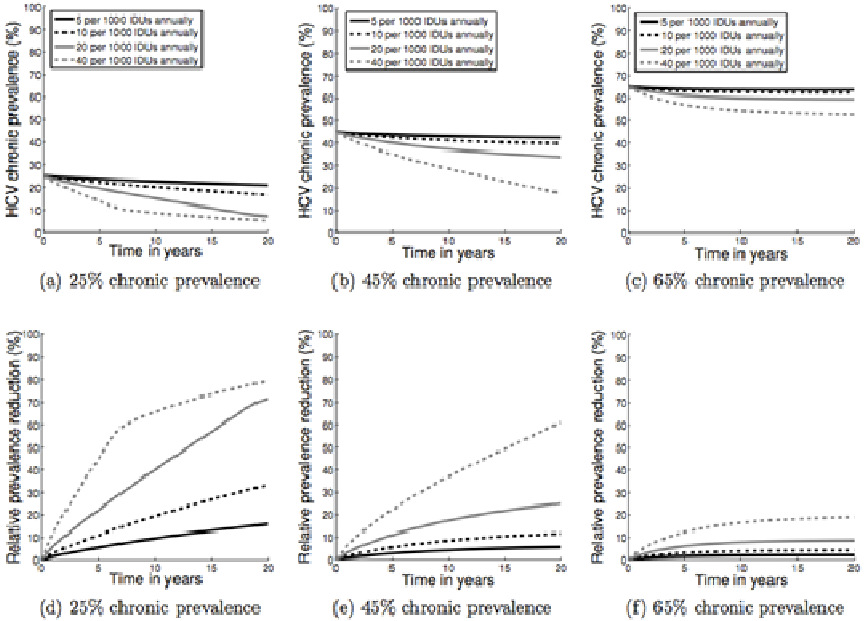
If treatment rates are 5 per 1000 IDU annually then substantial prevalence reductions (>15%) within 20 years only occur in the 25% baseline chronic prevalence setting. In contrast, higher treatment rates (>20 per 1000 IDU annually) would be required to result in similar prevalence reductions in the high (65%) prevalence setting.

For a 25% baseline chronic prevalence, annually treating 10 cases per 1000 IDU results in an 11% relative reduction in prevalence within 5 years, nearly doubling to 20% after 10 years, and 33% after 20 years (Figure 3.3d). In contrast, if the baseline prevalence were 45%, then the same treatment rate reduces prevalence by 5% after 5 years, 8% after 10 years, and 12% after 20 years (Figure 3.3e). With a high 65% baseline prevalence, annually treating 10 cases per 1000 IDU may only achieve a 3% reduction in prevalence within 5 years, and a 4% reduction after 20 years (Figure 3.3 f).

If the treatment rate were increased to 20 cases per 1000 IDU annually then impact is doubled as compared to the 10 per 1000 IDU annually scenario. At a 25% baseline chronic prevalence, this leads to relative reductions of 22%, 40%, and 72% within 5, 10, and 20 years, respectively. With a 45% baseline prevalence, the same treatment rate results in 11%, 17%, and 25% relative reductions at 5, 10, and 20 years, respectively. Finally, with a 65% baseline prevalence the reductions reach 6%, 8%, and 9% at 5, 10, and 20 years, respectively.

High treatment rates of 40 per 1000 IDUs annually result in substantial (>15%) and swift (within 10 years) reductions in prevalence in all baseline prevalence scenarios. The relative reductions are most pronounced in the low (25%) prevalence scenario, with reductions of 45% within 5 years and 66% at 10 years. Reductions are still substantial at the 45% prevalence scenario, with 22%, 37% relative reductions within 5 and 10 years, respectively. Even in the high (65%) prevalence setting, reductions of 17% could be seen within 10 years.

Figure 3.3: Projected prevalence (top row) and relative prevalence reductions (bottom row) over time for three baseline chronic prevalence scenarios: (a,d) 25% baseline chronic prevalence, (b,e) 45% baseline chronic prevalence, and (c,f) 65% baseline chronic prevalence. Projections are shown for four treatment rates: 5, 10, 20, and 40 per 1000 IDUs annually.



The predicted prevalence reductions flatten off in the long-term (20 years) for higher treatment rates (20-40 per 1000 IDU annually) at low prevalence (25%) due to the persistence of a non-responder population.

3.4.4. Sensitivity analysis

3.4.4.1. 'Worst case scenario: high exit rate'

In this scenario the model projects reduced impact for a given treatment rate as compared to the baseline scenarios, due to the higher exit rate (shorter injecting duration and higher death rate). We project the prevalence and relative prevalence reductions expected for the 45% (Figure 3.4a,c) and 65% (Figure 3.5a,c) baseline chronic prevalence scenarios.

In the 45% baseline prevalence, annually treating 10 cases per 1000 IDU reduces impact by over one-third as compared to the baseline scenario, with 5% and 7% relative reductions in prevalence at 5 and 20 years, respectively. If the baseline prevalence were 65%, then within 20 years the impact is halved, with a relative prevalence reduction of only 2%, compared to 4% in the baseline scenario.

At higher treatment rates (40 cases per 1000 IDUs annually), impact is reduced but is still substantial at the 45% prevalence scenario, with 19%, 28%, and 36% relative reductions expected after 5, 10, and 20 years, respectively. Even in the high (65%) prevalence setting, reductions of 10% could still be achieved within 20 years, but this is nearly halved from 19% relative reductions in the baseline scenario.

3.4.4.2. 'Best case scenario: low exit rate'

In this scenario the model projects increased impact for a given treatment rate as compared to the baseline scenarios, due to the lower than baseline exit rate (longer injecting duration). We project the prevalence and relative prevalence reductions expected for the 45% (Figure 3.4b,d) and 65% (Figure 3.5b,d) baseline chronic prevalence scenarios.

In the 45% baseline prevalence scenario, annually treating 10 cases per 1000 IDU results in marginally more impact at 5 years (6% relative reduction, as compared to 5% in the baseline scenario), but over 50% more impact at 20 years, with a 17% reduction as compared to 12% in the baseline scenario. If the baseline prevalence were 65%, then within 20 years the impact is nearly doubled, with a relative prevalence reduction of 8%, compared to 4% in the baseline scenario.

At higher treatment rates (40 cases per 1000 IDUs annually), reductions are similar and still substantial at the 45% prevalence scenario, with 23%, 43%, and 61% reductions expected within 5, 10, and 20 years, respectively. In the 65% prevalence setting, impact nearly doubled at 20 years, with reductions of 36% as compared to 19% in the baseline scenario.

3.4.4.3. Increased SVR

Raising the SVR rate (80% SVR across all genotypes) increases impact in all settings.

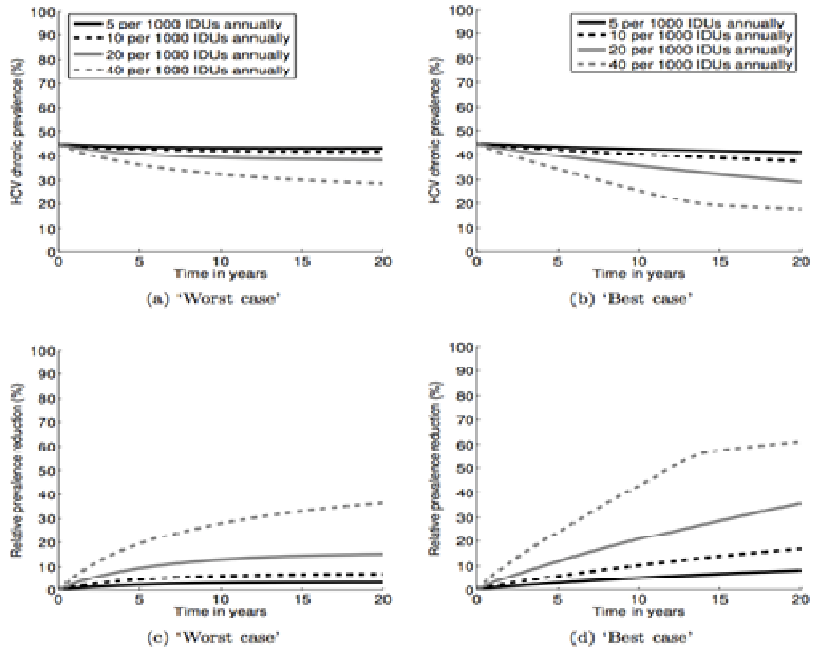
shows the prevalence and relative prevalence reductions seen in the 45% and 65% scenarios over time.

In the 45% baseline prevalence scenario, annually treating 10 cases per 1000 IDU increases impact by one-half as compared to the baseline scenario, with an 8% relative reduction, as compared to 5% for the baseline scenario at 5 years, and 17% relative prevalence reduction compared to 12% for the baseline scenario at 20 years. Similarly, impact is increased by 50% at 20 years for the 65% prevalence scenario, with a relative prevalence reduction of 6%.

At higher treatment rates (40 cases per 1000 IDUs annually), impact again increases by 40-50%, with 31%, 55%, and 90% reductions expected within 5, 10, and 20 years, respectively in the 45% baseline scenario. In the 65% prevalence setting, the model predicts relative prevalence reductions of 29% after 20 years, as compared to 19% in the baseline scenario.

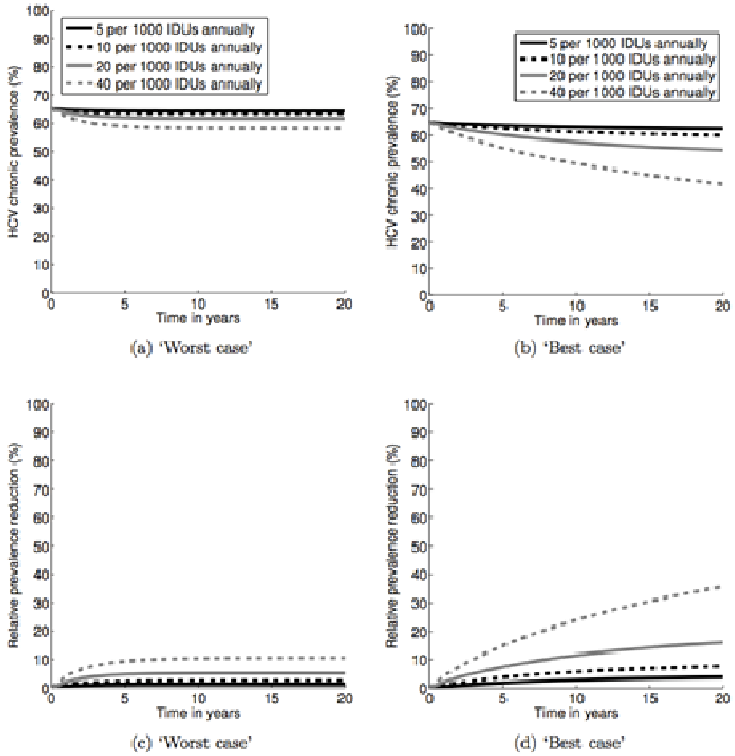
If a treatment rate of 80 per 1000 IDUs annually could be achieved with new HCV treatments, then substantial reductions in prevalence could be seen in the short-term. For example, in a 45% baseline chronic prevalence setting, 65% and 86% relative reductions in prevalence could occur within 5 and 10 years, respectively. Even in a 65% chronic prevalence setting, reductions of 36% and nearly 60% could be seen at 5 and 10 years, respectively. These reductions would be possible only if this treatment rate could be achieved and sustained despite the substantial reductions in chronically infected IDUs over time. Prevalence reductions flatten off after 10 or 15 years, due to the presence of a persistent non-SVR population which cannot be retreated, and the lack of chronically infected IDUs available to treat at very low prevalences.

Figure 3.4: Sensitivity analysis for the 45% baseline chronic prevalence scenario showing the "worst case" (a,c) and "best case" (b,d) scenario projections.



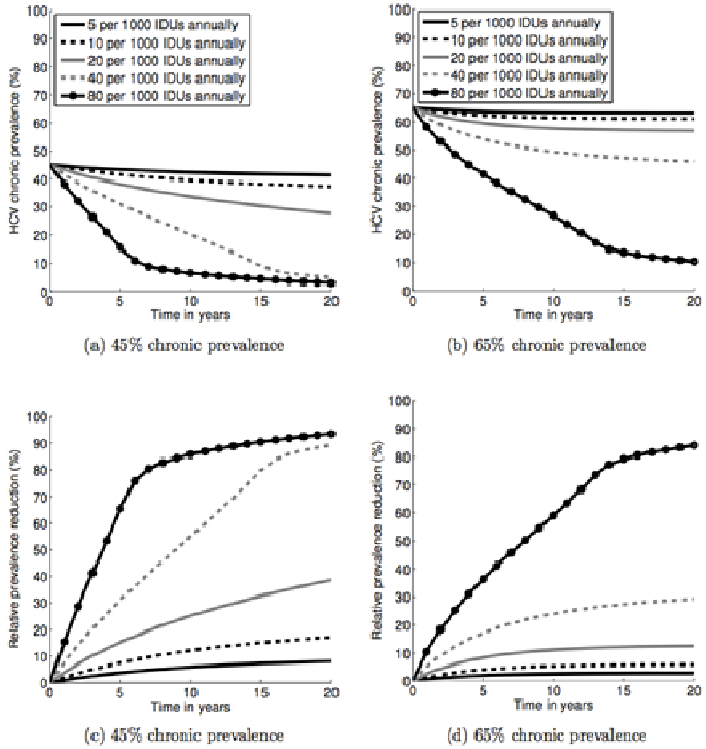
The `worst case scenario' projections (a,c) assume a short injecting duration (4 years) and a high IDU death rate (2% per year). The `best case scenario' projections (b,d) assume a long injecting duration (20 years) and baseline IDU death rate (1% per year). Projected prevalence (top row) and relative prevalence reductions (bottom row) are shown over time for four treatment rates: 5, 10, 20, and 40 per 1000 IDUs annually. Model parameters as in Table 3.6, except with exit rate (due to cessation or death) as noted above, and new injector rate fit to retain a total population of 1000 IDUs.

Figure 3.4: Sensitivity analysis for the 65% baseline chronic prevalence scenario showing the "worst case" (a,c) and "best case" (b,d) scenario projections.



The `worst case scenario' projections (a,c) assume a short injecting duration (4 years) and a high IDU death rate (2% per year). The `best case scenario' projections (b,d) assume a long injecting duration (20 years) and baseline IDU death rate (1% per year). Projected prevalence (top row) and relative prevalence reductions (bottom row) are shown over time for four treatment rates: 5, 10, 20, and 40 per 1000 IDUs annually. Model parameters as In Table 3.6, except with exit rate (due to cessation or death) as noted above, and new injector rate fit to retain a total population of 1000 IDUs.

Figure 3.5: Sensitivity analysis for the 45% (a,c) and 65% (b,c) prevalence scenarios using a higher SVR rate (80% genotype 1, 80% genotype 2), reflecting the potential higher efficacy of future antiviral treatments.



Projected prevalence (top row) and relative prevalence reductions (bottom row) are shown over time for five treatment rates: 5, 10, 20, 40, and 80 per 1000 IDUs annually. Model parameters as in Table 3.6, except for the SVR rate as noted above, and treatment duration of 24 weeks for all gentoypes.

3.4.5. Discussion

Our simple theoretical model indicates HCV antiviral treatment at achievable rates (5-40 per 1000 IDUs annually) may be an effective primary prevention tool for substantially reducing the prevalence of HCV infection in settings with a moderate baseline HCV prevalence, despite the persistent risk of re-infection. Even more substantial reductions in prevalence are possible with new direct-acting antiviral treatments. A shorter average duration of injecting career or increased IDU death rates (such as due to overdose) substantially reduces the expected impact on HCV prevalence, especially at higher prevalences and longer timescales, whereas longer durations of injecting increases the impact of treatment.

There are several limitations to the results presented. First, the findings are based on model projections of the treatment effect instead of experimental evidence. Second, the use of a fixed treatment rate annually assumed that treatment could be sustained at the same rate despite a reduction in prevalence. This means that as prevalence decreases, a larger proportion of infected IDU will be treated each year although the number treated remains constant. In the short term, this may be a reasonable assumption, but would require increasingly efficient and effective HCV testing and case finding to find those fewer infected IDU.

Third, the model assumed that all infected IDU have an equal probability of being treated, completing treatment, and achieving sustained viral response. In practice, barriers exist related to accessing IDU and ensuring they are referred to and remain in specialist care. Additionally, we assumed no difference in infection risk between those who have successfully completed treatment and those who were never infected. In reality, it is likely that there are heterogeneities in treatment presentation and completion (as well as in behavior and risk following treatment) both between different IDU and at different times during a person's injecting career. Equally, biological and behavioral heterogeneity in infection risk may reduce the impact of treatment for a specific baseline prevalence. For example, injectors in their first year of injecting, or times spent homeless, may be at a greater risk of becoming infected than at other times. In addition, we have assumed average cessation and drug related death rates – whereas these may vary in the first year or at other times during an injectors' career.[264] Furthermore, it is possible, though not well documented, that those undergoing or exiting treatment may exhibit increased cessation rates. This increased cessation during or after treatment could decrease the potential impact of treatment, although it would still reduce prevalence and HCV transmission due to infected IDU being removed from the pool of active injectors. Unfortunately, there is insufficient evidence to parameterize any of these consequences or changes, which can only be incorporated once additional clinical evidence has been collected.

Fourth, we did not explicitly stratify the populations by genotype. Stratifying the population by genotype could refine our model predictions because we could incorporate the dynamic effect of treatment on the proportion of each genotype in a given population. However, the introduction of new direct-acting antivirals (such as telaprevir and boceprevir) which increase SVR rates in genotype 1 to approximately equal to that of the current regimes for genotype 2/3 will reduce this potential genotype shift.

In summary, feasible levels of HCV antiviral treatment could play an important role in HCV prevention among IDUs across a wide range of prevalence settings found in Belgium. Further research surrounding treatment of injectors and the impact on prevalence in Belgium is warranted.

4. SUMMARY AND CONCLUSIONS

4.1. Introduction

4.1.1. Hepatitis C, the virus and the disease

Both the common routes of transmission and the options to treat hepatitis C change rapidly. It took until 1989 to discover the hepatitis C virus (HCV), an RNA virus causing the so called non-A non-B hepatitis cases. Soon thereafter (mid 1990) tests for antibodies to the virus were introduced to stop the transmission of HCV by blood products, transfusion or transplantation. This effort was followed by molecular diagnostics offering more sensitive detection and quantification of HCV-RNA and the determination of the HCV genotype and subtype.

Blood is central to the transmission of HCV. This includes the possible transmission by contaminated needles or other material in a medical or non-medical setting.

New infections with HCV are often asymptomatic. About a quarter of all new infections are cleared spontaneously, often within 6 months. Variations in the human genome near the interleukin-28B region have been shown to be predictive of such clearance, especially in genotype 1 infections. Subjects who remain infected (i.e. with detectable HCV-RNA) are at increased risk to develop liver disease after years or decades (fibrosis, cirrhosis, liver cancer).

Most models on the cost-effectiveness of treatment of hepatitis C assume that once the virus is cleared, the progression to liver disease becomes identical to that of the general population. This assumption is probably not correct. Despite successful treatment of hepatitis C, co-factors for liver disease progression (e.g. alcohol or cannabis use) may remain present. A higher progression rate to liver disease compared with the general population was recently confirmed using long term follow-up data of patients who had cleared the virus after treatment.

4.1.2. Hepatitis C epidemiology in Belgium

Transmission routes

In Belgium, patients who had received **blood products or a transplant** prior to mid 1990 formed the main group of patients identified with chronic hepatitis C in the nineties. Indeed, from 1991 to 2002 an increasing number of patients with chronic hepatitis C were identified each year in Belgium, often infected with HCV genotype 1. The number of genotyped new cases stabilized at around 2000 per year.

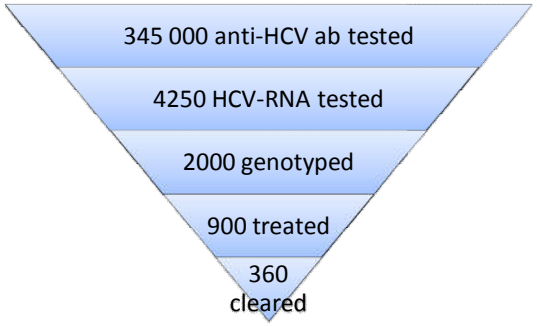
Over time, an increasing number of subjects infected with HCV using blood products before 1991, were identified or had died. The main route of infection in new identified cases became **injection drug use** (IDU). Especially the sharing of needles and other materials has been associated with a high risk of transmission. IDUs are typically infected with HCV subtype 3a and increasingly subtype 1a. Over 80% of all new HCV infections in Western Europe are now seen in IDUs. Often the infection occurs during the first year (or years) of injection drug use.

Another risk group identified in the last decade consists of human immunodeficiency virus **(HIV) positive men** having sex with men (MSM). Infections with HCV type 1 or 4 have been seen in men with clinical syphilis and/or lymphogranuloma venereum rectitis. **Medical procedures** continue to account for about 10% of all new HCV infections. In infected women **transmission to the baby** may occur at birth in 3% to 5%, especially in case of HIV co-infection and a high viral load of HCV. Finally, new HCV infections are also detected in **first generation immigrants** from countries with a higher HCV prevalence.

Prevalence

Based on a study performed in 1993-1994 the seroprevalence of HCV in Belgium was estimated at 0.87 to 1%. A more recent study published in 2007, found a seroprevalence in saliva of only 0.12% in the general population in Flanders. In absolute numbers this would indicate there are possibly between 10 000 and 75 000 chronically infected patients in Belgium.

Figure 4.1: Subjects tested for HCV versus treated for chronic hepatitis C per year in Belgium (2002-2009)



Ab: antibody. The actual number of patients treated may be 10 to 20% higher than mentioned above as in addition to the patients with regular health insurance, other patients had their treatment costs covered by the OCMW/CPAS, "medical need" programs, or the Ministry of Justice. These data are excluded from the RIZIV/INAMI/Farmanet statistics.

Based on the permanent population sample data, a quarter of the Belgian population (2.76 million individuals) was tested for anti-HCV during the period 2002-2009. The data suggest most women are tested for anti-HCV at each pregnancy. The data show that 29% of the birth cohort 1945-1965 was tested at least once for anti-HCV in the period 2002-2009. We can thus reasonably assume that over 50% of this birth cohort was tested at least once for anti-HCV in the period 1991-2011. The number of tests performed and treatments reimbursed by the national health insurance, show that over 2000 HCV-RNA positive patients were identified each year in Belgium of whom less than half started treatment. The number of patients genotyped and treated each year decreased slightly after 2002.

4.1.3. Treatment

Treatments were developed based on interferon-alpha (IFN) injections, which have a broad antiviral effect. Longer acting formulations (pegylation, PegIFN) and the addition of oral ribavirin (RBV) improved efficacy. The efficacy endpoint is a sustained virological response (SVR), defined as undetectable HCV-RNA 6 months after the end of treatment. Using the combination of pegIFN plus RBV, up to 80% of genotype 2/3 infections (after 6 months of treatment) and 45% of genotype 1 infections (after 12 months of treatment) showed an SVR in registration trials. The addition of a protease inhibitor (telaprevir or boceprevir) to pegIFN/RBV further improved the SVR rate from 45% to 70% in patients infected with HCV genotype 1, while the treatment duration could be shortened.

Unfortunately, there are more side-effects (Table 1) with this combination treatment, above and beyond the side-effects of the standard pegIFN/RBV. Fatigue and depression which may already occur in chronic hepatitis C patients without treatment often worsen under pegIFN/RBV treatment. These side-effects and a difficult psycho-social situation of the individual may hamper treatment uptake.

Table 4.1: Evolution in HCV route of infection and treatment for chronic hepatitis C

		Past	Today	Future ?
Route of infection		Blood products (G1,5) > IDU	IDU (G1a,3a) > HIV+ MSM (G1,4)	IDU (G1a>G3a) > HIV+ MSM (G1,4)
Treat-ment	Regimen	(peg)IFN + ribavirin G1,4:48 weeks G2,3:24 weeks	G1:pegIFN + ribavirin + telaprevir/ boceprevir: < 48 weeks	DAA combination, treatment as prevention?
	Respons rate (short term)	G1,4:45% SVR G2,3:80% SVR	G1:70% SVR	All G:> 80% SVR? Resistance?
	Side-effects	depression,anemia	+rash,+dysgeusia	few
	Uptake	low	low	high

IDU: injection drug user. G: genotype. HIV: human immunodeficiency virus. MSM: gay and bisexual men. DAA: directly acting antiviral. SVR: sustained viral response.

In 2011, the first cases of HCV clearance were presented, after a combination of two directly acting antivirals (DAAs), without pegIFN/RBV. Based on these data, experts predict better tolerated and highly effective treatment combinations will become available in the period 2015-2017, provided drug resistance can be controlled.

4.2. Aims and methods

The aims of this project were the following:

1. To document the effectiveness and cost-effectiveness of screening for hepatitis C in the general population or in specific target groups (excluding screening of the blood supply).
2. To document the effectiveness and cost-effectiveness of prevention programs for hepatitis C in injection drug users.
3. To describe the action plans and practice guidelines abroad (mainly surrounding countries) with regard to hepatitis C screening and prevention.

To answer the first two research questions we conducted a systematic literature search. To assess the effectiveness of the programs, we first searched the literature for randomized clinical trials. Next, because studies on screening and prevention programs require a lot of information from a wide range of sources to correctly inform decision makers, modelling studies on effectiveness were searched. To assess the cost-effectiveness, full economic evaluations comparing both costs and outcomes of at least two interventions were searched.

We also had the opportunity to use a dynamic mathematical model on the effectiveness of treating IDUs to prevent HCV transmission, developed by N. Martin, co-author of this report. This opportunity allowed us to also investigate the theoretical effectiveness of treating active IDUs as prevention program. It was based as much as possible on Belgian data.

The final outcome was HCV prevalence. Parameters were derived from the literature and from opinions of Belgian experts in hepatitis C and/or IDU management. For the analysis, several assumptions had to be made. Previous models indicated that the result is most sensitive to the SVR rates and the IDUs exit rates (including the cessation of drug use and IDUs death rates). The impact of these rates on the results was therefore tested in a univariate sensitivity analysis and a worst and best case scenario analysis. Several scenarios on baseline chronic HCV prevalence (25%, 45%, and 65%) and on treatment rates (5, 10, 20, and 40 per 1000 IDUs annually) were tested. In addition, a highly effective and well tolerated treatment scenario was modelled, reflecting an optimistic view on the future of DAA combination treatment.

The description of action plans and practice guidelines in other countries was based on the websites of HTA institutes and on contacts with official national institutions. France, the Netherlands and Germany were selected because of their geographic proximity. In addition, the United States and the UK (including Scotland) were chosen because they graded the level of evidence of their recommendations.

4.3. Results

4.3.1. Literature search strategy

The number of primary studies identified by the literature search is summarized in Table 4.2. Only very few RCTs were identified. Recommendations are therefore mostly based on the results of modelling studies on effectiveness and cost-effectiveness.

Table 4.2: Results of the literature search

Study design	Screening	Harm reduction measures for IDUs***	Treatment of IDUs
RCT	0	4	2
Modelling studies on effectiveness	1*	4	3
Economic evaluations	6**	4	3

**The impact of screening was only tested in the sensitivity analysis and not enough details were given hampering further analyses. ** Multiple population groups such as the general population and IDUs were sometimes studied in the same economic evaluation. ***These measures include needle and syringe programs and opioid substitution programs.*

4.3.2. Screening programs for HCV

4.3.2.1. Economic evaluations

Screening of the general population

Economic evaluations assessed the cost-effectiveness of screening the general population in Japan, the UK and the US. Whereas studies for Japan and the UK conclude in favour of screening, the more recent US study did not recommend screening of the general population. While our report was being finalized a second report was published for the US, supporting the screening of the birth cohorts 1945-1965. The authors used an HCV seroprevalence of 3.6% in this population and a proportion of 25% of the population that had ever been tested. In Belgium the seroprevalence estimates are lower (possibly 0.1 to 1%) and the proportion already tested is most probably over 50%. Therefore, these results as such cannot be transferred to the Belgian situation.

Screening of target groups

The screening of **prisoners** in the UK is no longer considered as cost-effective according to the UK threshold for the incremental cost-effectiveness ratio of £30 000 when costs and effects are discounted equally in accordance with the updated NICE guidance.

Economic evaluations on the screening of **IDUs** in the UK, Italy and the US conclude in favour of screening of IDUs for HCV. However, if equal discount rates are used as recently recommended in the UK, screening is no longer cost-effective according to the UK threshold.

For patients in **drug and alcohol services**, an economic evaluation in the UK concludes that screening is likely cost-effective compared with no screening (UK threshold). This study has however not been repeated using the updated equal discounting rates.

An economic evaluation in Japan on patients with **high aminotransferase** levels, major **surgery** or **blood transfusion**, concluded that the screening of these patients was cost-effective compared with no screening. The screening of patients with surgery was not cost-effective, as reported in an Italian study. A US study on the screening of **pregnant women** concluded that it was not a cost-effective strategy compared with no screening. For other at risk groups, no economic evaluation was identified.

Discussion

Most studies identified did not perform any probabilistic sensitivity analyses to cope with the uncertainty of parameters. In general, disease progression rates varied significantly between models. The modelled long term effect of treatment did not take into account the potential impact of co-factors on disease progression. The switch in the UK 5 years ago from different to identical discount rates for costs and effects was critical for the studies' results. Conclusions drawn for other countries cannot be easily transferred to the Belgian situation. For example, the progression rate to liver cancer is higher in Japan.

4.3.2.2. Practice Guidelines

Risk groups for which hepatitis C screening is appropriate according to the Belgian Association for the Study of the Liver (BASL).

- **Persons who had following medical events in Belgium before 01.07.1990, starting date of anti-HCV testing of blood and blood derivatives: blood transfusion, major surgical procedures (cardiac, vascular, digestive, pulmonary, gynaeco-obstetric, orthopaedic,…), stay in intensive care unit including neonatal intensive care, difficult parturition, digestive bleeding, tissue, cell or organ transplantation**
- **Dialysis patients**
- **Persons who were drugs users by intravenous or intranasal route**
- **Children from mothers seropositive for HCV**
- **Sexual partners and household members of hepatitis patients**
- **Persons who had tattoos, piercing, acupuncture without use of single use or personal equipment**
- **Persons who had medical care in countries with high prevalence of HCV (South East Asia, Middle East, Africa, South America)**
- **Persons with unexplained elevations of transaminases**
- **Patients seropositive for HIV or HBV**
- **Persons with unexplained asthenia**
- **Persons with history of unexplained jaundice**

According to the practice guidelines reviewed, the information of the population about HCV risk factors and offering testing to high risk groups is considered as good clinical practice. However, based on expert opinion, slightly different high risk target groups are defined in each country studied.

It is unlikely that the large volume of anti-HCV antibody tests currently performed in Belgium (over 673 000 tests each year) is targeted to these risk groups. Many gynaecologists for example routinely test all pregnant women for anti-HCV antibodies.

Practice guidelines in all countries studied no longer exclude IDUs from hepatitis C treatment. An individual approach is recommended by the BASL guidelines. The IDU population tends to be quite mobile hampering treatment follow-up. The decision to test and treat IDUs should not be taken without having the social and psychological support in place. This support system should be flexible and mobile to ensure follow-up during the entire treatment period.

Testing may be justified for epidemiological monitoring, however this should be performed in the context of scientifically valid research protocols.

The Belgian health insurance currently reimburses up to 4 HCV-RNA tests per patient and per treatment cycle. No tests are covered for monitoring re-infection in risk groups. This is an issue not covered by the study but raised by experts in the field. Risk groups such as IDUs and HIV+ MSM may remain at risk of HCV re-infection after obtaining an SVR (or a spontaneous clearance). Follow-up monitoring for re-infection cannot be performed using anti-HCV antibody tests as these tests remain positive (or are not reliable in case of advanced immune deficiency). Therefore regular (e.g. yearly) tests may be indicated in subjects suspected of possible re-infection. Neither the HCV-RNA test nor the HCV core antigen test (cheaper and easier to use, but slightly less sensitive[22, 23]) has however been critically evaluated in this report for the detection of re-infection.

4.3.3. Prevention programs for HCV transmission among IDUs

4.3.3.1. Results of the literature review

Needle and syringe programs (NSP) and opioid substitution therapy (OST) are now available in all EU countries.

The literature review showed NSP and OST programs had a clear impact on HIV transmission. Low level evidence also suggests the combination of NSP and OST programs also reduces HCV transmission.

These programs are considered as cost-effective mostly due to their effect on HIV transmission.

4.3.3.2. The treatment as prevention model

Treatment as prevention of HCV transmission in IDUs is a relatively new research concept. The goal is to reduce transmission of the virus by treating individuals in the at risk community. Our model is based on the untested assumption that the probability to transmit HCV is independent of the willingness of the IDU to be tested and treated.

Some key input parameters need to be better documented for Belgium before conclusions can be drawn:

- the baseline prevalence of chronic hepatitis C in IDUs,
- the proportion of current IDUs that can be treated each year,
- the treatment response rate in current IDUs and IDUs not under OST (not well documented, as treatment studies in IDUs often used highly selected patients on OST and treated in expert centers)

Input from the ongoing field trials abroad will also be helpful to improve the model.

In 2015-2017, highly effective and better tolerated (interferon free) combinations of antivirals are expected to become available. If realized, such treatment combinations are likely to increase treatment uptake. However, treatment compliance may even become more important, in order to avoid the development of drug resistance. Provided drug resistance problems can be controlled, this evolution could also accelerate the study of treatment as prevention in IDUs.

RECOMMENDATIONS[c]

- **Based on the published studies on effectiveness or cost-effectiveness the screening of the general population for hepatitis C is currently not recommended.**
- **Based on the published studies on effectiveness or cost-effectiveness the screening of injection drug users for hepatitis C could be envisaged. However, the decision to test and treat should not be taken without having a social and psychological support in place. Such a flexible and mobile support system should aim to improve treatment safety and efficacy.**
- **In view of the large volume of tests for anti-HCV antibodies in Belgium, it is recommended to remind the medical community of the list of appropriate indications for testing for anti-HCV antibodies in clinical practice.**

RESEARCH AGENDA

- **As only few seroprevalence and HCV-RNA prevalence estimates for the general population and specific risk groups (eg injection drug users) in Belgium are available, further well-designed epidemiological research is indicated.**
- **In addition, more data on treatment uptake and response in current injection drug users are to be collected for the Belgian setting, in order to improve the theoretical model on treatment for prevention of HCV transmission.**
- **Injection drug users and HIV+ homosexual men may remain at risk of HCV re-infection after clearing a previous HCV infection. Currently, no tests are reimbursed for this indication. The most appropriate and cost-effective test in this indication remains to be determined.**

[c] The KCE is the only responsible for the recommendations given to the public authorities

5. REFERENCES

1. Iwarson S, Norkrans G, Wejstal R. Hepatitis C: natural history of a unique infection. Clin.Infect.Dis. 1995;20(5):1361-70.
2. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science. 1989;244(4902):359-62.
3. Chevaliez S. Virological tools to diagnose and monitor hepatitis C virus infection. Clin Microbiol Infect. 2011;17(2):116-21.
4. Albeldawi M, Ruiz-Rodriguez E, Carey WD. Hepatitis C virus: Prevention, screening, and interpretation of assays. Cleve Clin J Med. 2010;77(9):616-26.
5. Van den Bruel A, Cleemput I, Huybrechts M, Bonneux L, Ramaekers D, Hulstaert F. HTA Molecular Diagnostics Supplement I:Molecular testing for hepatitis C: a review of the existing evidence. Brussels: Belgian health care knowledge centre (KCE); 2005.
6. Hellard M, Sacks-Davis R, Gold J. Hepatitis C treatment for injection drug users: a review of the available evidence. Clin Infect Dis. 2009;49(4):561-73.
7. Hagan H, Pouget ER, Des Jarlais DC, Lelutiu-Weinberger C. Meta-regression of hepatitis C virus infection in relation to time since onset of illicit drug injection: the influence of time and place. Am J Epidemiol. 2008;168(10):1099-109.
8. Nelson PK, Mathers BM, Cowie B, Hagan H, Des Jarlais D, Horyniak D, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. Lancet. 2011;378(9791):571-83.
9. Aaron S, McMahon JM, Milano D, Torres L, Clatts M, Tortu S, et al. Intranasal transmission of hepatitis C virus: virological and clinical evidence. Clin Infect Dis. 2008;47(7):931-4.
10. Pelgrom JM, Vogelaers D, Colle I. Hepatitis C-seroconversion within three to six months after having contracted clinical syphilis and/or lymphogranuloma venereum rectitis in five homosexually active, HIV seropositive men. Acta Clin Belg. 2008;63(5):335-8.
11. van der Helm JJ, Prins M, del Amo J, Bucher HC, Chene G, Dorrucci M, et al. The hepatitis C epidemic among HIV-positive MSM: incidence estimates from 1990 to 2007. AIDS. 2011;25(8):1083-91.
12. Bottieau E, Apers L, Van Esbroeck M, Vandenbruaene M, Florence E. Hepatitis C virus infection in HIV-infected men who have sex with men: sustained rising incidence in Antwerp, Belgium, 2001-2009. Euro Surveill. 2010;15(39):19673.
13. Urbanus AT, van den Hoek A, Boonstra A, van Houdt R, de Bruijn LJ, Heijman T, et al. People with Multiple Tattoos and/or Piercings Are Not at Increased Risk for HBV or HCV in The Netherlands. PLoS One. 2011;6(9):e24736.
14. Lauer GM, Walker BD. Hepatitis C virus infection. N.Engl.J.Med. 2001;345(1):41-52.
15. Arshad M, El-Kamary SS, Jhaveri R. Hepatitis C virus infection during pregnancy and the newborn period--are they opportunities for treatment? J Viral Hepat. 2011;18(4):229-36.
16. Urbanus AT, van de Laar TJ, van den Hoek A, Zuure FR, Speksnijder AG, Baaten GG, et al. Hepatitis C in the general population of various ethnic origins living in the Netherlands: should non-Western migrants be screened? J Hepatol. 2011.
17. O'Brien TR. Interferon-alfa, interferon-lambda and hepatitis C. Nat Genet. 2009;41(10):1048-50.
18. Suppiah V, Moldovan M, Ahlenstiel G, Berg T, Weltman M, Abate ML, et al. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. Nat Genet. 2009;41(10):1100-4.
19. Tanaka Y, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, Sakamoto N, et al. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. Nat Genet. 2009;41(10):1105-9.
20. Thomas DL, Thio CL, Martin MP, Qi Y, Ge D, O'Huigin C, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature. 2009;461(7265):798-801.

21. Asselah T, Marcellin P. New direct-acting antivirals' combination for the treatment of chronic hepatitis C. Liver Int. 2011;31 Suppl 1:68-77.
22. Medici MC, Furlini G, Rodella A, Fuertes A, Monachetti A, Calderaro A, et al. Hepatitis C virus core antigen: analytical performances, correlation with viremia and potential applications of a quantitative, automated immunoassay. J Clin Virol. 2011;51(4):264-9.
23. Ross RS, Viazov S, Salloum S, Hilgard P, Gerken G, Roggendorf M. Analytical performance characteristics and clinical utility of a novel assay for total hepatitis C virus core antigen quantification. J Clin Microbiol. 2010;48(4):1161-8.
24. Muhlberger N, Schwarzer R, Lettmeier B, Sroczynski G, Zeuzem S, Siebert U. HCV-related burden of disease in Europe: a systematic assessment of incidence, prevalence, morbidity, and mortality. BMC Public Health. 2009;9:34.
25. Hoofnagle JH. Hepatitis C: the clinical spectrum of disease. Hepatology. 1997;26(3 Suppl 1):15S-20S.
26. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis. 2005;5(9):558-67.
27. Hoofnagle JH. Therapy of viral hepatitis. Digestion. 1998;59(5):563-78.
28. Mauss S. Effects of illicit and legal drugs on the liver in patients with chronic hepatitis C. 2nd International Symposium on Hepatitis care in substance users. Oral presentation. Suchtmedizin in Forschung und Praxis. 2011;4:165.
29. EASL. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol. 2011;55(2):245-64.
30. Bruno S, Crosignani A, Facciotto C, Rossi S, Roffi L, Redaelli A, et al. Sustained virologic response prevents the development of esophageal varices in compensated, Child-Pugh class A hepatitis C virus-induced cirrhosis. A 12-year prospective follow-up study. Hepatology. 2010;51(6):2069-76.
31. Di Martino V, Crouzet J, Hillon P, Thevenot T, Minello A, Monnet E. Long-term outcome of chronic hepatitis C in a population-based cohort and impact of antiviral therapy: a propensity-adjusted analysis. J Viral Hepat. 2011;18(7):493-505.
32. Adler M, Goubau P, Leroux-Roels G, Sprengers D, Pawlotsky JM. Practical use of hepatitis C and B molecular tools: Belgian guidelines. Acta Gastroenterol Belg. 2005;68(3):308-13.
33. Ebner N, Wanner C, Winklbaur B, Matzenauer C, Jachmann CA, Thau K, et al. Retention rate and side effects in a prospective trial on hepatitis C treatment with pegylated interferon alpha-2a and ribavirin in opioid-dependent patients. Addict Biol. 2009;14(2):227-37.
34. Brady B, Siebert U, Sroczynski G, Murphy G, Husereau D, Sherman M, et al. Pegylated interferon combined with ribavirin for chronic hepatitis C virus infection: an economic evaluation. Report. Canadian Agency for Drugs and Technologies in Health (CADTH); 2007. Technology Report No 82 Available from: http://www.cadth.ca/index.php/en/hta/reports-publications/search/publication/697
35. Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N. Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation. Systematic review. National Coordinating Centre for Health Technology Assessment (NCCHTA); 2007. 1111 Available from: http://www.hta.ac.uk
36. Siebert U, Sroczynski G, Aidelsburger P, Rossol S, Wasem J, Manns MP, et al. Clinical effectiveness and cost effectiveness of tailoring chronic hepatitis C treatment with peginterferon alpha-2b plus ribavirin to HCV genotype and early viral response: a decision analysis based on German guidelines. Pharmacoeconomics. 2009;27(4):341-54.
37. Innes HA, Hutchinson SJ, Allen S, Bhattacharyya D, Bramley P, Delahooke TE, et al. Excess liver-related morbidity of chronic hepatitis C patients, who achieve a sustained viral response, and are discharged from care. Hepatology. 2011;54(5):1547-58.

38. Wedemeyer H. New antiviral treatments and small molecules in the treatment of hepatitis in substance users. Suchtmed. Forsch. Prax. 2011;4:165.

39. Grebely J, Raffa JD, Lai C, Krajden M, Kerr T, Fischer B, et al. Low uptake of treatment for hepatitis C virus infection in a large community-based study of inner city residents. J Viral Hepat. 2009;16(5):352-8.

40. Hansen N, Obel N, Christensen PB, Krarup H, Laursen AL, Clausen MR, et al. Predictors of antiviral treatment initiation in hepatitis C virus-infected patients: a Danish cohort study. J Viral Hepat. 2009;16(9):659-65.

41. Backus LI, Boothroyd DB, Phillips BR, Mole LA. Predictors of response of US veterans to treatment for the hepatitis C virus. Hepatology. 2007;46(1):37-47.

42. Hansen N, Obel N, Christensen PB, Kjaer M, Laursen AL, Krarup HB, et al. Effectiveness of treatment with pegylated interferon and ribavirin in an unselected population of patients with chronic hepatitis C: A Danish nationwide cohort study. BMC Infect Dis. 2011;11(1):177.

43. Robaeys G, Van Vlierberghe H, Mathei C, Van Ranst M, Bruckers L, Buntinx F, et al. Similar compliance and effect of treatment in chronic hepatitis C resulting from intravenous drug use in comparison with other infection causes. Eur J Gastroenterol Hepatol. 2006;18(2):159-66.

44. Vandepoortaele G. Rapport de l'analyse des données receuillies par la recherche socio-anthropologique. Annexe au rapport d'activité 2010, Réseau Hépatite C, Brussels. 2010.

45. Schulte B, Reimer J, Schmidt C, Goelz J, Verthein U, Backmund M. Optimizing HCV therapy: the impact of psychoeducation on retention and SVR in opiate substituted patients. 2nd International Symposium on Hepatitis care in substance users. Oral presentation. Suchtmedizin in Forschung und Praxis. 2011;4:168.

46. Henrion J, De Maeght S, Deltenre P, Ghilain JM, Maisin JM, Schapira M, et al. Impact of hepatitis C virus infection on the aetiology of cirrhosis and hepatocarcinoma in three affiliated hospitals in southern Belgium. Acta Gastroenterol Belg. 2002;65(2):80-2.

47. Van Vlierberghe H, Colle I, Henrion J, Michielsen P, Delwaide J, Reynaert H, et al. The HepCar registry: report on a one-year registration program of hepatocellular carcinoma (HCC) in Belgium. What is daily practice in HCC? Acta Gastroenterol Belg. 2005;68(4):403-11.

48. Yerna BL, Mélotte C, Closon JP. Indemnification of the victims who contracted HIV or hepatitis C through a contaminated blood transfusion. Health Services Research (HSR). Brussels: Belgian health care knowledge centre (KCE); 2010. KCE Reports 134. D/2010/10.273/47

49. Beutels M, Van Damme P, Aelvoet W, Desmyter J, Dondeyne F, Goilav C, et al. Prevalence of hepatitis A, B and C in the Flemish population. Eur J Epidemiol. 1997;13(3):275-80.

50. Gerkens S, Nechelput M, Annemans L, Peraux B, Beguin C, Horsmans Y. A health economic model to assess the cost-effectiveness of pegylated interferon alpha-2a and ribavirin in patients with moderate chronic hepatitis C and persistently normal alanine aminotransferase levels. Acta Gastroenterol Belg. 2007;70(2):177-87.

51. Gerkens S, Nechelput M, Annemans L, Peraux B, Mouchart M, Beguin C, et al. A health economic model to assess the cost-effectiveness of PEG IFN alpha-2a and ribavirin in patients with mild chronic hepatitis C. J Viral Hepat. 2007;14(8):523-36.

52. Van Damme P, Thyssen A, Van Loock F. Epidemiology of hepatitis C in Belgium: present and future. Acta Gastroenterol Belg. 2002;65(2):78-9.

53. Quoilin S, Hutse V, Vandenberghe H, Claeys F, Verhaegen E, De Cock L, et al. A population-based prevalence study of hepatitis A, B and C virus using oral fluid in Flanders, Belgium. European Journal of Epidemiology. 2007;22(3):195-202.

54. Delarocque-Astagneau E, Meffre C, Dubois F, Pioche C, Le Strat Y, Roudot-Thoraval F, et al. The impact of the prevention programme of hepatitis C over more than a decade: the French experience. J Viral Hepat. 2010;17(6):435-43.

55. Todts S, Hariga F, Pozza M, Leclercq D, Glibert P, Micalessi M-I. Drug Use in Belgian Prisons, Monitoring of Health Risks. Institute of Public Health, Brussels, Modus Vivendi, Brussels and Streetwise, Antwerp, Belgium; 2006.

56. Plasschaert S, Ameye L, De Clercq T, Walckiers D, Sartor F, Micalessi I, et al. Study on HCV, HBV and HIV seroprevalence in a sample of drug users in contact with treatment centres or in prisons in Belgium. IPH/EPI Reports Nr 2005-029. 2004. Available from: https://www.wiv-isp.be/reitox/Publications/inf05.pdf

57. Micalessi MI, Gerard C, Ameye L, Plasschaert S, Brochier B, Vranckx R. Distribution of hepatitis C virus genotypes among injecting drug users in contact with treatment centers in Belgium, 2004-2005. J Med Virol. 2008;80(4):640-5.

58. Removille N, Origer A, Couffignal S, Vaillant M, Schmit JC, Lair ML. A hepatitis A, B, C and HIV prevalence and risk factor study in ever injecting and non-injecting drug users in Luxembourg associated with HAV and HBV immunisations. BMC Public Health. 2011;11:351.

59. Michielsen P, Brenard R, Bourgeois N, De Galocsy C, Delwaide J, Henrion J, et al. Hepatitis C: screening, treatment and prevention practical guidelines. Acta Gastroenterol Belg. 2003;66(1):15-9.

60. Robaeys G, Buntinx F, Bottieau E, Bourgeois S, Brenard R, Colle I, et al. Guidelines for the management of chronic hepatitis C in patients infected after substance use. Acta Gastroenterol Belg. 2005;68(1):38-45.

61. Delwaide J, Lamproye A, Belaiche J. [Challenges to reduce mortality due to hepatitis C: improving accessibility to therapy and compliance]. Rev Med Liege. 2010;65(5-6):354-7.

62. Gerard C, Delwaide J, Vaira D, Bastens B, Servais B, Wain E, et al. Evolution over a 10 year period of the epidemiological profile of 1,726 newly diagnosed HCV patients in Belgium. J Med Virol. 2005;76(4):503-10.

63. De Maeght S, Henrion J, Bourgeois N, de Galocsy C, Langlet P, Michielsen P, et al. A pilot observational survey of hepatitis C in Belgium. Acta Gastroenterol Belg. 2008;71(1):4-8.

64. Mathei C, Van Dooren S, Lemey P, Van Damme P, Buntinx F, Vandamme AM. The epidemic history of hepatitis C among injecting drug users in Flanders, Belgium. J Viral Hepat. 2008;15(6):399-408.

65. Mathei C, Wollants E, Verbeeck J, Van Ranst M, Robaeys G, Van Damme P, et al. Molecular epidemiology of hepatitis C among drug users in Flanders, Belgium: association of genotype with clinical parameters and with sex- and drug-related risk behaviours. Eur J Clin Microbiol Infect Dis. 2005;24(8):514-22.

66. Putzeys V, Gerard C, Bastens B, Wain E, Bataille C, Defrance P, et al. Hepatitis C of genotype 2: the role of medical invasive exams. Acta Gastroenterol Belg. 2011;74(2):277-80.

67. Mathei C, Robaeys G, Van Ranst M, Van Damme P, Buntinx F. The epidemiology of hepatitis C among injecting drug users in Belgium. Acta Gastroenterol Belg. 2005;68(1):50-4.

68. Ledoux Y. Synthese van de studie "Evaluatie van de methadon verstrekking in België". Algemene Pharmaceutische Bond - APB. In; 2004.

69. Lamkaddem B. Belgian National Report on drugs 2008. In. Brussels: Epidemiology Unit, Scientific Institute of Public Health; 2008.

70. Vlaams Agentschap Zorg & Gezondheid Organisaties voor spuitenruil [Brussel: Vlaams Agentschap Zorg & Gezondheid;2011 [cited November 2011]. Available from: http://www.zorg-en-gezondheid.be/Zorgaanbod/Preventieve-gezondheidszorg/Organisaties-terreinwerking/Organisaties-voor-spuitenruil/

71. Todts S. Country Report Belgium. In: EMCDDA (2003). (European Monitoring Centre for Drugs and Drug Addiction). Legal aspects of substitution treatment: an insight into nine EU countries. (28-35). 2003.

72. Picard E. Legal Action against the Belgian medical Association's restriction of methadone treatment. In: Aids and drugs in the European Community, Reisinger, M (ed), Lisbon, EMCDDA, 41, 1993. 1993.

73. RIZIV-INAMI. Info spot - les préparations magistrales - avril-mai-juin 2011. Bruxelles: Institut national d'assurance maladie-invalidité; 2011.

74. Vice-eerstminister en minister van Sociale Zaken en Volksgezondheid. Schriftelijke vraag van de heer Louis Ide d.d. 1 february 2010. Brussel: FOD sociale zekerheid; 2010.

75. Verslype C, Michielsen P, Adler M, Orlent H, Sprengers D, Delwaide J, et al. The management of patients with mild hepatitis C. Acta Gastroenterol Belg. 2005;68(3):314-8.

76. Wilson JM, Jungner YG. Principles and practice of screening for disease. Geneva: World Health Organization; 1968.

77. De Laet C, Neyt M, Vinck I, Lona M, Cleemput I, Van De Sande S. Screening for Colorectale Cancer : current evidence and budget impact for Belgium. Health Technology Assessment. . Brussels: Belgian Health Care Knowledge Centre (KCE); 2006. KCE reports 45 B (D/2006/10.273/58)

78. Ministère de la Santé et des Sports. Plan national de lutte contre les hépatites B et C 2009-2012. Paris: Ministère de la Santé et des Sports; 2009.

79. Karnon J, Goyder E, Tappenden P, McPhie S, Towers I, Brazier J, et al. A review and critique of modelling in prioritising and designing screening programmes. Health Technol Assess. 2007;11(52):iii-iv, ix-xi, 1-145.

80. NSC Programme appraisal criteria [UK: National screening committee;2011 [cited June 28, 2011]. Available from: http://www.screening.nhs.uk/criteria

81. Ho SB, Groessl E, Dollarhide A, Robinson S, Kravetz D, Dieperink E. Management of chronic hepatitis c in veterans: The potential of integrated care models. Am. J. Gastroenterol. 2008;103(7):1810-23.

82. Templeton DJ. Sexually transmitted infection and blood-borne virus screening in juvenile correctional facilities: A review of the literature and recommendations for Australian centres. J. Clin. Forensic Med. 2006;13(1):30-6.

83. Vogel M, Boesecke C, Rockstroh JK. Acute hepatitis C infection in HIV-positive patients. Curr. Opin. Infect. Dis. 2011;24(1):1-6.

84. Whang CS, Hu KQ. Hepatitis C in patients with chronic kidney disease: Course and management. Curr. Hepatitis Rep. 2007;6(3):96-102.

85. Chou R, Clark E, Helfand E. Screening for Hepatitis C Virus Infection. Rockville: Agency for Healthcare Research and Quality; 2004.

86. Sroczynski G, Esteban E, Conrads-Frank A, Schwarzer R, Muhlberger N, Wright D, et al. Long-term effectiveness and cost-effectiveness of screening for hepatitis C virus infection. Eur J Public Health. 2009;19(3):245-53.

87. Stein K, Dalziel K, Walker A, McIntyre L, Jenkins B, Horne J, et al. Screening for hepatitis C among injecting drug users and in genitourinary medicine clinics: Systematic reviews of effectiveness, modelling study and national survey of current practice. Health Technol. Assess. 2002;6(31).

88. Deuffic-Burban S, Deltenre P, Louvet A, Canva V, Dharancy S, Hollebecque A, et al. Impact of viral eradication on mortality related to hepatitis C: a modeling approach in France. J Hepatol. 2008;49(2):175-83.

89. Kershenobich D, Razavi HA, Sanchez-Avila JF, Bessone F, Coelho HS, Dagher L, et al. Trends and projections of hepatitis C virus epidemiology in Latin America. Liver Int. 2011;31(SUPPL. 2):18-29.

90. Mather D. A Computer Simulation of the Spread of Hepatitis C. Monash University; 1995. Monash Econometrics and Business Statistics Working Papers 8/95

91. Rein DB, Wittenborn JS, Weinbaum CM, Sabin M, Smith BD, Lesesne SB. Forecasting the morbidity and mortality associated with prevalent cases of pre-cirrhotic chronic hepatitis C in the United States. Dig Liver Dis. 2011;43(1):66-72.

92. Benet T, D'Oliveira A, Jr., Voirin N, Livrozet JM, Cotte L, Peyramond D, et al. Characteristics and survival of HIV-infected patients not screened for hepatitis C virus infection in a hospital-based cohort. J Viral Hepat. 2007;14(10):730-5.

93. Chapko MK, Sloan KL, Davison JW, Dufour DR, Bankson DD, Rigsby M, et al. Cost effectiveness of testing strategies for chronic hepatitis C. Am. J. Gastroenterol. 2005;100(3):607-15.

94. Coon JT, Castelnuovo E, Pitt M, Cramp M, Siebert U, Stein K. Case finding for hepatitis C in primary care: a cost utility analysis. Family Practice. 2006;23(4):393-406.

95. D'Souza G, Arafat R, Hwang L, Cunningham C, Shah S, Reynolds K. Cross-sectional survey of the extent and indicators of hepatitis C virus infection in Houston Department of Health and Human Services' sexually transmitted disease clinics. J Viral Hepat. 2003;10(2):134-40.

96. Fischer LR, Tope DH, Conboy KS, Hedblom BD, Ronberg E, Shewmake DK, et al. Screening for hepatitis C virus in a health maintenance organization. Arch Intern Med. 2000;160(11):1665-73.

97. Helsper CW, Borkent-Raven BA, De Wit NJ, Van Essen GA, Bonten M, Janssen MP, et al. Cost-effectiveness of targeted screening for hepatitis c in the Netherlands. Value Health. 2009;12(7):A429.

98. Honeycutt AA, Harris JL, Khavjou O, Buffington J, Jones TS, Rein DB. The costs and impacts of testing for hepatitis C virus antibody in public STD clinics. Public Health Rep. 2007;122(Supplement 2):55-62.

99. Jhaveri R, Grant W, Kauf TL, McHutchison J. The burden of hepatitis C virus infection in children: estimated direct medical costs over a 10-year period. J Pediatr. 2006;148(3):353-8.

100. Jusot JF, Colin C. Cost-effectiveness analysis of strategies for hepatitis C screening in French blood recipients. Eur. J. Public Health. 2001;11(4):373-9.

101. Kirkizlar E, Faissol DM, Griffin PM, Swann JL. Timing of testing and treatment for asymptomatic diseases. Math. Biosci. 2010;226(1):28-37.

102. Lapane KL, Jakiche AF, Sugano D, Weng CS, Carey WD. Hepatitis C infection risk analysis: who should be screened? Comparison of multiple screening strategies based on the National Hepatitis Surveillance Program. Am J Gastroenterol. 1998;93(4):591-6.

103. Loubiere S, Rotily M, Moatti JP. Prevention could be less cost-effective than cure: The case of hepatitis C screening policies in France. Int. J. Technol. Assess. Health Care. 2003;19(4):632-45.

104. Loubiere S, Rotily M, Portal I, Bourliere M, Moatti JP. Economic evaluation of screening strategies for chronic hepatitis C. Med. Mal. Infect. 1999;29(5):337-44.

105. Nakamura J, Terajima K, Aoyagi Y, Akazawa K. Cost-effectiveness of the national screening program for hepatitis C virus in the general population and the high-risk groups. Tohoku J. Exp. Med. 2008;215(1):33-42.

106. Pereira A. Health and economic consequences of HCV lookback. Transfusion. 2001;41(6):832-9.

107. Pereira A, Sanz C. A model of the health and economic impact of posttransfusion hepatitis C: Application to cost-effectiveness analysis of further expansion of HCV screening protocols. Transfusion. 2000;40(10):1182-91.

108. Plunkett BA, Grobman WA. Routine hepatitis C virus screening in pregnancy: A cost-effectiveness analysis. Am. J. Obstet. Gynecol. 2005;192(4):1153-61.

109. Rotily M, Loubiere S, Nixon J, Bourliere M, Halfon P, Moatti JP. Faut-il depister l'hepatite C? Analyse socio(-)economique de differentes strategies de depistage de l'hepatite chronique C dans la population francaise. Gastroenterol Clin Biol. 1997;21(1 Pt 2):S33-40.

110. Saab S, Brezina M, Gitnick G, Martin P, Yee HF, Jr. Hepatitis C screening strategies in hemodialysis patients. Am J Kidney Dis. 2001;38(1):91-7.

111. Singer ME, Younossi ZM. Cost effectiveness of screening for hepatitis C virus in asymptomatic, average-risk adults. Am. J. Med. 2001;111(8):614-21.

112. Stein K, Dalziel K, Walker A, Jenkins B, Round A, Royle P. Screening for hepatitis C in genito-urinary medicine clinics: A cost utility analysis. J. Hepatol. 2003;39(5):814-25.

113. Stein K, Dalziel K, Walker A, Jenkins B, Round A, Royle P. Screening for hepatitis C in injecting drug users: A cost utility analysis. J. Public Health (United Kingdom). 2004;26(1):61-71.

114. Sutton AJ, Edmunds WJ, Gill ON. Estimating the cost-effectiveness of detecting cases of chronic hepatitis C infection on reception into prison. BMC Public Health. 2006;6.

115. Sypsa V, Hadjipaschali E, Hatzakis A. Prevalence, risk factors and evaluation of a screening strategy for chronic hepatitis C and B virus infections in healthy company employees. Eur. J. Epidemiol. 2001;17(8):721-8.

116. Tramarin A, Gennaro N, Compostella FA, Gallo C, Wendelaar Bonga LJ, Postma MJ. HCV screening to enable early treatment of hepatitis C: A mathematical model to analyse costs and outcomes in two populations. Curr. Pharm. Des. 2008;14(17):1655-60.

117. Castelnuovo E, Thompson-Coon J, Pitt M, Cramp M, Siebert U, Price A, et al. The cost-effectiveness of testing for hepatitis C in former injecting drug users. Health Technol Assess. 2006;10(32):iii-iv, ix-xii, 1-93.

118. Leal P, Stein K, Rosenberg W. What is the cost utility of screening for hepatitis C virus (HCV) in intravenous drug users? J. Med. Screen. 1999;6(3):124-31.

119. OECD OECD.Stat Extracts [Organisation for economic co-operation and development;2010 [cited November 3, 2010]. Available from: http://stats.oecd.org/index.aspx

120. Eurostat Statistiques par thème [Commission Européenne;2010 [cited November 3, 2010]. Available from: http://epp.eurostat.ec.europa.eu/portal/page/portal/statistics/search_database

121. Deuffic-Burban S, Abiteboul D, Lot F, Branger M, Bouvet E, Yazdanpanah Y. Costs and cost-effectiveness of different follow-up schedules for detection of occupational hepatitis C virus infection. GUT. 2009;58(1):105-10.

122. Nguyen KA, Busch MP. Evolving strategies for diagnosing human immunodeficiency virus infection. Am. J. Med. 2000;109(7):595-7.

123. Alzahrani AJ. Analysis of hepatitis C virus core antigenemia in Saudi drug users. Saudi Med. J. 2005;26(10):1645-6.

124. Bruguera M, Forns X. Hepatitis C in Spain. Med. Clin. 2006;127(3):113-7.

125. Contreras-Navarro AM, Tornero-Romo CM, Orozco-Hernandez A, Hernandez-Lugo MI, Romero-Flores P, De La Rosa AC. Rediscovering hepatitis C antibody. New screening and diagnostic strategies. Gac. Med. Mex. 2007;143(SUPPL. 2):3-12.

126. Dal Molin G, Tiribelli C, Campello C. A rational use of laboratory tests in the diagnosis and management of hepatitis C virus infection. Ann Hepatol. 2003;2(2):76-83.

127. Kim WR, Flamm SL, Di Bisceglie AM, Bodenheimer Jr HC. Serum activity of alanine aminotransferase (ALT) as an indicator of health and disease. Hepatology. 2008;47(4):1363-70.

128. McHutchison JG, Bacon BR. Chronic hepatitis C: An age wave of disease burden. Am. J. Managed Care. 2005;11(SUPPL. 10):S286-S95.

129. Mizui M, Moriya T, Yoshizawa H, Kondo M, Saito T, Imai M, et al. A novel agglutination method for screening of HIV and HCV antibody testing with 5-(mu)l reagents: Reduction of cost and time with high sensitivity. VOX SANG. 1994;67(3):315-6.

130. Sterling RK, Brown RS, Hofmann CM, Luketic VA, Stravitz RT, Sanyal AJ, et al. The spectrum of chronic hepatitis C virus infection in the Virginia correctional system: development of a strategy for the evaluation and treatment of inmates with HCV. Am. J. Gastroenterol. 2005;100(2):313-21.

131. Udeagu Pratt CCN, Paone D, Carter RJ, Layton MC. Hepatitis C screening and management practices: A survey of drug treatment and syringe exchange programs in New York City. Am. J. Public Health. 2002;92(8):1254-6.

132. Wozny W, Piasek A, Elbaum D. Simultaneous detection of hepatitis C virus and human immunodeficiency virus RNA in serum using amplicor PCR tests. VIRAL IMMUNOL. 1997;10(2):73-82.

133. Leal P, Stein K. Screening for hepatitis C in intravenous drug users and genito-urinary clinic attendees. Report. Wessex Institute for Health Research and Development (WIHRD); 1998. DEC Report No. 81 Available from: http://www.hta.ac.uk/rapidhta/publications.htm

134. Batra N. Hepatitis C screening and treatment versus liver transplantation: A financial option appraisal and commissioning model for purchasers. Dis. Manage. Health Outcomes. 2001;9(7):371-84.

135. Desenclos JC, Dubois F, Mariotte N, Goudeau A. Analysis of oriented screening strategies for hepatitis C virus infection. GASTROENTEROL. CLIN. BIOL. 1997;21(1 BIS):S25-S32.

136. Gordon FD. Cost-effectiveness of screening patients for hepatitis C. Am. J. Med. 1999;107(6 SUPPL. 2):36-40.

137. Josset V, Chamouni P, Tavolacci MP, Merle V, Delbos V, Froment L, et al. Evaluation medicoeconomique du suivi serologique peritransfusionnel du virus de l'hepatite C. Transfus Clin Biol. 2004;11(4):186-91.

138. Josset V, Torre JP, Tavolacci MP, Van Rossem-Magnani V, Anselme K, Merle V, et al. Efficiency of hepatitis C virus screening strategies in general practice. Gastroenterol. Clin. Biol. 2004;28(4):351-7.

139. Kaur S, Rybicki L, Bacon BR, Gollan JL, Rustgi VK, Carey WD. Performance characteristics and results of a large-scale screening program for viral hepatitis and risk factors associated with exposure to viral hepatitis B and C: results of the National Hepatitis Screening Survey. National Hepatitis Surveillance Group. HEPATOLOGY. 1996;24(5):979-86.

140. Leikin EL, Reinus JF, Schmell E, Tejani N. Epidemiologic predictors of hepatitis C virus infection in pregnant women. OBSTET. GYNECOL. 1994;84(4 I):529-34.

141. Monnet E, Mercet P, Woronoff Lemsi MC, Bresson Hadni S, Pruniaux J, Cottray P, et al. Depistage organise de l'hepatite virale C. Resultats et cout d'un an de campagne dans un departement pilote. [Organized hepatitis C screening. Results and cost of a one-year campaign in a pilot area]. Gastroenterol Clin Biol. 2000;24(5):541-6.

142. Seme K, Mocilnik T, Fujs K, Babic DZ, Todorovic A, Fras-Stefan T, et al. Twenty-four mini-pool HCV RNA screening outside a blood transfusion setting: Results of a 2-year prospective study. J. Virol. Methods. 2007;140(1-2):218-21.

143. Somsouk M, Langfield DE, Inadomi JM, Yee Jr HF. A cost-identification analysis of screening and surveillance of hepatitis C infection in a prospective cohort of dialysis patients. Dig. Dis. Sci. 2008;53(4):1093-9.

144. Anonymous. Hepatites B et hepatites C, un enjeu majeur de Sante publique: comment concilier maitrise des depenses de sante et couts de sante publique? Allerg Immunol (Paris). 1997;29(7):215-8.

145. Anonymous. Coalition seeks funding for HCV/HIV co-infection. Integrating services makes economic, medical sense. Aids Alert. 2003;18(5):63-5.

146. Barnett ED. Immunizations and infectious disease screening for internationally adopted children. Pediatr. Clin. North Am. 2005;52(5):1287-309.

147. Boutwell AE, Allen SA, Rich JD. Opportunities to address the hepatitis C epidemic in the correctional setting. Clin. Infect. Dis. 2005;40(SUPPL. 5):S367-S72.

148. Calonge N, Randhawa G. The meaning of the U.S. Preventive Services Task Force grade I recommendation: Screening for hepatitis C virus infection. Ann. Intern. Med. 2004;141(9):718-9.

149. Fabrizi F, Lunghi G, Raffaele L, Guarnori I, Bacchini G, Corti M, et al. Serologic survey for control of hepatitis C in haemodialysis patients: Third-generation assays and analysis of costs. NEPHROL. DIAL. TRANSPLANT. 1997;12(2):298-303.

150. Fabrizi F, Poordad FF, Martin P. Diagnostic workup of hepatitis C and the patient on maintenance dialysis. Int. J. Artif. Organs. 2001;24(12):843-52.

151. Ferguson R, Greener M. Hepatitis C presents a growing challenge for community pharmacists. Pharm. Pract. 2005;15(5):211-4.

152. Hagedorn H, Dieperink E, Dingmann D, Durfee J, Ho SB, Isenhart C, et al. Integrating hepatitis prevention services into a substance use disorder clinic. J. Subst. Abuse Treat. 2007;32(4):391-8.

153. Hill L, Henry B, Schweikert S, Bretsch JK. Screening for chronic hepatitis C: American College of Preventive Medicine practice policy statement. Am. J. Prev. Med. 2005;28(3):327-30.

154. Jullien-Depradeux AM, Bloch J, Le Quellec-Nathan M, Abenhaim A. National campaign against hepatitis C in France (1999-2002). Acta Gastroenterol Belg. 2002;65(2):112-4.

155. Jusot JF, Aubert C, des Floris MF, Rotily M, Lancon F, Colin C, et al. Declared hepatitis C screening strategies in blood recipients in French hospitals. Transfus Clin Biol. 2002;9(2):130-6.

156. Klein SJ, Flanigan CA, Cooper JG, Holtgrave DR, Carrascal AF, Birkhead GS. Wanted: An effective public health response to hepatitis c virus in the United States. J. Public Health Manage. Pract. 2008;14(5):471-5.

157. Loubiere S, Rotily M, Moatti JP. Appraisal of economic evaluations of treatment and screening for hepatitis C. Med. Sci. 2002;18(3):325-33.

158. McCaughan GW, Omata M, Amarapurkar D, Bowden S, Chow WC, Chutaputti A, et al. Asian Pacific Association for the Study of the Liver consensus statements on the diagnosis, management and treatment of hepatitis C virus infection. J. Gastroenterol. Hepatol. 2007;22(5):615-33.

159. Rosenberg S, Tarre H. Tracking and treating Hep C infection. Bus Health. 1999;17(2):41-2.

160. Thomas DL. Improving the detection and care of people with hepatitis B and C. Gastroenterol. Hepatol. 2010;6(6):363-5.

161. Toledo AC, Jr., Januario JN, Rezende RM, Siqueira AL, Mello BF, Fialho EL, et al. Dried blood spots as a practical and inexpensive source for human immunodeficiency virus and hepatitis C virus surveillance. Mem Inst Oswaldo Cruz. 2005;100(4):365-70.

162. Trepo C. Benefits of hepatitis C screening. GASTROENTEROL. CLIN. BIOL. 1997;21(1 BIS):S1-S3.

163. Williams JL, Cagle HH, Christensen CJ, Fox Leyva LK, McMahon BJ. Results of a hepatitis C general transfusion lookback program for patients who received blood products before July 1992. TRANSFUSION. 2005;45(6):1020-6.

164. Yoho RA, Cruz LL, Mazaheri R, Cruz AT. Hepatitis C: A review. Plast. Reconstr. Surg. 2003;112(2):597-605.

165. Zaller ND, Taylor LE, Allen S, Rich JD. Hepatitis C in correctional institutions. Curr. Hepatitis Rep. 2007;6(3):114-8.

166. ANAES. Dépistage de l'hépatite C. Populations à dépister et modalités du dépistage. Recommandations du comité d'experts réuni par l'ANAES. Paris: Agence nationale d'accréditation et d'évaluation en santé; 2001.

167. CDC. Recommendations for Prevention and Control of Hepatitis C Virus (HCV) Infection and HCV-Related Chronic Disease Atlanta: Centers for Disease Control and Prevention; 1998. 47

168. Chou R, Clark EC, Helfand M. Screening for hepatitis C virus infection: a review of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2004;140(6):465-79.

169. Gezondheidsraad. Opsporing en behandeling van mensen met hepatitis C. Den Haag: Health Council of the Netherlands; 2004.

170. U. S. Preventive Services Task Force. Screening for hepatitis C virus infection in adults: recommendation statement. Ann Intern Med. 2004;140(6):462-4.

171. Sutton AJ, Edmunds WJ, Sweeting MJ, Gill ON. The cost-effectiveness of screening and treatment for hepatitis C in prisons in England and Wales: A cost-utility analysis. J. Viral Hepatitis. 2008;15(11):797-808.

172. ECDC. Hepatitis B and C in the EU neighbourhood: prevalence, burden of disease and screening policies. Stockholm: European Centre for Disease Prevention and Control; 2010. Available from: www.ecdc.europa.eu

173. Renard F, Autier M, Doumont D. L'hépatite C en Belgique. Comment améliorer le dépistage et la prévention? Brussels: RESO - Université cathiolique de Louvain; 2005.

174. Shah BB, Wong JB. The Economics of Hepatitis C Virus. Clin. Liver Dis. 2006;10(4):717-34.

175. Ishizuka M. Economic evaluation of health care program for hepatitis C virus antibody screening. Japanese Journal of Public Health. 1999;46(6):447-65.

176. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet. 2001;358(9286):958-65.

177. Delwaide J, El Saouda R, Gerard C, Belaiche J, Groupe Liegeois d'Etude des Virus H. Hepatitis C infection: eligibility for antiviral therapies. Eur J Gastroenterol Hepatol. 2005;17(11):1185-9.

178. Wright M, Grieve R, Roberts J, Main J, Thomas HC, Investigators UKMHCT. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. Health Technol Assess. 2006;10(21):1-113, iii.

179. Hornberger J, Torriani FJ, Dieterich DT, Brau N, Sulkowski MS, Torres MR, et al. Cost-effectiveness of peginterferon alfa-2a (40kDa) plus ribavirin in patients with HIV and hepatitis C virus co-infection. J Clin Virol. 2006;36(4):283-91.

180. Bonkovsky HL, Snow KK, Malet PF, Back-Madruga C, Fontana RJ, Sterling RK, et al. Health-related quality of life in patients with chronic hepatitis C and advanced fibrosis. J Hepatol. 2007;46(3):420-31.

181. Kallman J, O'Neil MM, Larive B, Boparai N, Calabrese L, Younossi ZM. Fatigue and health-related quality of life (HRQL) in chronic hepatitis C virus infection. Dig Dis Sci. 2007;52(10):2531-9.

182. Wong JB. Hepatitis C: cost of illness and considerations for the economic evaluation of antiviral therapies. Pharmacoeconomics. 2006;24(7):661-72.

183. Ratcliffe J, Longworth L, Young T, Bryan S, Burroughs A, Buxton M, et al. Assessing health-related quality of life pre- and post-liver transplantation: a prospective multicenter study. Liver Transpl. 2002;8(3):263-70.

184. Buti M, Casado MA, Fosbrook L, Wong JB, Esteban R. Cost-effectiveness of combination therapy for naive patients with chronic hepatitis C. J Hepatol. 2000;33(4):651-8.

185. Wong JB, Bennett WG, Koff RS, Pauker SG. Pretreatment evaluation of chronic hepatitis C: risks, benefits, and costs. JAMA. 1998;280(24):2088-93.

186. Wong JB, Koff RS. Watchful waiting with periodic liver biopsy versus immediate empirical therapy for histologically mild chronic hepatitis C. A cost-effectiveness analysis. Ann Intern Med. 2000;133(9):665-75.

187. Wong JB, Poynard T, Ling MH, Albrecht JK, Pauker SG. Cost-effectiveness of 24 or 48 weeks of interferon alpha-2b alone or with ribavirin as initial treatment of chronic hepatitis C. International Hepatitis Interventional Therapy Group. Am J Gastroenterol. 2000;95(6):1524-30.

188. Younossi ZM, Singer ME, McHutchison JG, Shermock KM. Cost effectiveness of interferon alpha2b combined with ribavirin for the treatment of chronic hepatitis C. Hepatology. 1999;30(5):1318-24.

189. Wong JB, Nevens F. Cost-effectiveness of peginterferon alfa-2b plus ribavirin compared to interferon alfa-2b plus ribavirin as initial treatment of chronic hepatitis C in Belgium. Acta Gastroenterol Belg. 2002;65(2):110-11.

190. Sarrazin C, Berg T, Ross RS, Schirmacher P, Wedemeyer H, Neumann U, et al. Update der S3-Leitlinie Prophylaxe, Diagnostik und Therapie der Hepatitis-C-Virus(HCV)-Infektion, AWMF-Register-Nr.: 021/012 Prophylaxis, Diagnosis and Therapy of Hepatitis C Virus (HCV) Infection: The German Guidelines on the Management of HCV Infection. Z Gastroenterol. 2010;48:289–351.

191. SIGN. Management of hepatitis C. A national clinical guideline. Edinburgh: Scottish Intercollegiate Guidelines Network; 2006.

192. NSC The UK NSC policy on Hepatitis C screening in adults [UK: National screening committee;2011 [cited June 28, 2011]. Available from: http://www.screening.nhs.uk/policydb.php?policy_id=15

193. NSC The UK NSC policy on Hepatitis C screening in pregnancy [UK: National screening committee;2011 [cited June 28, 2011]. Available from: http://www.screening.nhs.uk/policydb.php?policy_id=98

194. HAS. Stratégies de dépistage biologique des hépatites virales B et C. Saint-Denis: Haute autorité de santé; 2011.

195. Gezondheidsraad. Opsporing en behandeling van mensen met hepatitis C. Rijswijk: Gezondheidsraad: Commissie Hepatitis C; 1997. 1997/19

196. Department of Health. Hepatitis C: Essential information for professionals and guidance on testing. London: NHS Department of Health / General Health Protection; 2004.

197. Gillies M, Palmateer N, Hutchinson S, Ahmed S, Taylor A, Goldberg D. The provision of non-needle/syringe drug injecting paraphernalia in the primary prevention of HCV among IDU: a systematic review. BMC Public Health. 2010;10(721):2010.

198. Hagan H, Pouget ER, Des Jarlais DC. A systematic review and meta-analysis of interventions to prevent hepatitis C virus infection in people who inject drugs. J. Infect. Dis. 2011;204(1):74-83.

199. Jones L, Pickering L, Sumnall H, McVeigh J, Bellis MA. Optimal provision of needle and syringe programmes for injecting drug users: A systematic review. Int J Drug Policy. 2010;21(5):335-42.

200. Palmateer N, Kimber J, Hickman M, Hutchinson S, Rhodes T, Goldberg D. Evidence for the effectiveness of sterile injecting equipment provision in preventing hepatitis C and human immunodeficiency virus transmission among injecting drug users: a review of reviews. Addiction. 2010;105(5):844-59.

201. Tilson H, Aramrattana A, Bozzette SA, Celentano DD, Falco M, Hammett TM, et al. Preventing HIV infection among injecting drug users in high-risk countries. An assessment of the evidence. Washington: Institute of Medicine of the National Academies; 2006.

202. Wright NMJ, Tompkins CNE. A review of the evidence for the effectiveness of primary prevention interventions for Hepatitis C among injecting drug users. Harm Reduct. J. 2006;3.

203. Mauss S, Schmutz G. Therapie of chronic hepatitis C in patients in opioid maintenance treatment. Suchtmed. Forsch. Prax. 2004;6(2):185-8.

204. Novick DM, Kreek MJ. Critical issues in the treatment of hepatitis C virus infection in methadone maintenance patients (Structured abstract). 2008;103(6):905-18.

205. Pellicelli AM, Barbaro G, Barbarini G, Soccorsi F. Management of chronic hepatitis in drug addicts: A systematic review. Clin. Ter. 2008;159(1):41-9.

206. Schafer M, Berg T. Epidemiology and treatment options for chronic hepatitis C infection among patients with intravenous drug addiction. Sucht. 2005;51(2):97-108.

207. Zanini B, Covolo L, Donato F, Lanzini A. Effectiveness and tolerability of combination treatment of chronic hepatitis C in illicit drug users: meta-analysis of prospective studies. Clin Ther. 2010;32(13):2139-59.

208. Zanini B, Lanzini A. Antiviral treatment for chronic hepatitis C in illicit drug users: a systematic review. Antivir Ther. 2009;14(4):467-79.

209. Esposito N, Rossi C. A nested-epidemic model for the spread of hepatitis C among injecting drug users. Mathematical Biosciences. 2004;188:29-45.

210. Mather D, Crofts N. A computer model of the spread of hepatitis C virus among injecting drug users. Eur J Epidemiol. 1999;15(1):5-10.

211. Hutchinson SJ, Bird SM, Taylor A, Goldberg DJ. Modelling the spread of hepatitis C virus infection among injecting drug users in Glasgow: Implications for prevention. Int. J. Drug Policy. 2006;17(3):211-21.

212. Murray JM, Law MG, Gao Z, Kaldor JM. The impact of behavioural changes on the prevalence of human immunodeficiency virus and hepatitis C among injecting drug users. Int J Epidemiol. 2003;32(5):708-14.

213. Vickerman P, Hickman M, Judd A. Modelling the impact on Hepatitis C transmission of reducing syringe sharing: London case study. Int J Epidemiol. 2007;36(2):396-405.

214. Kwon JA, Iversen J, Maher L, Law MG, Wilson DP. The impact of needle and syringe programs on HIV and HCV transmissions in injecting drug users in Australia: a model-based analysis. J Acquir Immune Defic Syndr. 2009;51(4):462-9.

215. Martin NK, Vickerman P, Foster GR, Hutchinson SJ, Goldberg DJ, Hickman M. Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility. J. Hepatol. 2011;54(6):1137-44.

216. Martin NK, Vickerman P, Hickman M. Mathematical modelling of hepatitis C treatment for injecting drug users. J Theor Biol. 2011;274(1):58-66.

217. Zeiler I, Langlands T, Murray JM, Ritter A. Optimal targeting of Hepatitis C virus treatment among injecting drug users to those not enrolled in methadone maintenance programs. Drug Alcohol Depend. 2010;110(3):228-33.

218. Turner K, Hutchinson S, Vickerman P, Hope V, Craine N, Palmateer N, et al. The impact of needle and syringe provision and opiate substitution therapy on the incidence of Hepatitis C virus in injecting drug users: pooling of UK evidence. Addiction. 2011.

219. Vickerman P, Hickman M, May M, Kretzschmar M, Wiessing L. Can hepatitis C virus prevalence be used as a measure of injection-related human immunodeficiency virus risk in populations of injecting drug users? An ecological analysis. Addiction. 2010;105(2):311-8.

220. Vickerman P, Martin N, Hickman M. Can Hepatitis C virus treatment be used as a prevention strategy? Additional model projections for Australia and elsewhere. Drug Alcohol Depend. 2011;113(2-3):83-5; discussion 6-7.

221. Health Outcomes International Pty Ltd, The National Centre for HIV Epidemiology and Clinical Research, Drummond M. Return on investment in needle and syringe programs in Australia. Canberra: Commonwealth Department of Health and Ageing; 2002.

222. Shiell A, Law MG. The cost of hepatitis C and the cost-effectiveness of its prevention. Health Policy. 2001;58(2):121-31.

223. Vickerman P, Miners A, Williams J. Assessing the cost-effectiveness of interventions linked to needle and syringe programmes for injecting drug users: An economic modelling report. London: National Institute for Health and Clinical Excellence (NICE); 2008. Available from: www.nice.org.uk/nicemedia/live/11829/40965/40965.pdf

224. Dolan K, Clement N, Rouen D, Rees V, Shearer J, Wodak A. Can drug injectors be encouraged to adopt non-injecting routes of administration (NIROA) for drugs? Drug Alcohol Rev. 2004;23(3):281-6.

225. Foster GR. Risks and benefits of treating chronic hepatitis C virus infection in injecting drug users. Hot Top. Viral Heptatitis. 2009;5(13):7-10.

226. Pollack HA. Can We Protect Drug Users from Hepatitis C? Journal of Policy Analysis and Management. 2001;20(2):358-64.

227. Robaeys G. Management of substance use induced hepatitis C viral infection. An Update. Suchtmed. Forsch. Prax. 2009;11(5):219-23.

228. Sheerin IG, Green FT, Sellman JD. The costs of not treating hepatitis C virus infection in injecting drug users in New Zealand. Drug Alcohol Rev. 2003;22(2):159-67.

229. Warren E, Viney R, Shearer J, Shanahan M, Wodak A, Dolan K. Value for money in drug treatment: economic evaluation of prison methadone. Drug Alcohol Depend. 2006;84(2):160-6.

230. El Saadany S, Coyle D, Giulivi A, Afzal M. Economic Burden of Hepatitis C in Canada and the Potential Impact of Prevention: Results from a Disease Model. European Journal of Health Economics. 2005;6(2):159-65.

231. Krahn MD, John-Baptiste A, Yi Q, Doria A, Remis RS, Ritvo P, et al. Potential cost-effectiveness of a preventive hepatitis C vaccine in high risk and average risk populations in Canada. Vaccine. 2005;23(13):1549-58.

232. Rich JD, Wakeman SE, Dickman SL. Medicine and the epidemic of incarceration in the United States. New Engl. J. Med. 2011;364(22):2081-3.

233. Bayoumi AM, Zaric GS. The cost-effectiveness of Vancouver's supervised injection facility. CMAJ. 2008;179(11):1143-51.

234. Pollack HA. Cost-effectiveness of harm reduction in preventing hepatitis C among injection drug users. Med Decis Making. 2001;21(5):357-67.

235. Sheerin IG, Green FT, Sellman JD. What is the cost-effectiveness of hepatitis C treatment for injecting drug users on methadone maintenance in New Zealand? Drug Alcohol Rev. 2004;23(3):261-72.

236. Martin NK, Vickerman P, Miners A, Foster GR, Hutchinson SJ, Goldberg D, et al. The cost-effectiveness of HCV antiviral treatment for injecting drug user populations. Hepatology. 2011.

237. EMCDDA. Harm reduction: evidence, impacts and challenges. Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2010.

238. Association française pour l'étude du foie, Société nationale française de gastroentérologie, Société de Pathologie Infectieuse de Langue Française, Société Nationale Française de Médecine Interne, Fédération Nationale des Pôles de Références et Réseaux Hépatites, Agence Nationale d'Accréditation et d'Évaluation en Santé, et al. Consensus conference. Treatment of hepatitis C. Paris: Maison de la Chimie; 2002 February 27-28.

239. NICE. NICE technology appraisal guidance 106: peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. London: National Institute for Health and Clinical Excellence; 2006.

240. RCGP. Guidance for the prevention, testing, treatment and management of hepatitis C in primary care. UK: Royal College of General Practitioners, ; 2007.

241. NIH. Consensus statement on management of hepatitis C. NIH Consens State Sci Statements. 2002;19:1-46.

242. Reimer J, Schulte B, Castells X, Schafer I, Polywka S, Hedrich D, et al. Guidelines for the treatment of hepatitis C virus infection in injection drug users: status quo in the European Union countries. Clin Infect Dis. 2005;40 Suppl 5:S373-8.

243. Grebely J, Conway B, Raffa J, Lai C, Krajden M, Tyndall MW. Uptake of hepatitis C virus (HCV) treatment among injection drug users (IDUS) in Vancouver, Canada. Journal of Hepatology. 2006;44(2):S214-S5.

244. Seal KH, Kral AH, Lorvick J, Gee L, Tsui JI, Edlin BR. Among injection drug users, interest is high, but access low to HCV antiviral therapy. J Gen Intern Med. 2005;20(suppl 1):171.

245. Foster GR. Injecting drug users with chronic hepatitis C: should they be offered antiviral therapy? Addiction. 2008;103(9):1412-3.

246. Robaeys G, Mathei C, Buntinx F, Vanranst M. Management of hepatitis C virus infections in intravenous drug users. Acta Gastroenterol Belg. 2002;65(2):99-100.

247. Backmund M, Meyer K, Von Zielonka M, Eichenlaub D. Treatment of hepatitis C infection in injection drug users. Hepatology. 2001;34(1):188-93.

248. Dore GJ, Hellard M, Matthews GV, Grebely J, Haber PS, Petoumenos K, et al. Effective treatment of injecting drug users with recently acquired hepatitis C virus infection. Gastroenterology. 2010;138(1):123-35 e1-2.

249. Wilkinson M, Crawford V, Tippet A, Jolly F, Turton J, Sims E, et al. Community-based treatment for chronic hepatitis C in drug users: high rates of compliance with therapy despite ongoing drug use. Aliment Pharmacol Ther. 2009;29(1):29-37.

250. Dalgard O. Follow-up studies of treatment for hepatitis C virus infection among injection drug users. Clin Infect Dis. 2005;40 Suppl 5:S336-8.

251. Grady M. Low rate of reinfection with hepatitis C virus following sustained virological response among active drug users in Amsteram. In: International symposium on hepatitis care in substance users. Brussels: INHSU; 2011.

252. Grebely J, Knight E, Ngai T, Genoway KA, Raffa JD, Storms M, et al. Reinfection with hepatitis C virus following sustained virological response in injection drug users. J Gastroenterol Hepatol. 2010;25(7):1281-4.

253. Hofer H, Watkins Riedel T, Janata O, Penner E, Holzmann H, Steindl Munda P, et al. Spontaneous viral clearance in patients with acute hepatitis C can be predicted by repeated measurements of serum viral load. Hepatology. 2003;37(1):60-4.

254. Herrmann E, Lee JH, Marinos G, Modi M, Zeuzem S. Effect of ribavirin on hepatitis C viral kinetics in patients treated with pegylated interferon. Hepatology. 2003;37(6):1351-8.

255. Neumann AU, Lam NP, Dahari H, Gretch DR, Wiley TE, Layden TJ, et al. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy. Science. 1998;282(5386):103-7.

256. Witteck A, Schmid P, Hensel-Koch K, Thurnheer MC, Bruggmann P, Vernazza P. Management of hepatitis C virus (HCV) infection in drug substitution programs. Swiss Med Wkly. 2011;141:w13193.

257. De Angelis D, Hickman M, Yang S. Estimating long-term trends in the incidence and prevalence of opiate use/injecting drug use and the number of former users: back-calculation methods and opiate overdose deaths. Am J Epidemiol. 2004;160(10):994-1004.

258. Law MG, Lynskey M, Ross J, Hall W. Back-projection estimates of the number of dependent heroin users in Australia. Addiction. 2001;96(3):433-43.

259. Nordt C, Stohler R. Incidence of heroin use in Zurich, Switzerland: a treatment case register analysis. Lancet. 2006;367(9525):1830-4.

260. Sweeting M, De Angelis D, Ades A, Hickman M. Estimating the prevalence of ex-injecting drug use in the population. Stat Methods Med Res. 2009;18(4):381-95.

261. Cornish R, Macleod J, Strang J, Vickerman P, Hickman M. Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. BMJ. 2010;341:c5475.

262. Mossner BK, Jørgensen TR, Skamling M, Pedersen C, Christensen PB. 740 Outreach screening of drug users with Fibroscan® identifies a high proportion of severe fibrosis not previously recognized. Journal of Hepatology. 2008;48(supplement 2):S276.

263. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. J Viral Hepat. 2006;13(1):34-41.

264. Kimber J, Copeland L, Hickman M, Macleod J, McKenzie J, De Angelis D, et al. Survival and cessation in injecting drug users: prospective observational study of outcomes and effect of opiate substitution treatment. BMJ. 2010;341:c3172.