Who to screen for hepatitis C? A cost-effectiveness study in Belgium of comprehensive hepatitis C screening in four target groups

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Abstract

Background and study aims **: Hepatitis C virus (HCV) infection often causes asymptomatic disease and patients are frequently diagnosed at an advanced stage. Oral direct acting antivirals (DAAs) are successful in treating HCV with high sustained virologic response (SVR) and excellent tolerability. The aim of this study is to evaluate cost-effectiveness of a broad screening strategy proposing screening to all undiagnosed members of a population (comprehensive HCV screening), in the general adult population, emergency department (ED) attendees, men who have sex with men (MSM) and people who inject drugs (PWID).**

Patients and methods **: We populated a theoretical model with Belgian data. A decision tree model simulating HCV screening and diagnosis was combined with a Markov state transition model simulating treatment. There was one screening round per year during five years. In the ED population only one screening round was considered.**

Results **: The model calculated that more HCV patients could be detected and treated with comprehensive screening compared to the current situation. Incremental cost per incremental quality adjusted life years (QALY) gained was lower than 10.000€/QALY for one and for five screening rounds in the general population (5.139 and 5.200 respectively), in ED attendees (one screening round 5.967), in MSMs (4.292 and 4.302 respectively) and in PWIDs (3.504 and 3.524 respectively).**

Conclusion **: A broad screening strategy combined with treatment is likely to be a cost-effective strategy to detect and treat HCV infected patients and diminish the HCV burden in Belgium.** (Acta gastroenterol. belg., **2019**, 82, **379-387**).

Key words : chronic HCV infection, comprehensive screening, cost-effectiveness analysis.

Introduction

Hepatitis C virus (HCV) infection leads to a chronic disease in approximately 75%-80% of HCV patients. Severe comorbidities including cirrhosis and hepatocellular carcinoma can develop over the course of several years (1). Chronic HCV infection often remains asymptomatic and undiagnosed until advanced liver damage has developed (2,3). Therefore a large number of individuals remain undetected and are diagnosed late.

It is estimated that HCV affects approximately 0,5% to 0,8% of the Belgian population and is responsible for about 30 liver transplantations, 300 hepatocellular carcinomas and 450 deaths in Belgium annually (4,5).

Oral direct acting antivirals (DAAs) are successful in treating HCV with high sustained virologic response (SVR) and excellent tolerability. Increased HCV screening to detect and treat infected individuals is a plausible health strategy. To date, no screening policy is available in Belgium.

We considered the cost-effectiveness of a screening policy where HCV screening is proposed by medical doctors during a consultation for whatever reason to all HCV undiagnosed individuals of a given target population. This screening policy is hereafter referred to as comprehensive HCV screening.

In order to compare cost and health outcomes of comprehensive screening to the current situation (no screening policy) in different target populations, we used a theoretical model populated with Belgian data. A decision tree model simulates the screening and diagnoses pathway. Results of the screening model were combined with a Markov transition state model, simulating the course of HCV disease and comparing natural disease progression (no treatment) to treatment with oral direct acting antivirals (DAA).

People who inject drugs (PWID) are an obvious target for increased screening as the estimated prevalence of HCV chronic infection in this small population of 10.100 Belgian PWIDs is 32% (6). It has been reported that men who have sex with men (MSM), especially those infected with human immunodeficiency virus (HIV) are at increased risk for HCV exposure (7). As HCV spread in non-HIV infected men might have gone unnoticed, it has been suggested to offer routine testing to all MSM (8). In the general adult population the risk for HCV exposure is limited and estimated prevalence is low (0,5 to 0,8% of the adult population) (4,5). However, we estimated that half of the infected individuals are undiagnosed, meaning that possibly 22.500 to 35.900 Belgian adults remain unaware of their chronic HCV infection. Every year, approximately 890.000 individuals consult an emergency department (ED) (9). Therefore, these structures might present an excellent opportunity to increase the screening offer among asymptomatic HCV infected individuals unaware of their HCV status.

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Submission date : 05/11/2018
Acceptance date : 26/03/2019

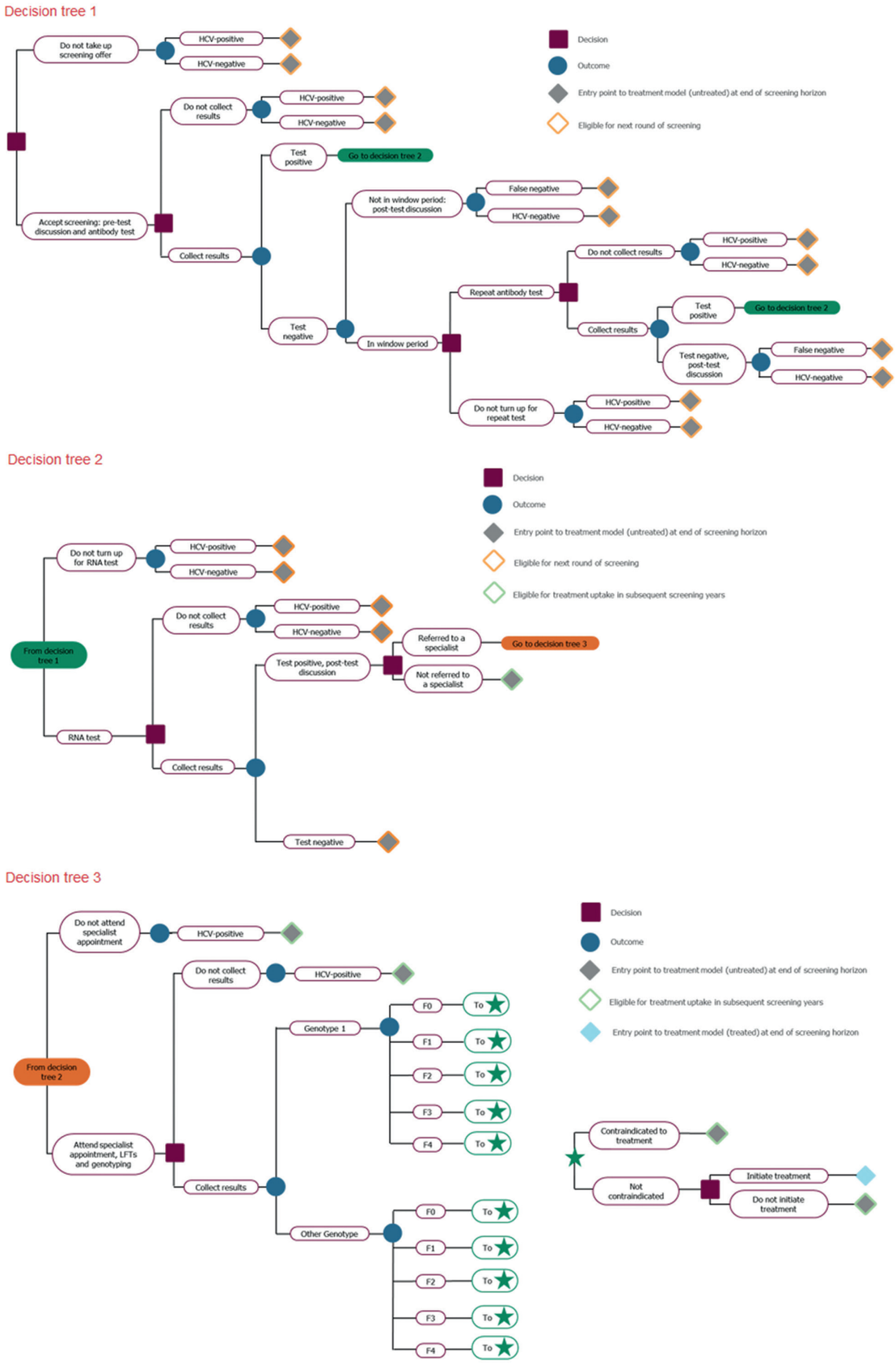

Figure 1. — Structure of the decision tree screening model (for readability, the decision tree has been split across three partial decision trees).

A theoretical modal populated with Belgian data, simulating HCV screening and treatment was used to calculate cost-effectiveness of a broad screening strategy, proposing screening to all HCV undiagnosed individuals during a medical consultation (comprehensive screening) compared to the current situation (no screening policy). Cost-effectiveness of comprehensive screening was evaluated in PWID and MSM at increased risk for HCV exposure and in the general adult population and ED attendees with a low HCV prevalence but a remaining number of undiagnosed individuals.

Materials and methods

In order to determine the overall cost-effectiveness of diagnosis followed by treatment of HCV in Belgium, a screening model has been developed and combined with a treatment model. These models have been populated with Belgian data.

Model structure: The screening model is a decision tree model simulating the screening process from initial antibody test to diagnosis (Figure 1). A detailed diagnosis pathway has been incorporated to reflect a patient's journey from screening to diagnosis and treatment initiation. It includes the possibility of a patient dropping out at any point along this diagnosis pathway. There is one screening round per year for five years in the general population, MSM and PWIDs. In the MSM and PWID population there is a high ongoing likelihood of infection and therefore repeat screening is appropriate. In the general population, transmission rate is low but it was assumed that only a small proportion of the general population will be screened in one year. Repeating the screening offer during five years will allow to reach more individuals.

ED attendees are different individuals every year, only one screening round is considered in this population.

The eligible screening population at any point in time excludes individuals who have been diagnosed as HCV positive and are aware of their status.

After a given round of screening, the eligible population for the next round of screening are those who are HCV-negative, plus those who are HCV-positive but did not receive a final diagnosis. The number of new infections since the last screening round are calculated based on the target population incidence rate.

The treatment model is a Markov state transition model simulating treatment with oral DAAs versus natural disease progression (no treatment) (Figure 2).

Individuals with the diagnosis of HCV in the screening model will enter the treatment model and a defined proportion will receive treatment. Undiagnosed HCV positive individuals will enter the treatment model and follow natural disease progression. Individuals who drop out of the screening pathway before a confirmed diagnosis has been made, are split into HCV positive and HCV negative cohorts according to the underlying disease prevalence. HCV positive individuals follow the natural disease progression, whilst HCV negative individuals do not enter the treatment model. The costs of screening of these HCV negative individuals is considered in the screening model.

Results from the screening model are calculated and then combined with results of the treatment model to provide overall cost-effectiveness results for both the diagnosis and treatment of HCV.

Time horizon and perspective of the analysis: Time horizon of the screening model was five years with one screening round per year. In the ED attendees time horizon of the screening model was one year as only one screening round was considered. The treatment model has a time horizon of 60 years to account for the burden of disease.

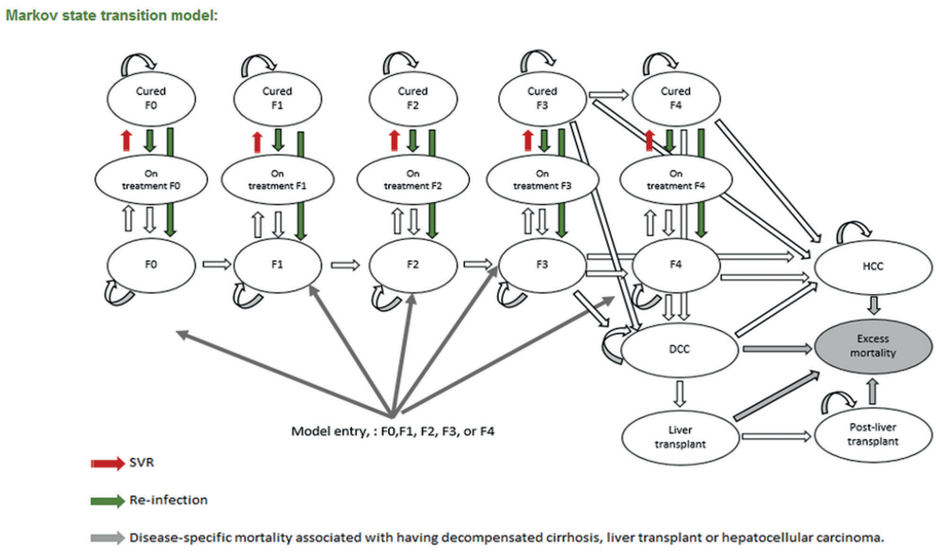

Figure 2. — Markov state transition treatment model.

Table 1. — **Input parameters for the screening model**

	General adult population	ED	MSM	PWID
Population size	8.982.329 (11)	898.233 (9)	106.336 (17)	10.100 (6)
Prevalence of chronic HCV infection	0,6%*	0,6%*	4,6%[$] (8,16,19)	32% (6)
HCV incidence (infections per 100 person years of exposure)	0,006 (4)	0,006 (4)	0,35[&] (4,6)	1,6 (6)
Spontaneous clearance rate	22% (20)	22% (20)	22% (20)	22% (20)
HCV status awareness in HCV positive subpopulation	50% (2,13-15)	61,5% (10)	50%*	52% (21)
Uptake probability per screening round initial antibody test	8%*	50%*	25%*	65%*

[$] Assumption derived from published data (8,16,19). [&] Assumption derived from published data (4,6). * Assumption.

The perspective of the analysis is the Belgian health care payer (RIZIV/INAMI). Only direct costs related to screening and treatment are considered in this analysis. Costs related to promote HCV screening or to identify and invite individuals for screening are not included in the analysis. Screening would be proposed when individuals have a contact with a health care professional such as the general practitioner for any other reason.

Model inputs: The different parameters concerning the target populations are based on published literature (1,2,4,6,9-22). If data were unavailable assumptions had to be made. Input parameters concerning the target populations are presented in Table 1.

With comprehensive screening, it is aimed to propose screening to all members of the target population. The estimated proportion of individuals accepting the screening offer is presented in table 1. Especially in the adult general population we estimated that the proportion of individuals accepting the screening offer would be low (8%). Only a proportion of the Belgian adults have a contact with a health care professional in one year and some of those individuals will refuse the screening offer.

At the time of the study, there were restrictions in Belgium for DAA treatment in patients with early fibrosis stages. Therefore, it was assumed that 70% of detected patients would be treated in the first year after diagnosis in the current situation. We estimated that 85% of detected patients would be treated in the first year after diagnosis with comprehensive screening as these restrictions disappeared in January 2019. This means that from the start of the year 2019 all patients have access to DAA treatment, independent of liver fibrosis stage.

Unit costs for the HCV testing are sourced from the INAMI/RIZIV web application Nomensoft (accessed April 2017). Cost is the INAMI/RIZIV cost for normally assured ambulatory patients without patient co-payment.

In the treatment model costs related to HCV treatment with direct acting antivirals (DAAs) and possible severe complications of natural disease progression are considered.

The cost of treatment of HCV with DAAs was aligned with the estimated cost of treatment with DAAs for non-cirrhotic patients mentioned in the KCE 276 report which was 40.000€ (22).

Existing literature was the base for the cost of severe complications in the liver due to chronic HCV infection such as decompensated cirrhosis, hepatocellular carcinoma and liver transplantation (23,24). All cost were discounted at 3% as recommended by the Belgian Health Knowledge Centre (25).

Utility inputs were sourced from published literature (26-28).

Model outcomes: Outcomes were expressed in terms of clinical outcomes (number of individuals diagnosed) and cost-utility outcomes: an incremental cost-effectiveness ratio (ICER) indicating the incremental cost per incremental quality adjusted life year (QALY). Outcomes are discounted at 1,5% per year as recommended by the Belgian Health Knowledge Centre (25).

Scenario analysis: A recent screening study in a Flemish ED department with 2.330 individuals screened, found 12 chronic HCV infections and a spontaneous HCV clearance rate of 29% (5). Based on these results a scenario analysis was undertaken in the general adult population. Model inputs for this scenario were HCV prevalence of 0,5% and spontaneous HCV clearance of 29%. For this scenario a conservative estimation of 70% of HCV infected individuals being aware of their positive HCV status was made. A second scenario with these inputs and a low estimated HCV prevalence of 0,15% was also calculated.

As price erosion of DAA might occur a third scenario in the general adult population was undertaken with the cost of DAA treatment estimated at 30.000€.

Sensitivity analysis: Deterministic sensitivity analysis (DSA) was conducted in order to identify input variables having most impact on model results. In the deterministic sensitivity analysis, all input variables were varied by +/- 20%.

A probabilistic sensitivity analysis was undertaken by randomly drawing values from a distribution around each of the inputs during 1.000 simulations. The results of these simulations were used to form a scatterplot of ICERs. A cost-effectiveness acceptability curve was calculated demonstrating the probability of cost-effectiveness at different willingness-to-pay thresholds.

Results

The number of patients with chronic HCV infection detected: Based on the current model inputs and assumptions and as expected, more individuals are detected with comprehensive screening compared to the current situation. During the first screening round in the general population the model calculated that 716.430 individuals would accept the screening offer and

Table 2. — **Number of patients with chronic HCV infection detected with comprehensive screening versus the current situation**

Population	First screening round		Five screening rounds (cumulative number of patients)	
	Comprehensive screening	Current situation	Comprehensive screening	Current situation
General adult population	1.826	867	8.310	4.231
ED	878	68	Not evaluated	Not evaluated
MSM	508	254	2.273	1.364
PWID	714	516	1.629	1.492

Table 3. — **ICER after one and after five screening rounds with comprehensive screening versus the current situation**

	ICER for the first screening year (€/QALY)	ICER for 5 screening years (€/QALY)
General adult population	5.139	5.200
ED	5.967	Not evaluated
MSM	4.292	4.302
PWID	3.504	3.524

Figure 3. — Probabilistic sensitivity analysis for one screening round.

1.826 (0,25%) individuals with chronic HCV infections would be diagnosed compared to the current situation with 340.304 individuals screened and 867 (0,25%) individuals diagnosed. In the ED populations with comprehensive screening 447.459 individuals would be screened and 878 (0,20%) infected individuals diagnosed compared to the current situation with 34.007 individuals screened and 68 (0,20%) individuals diagnosed. In the MSM population with comprehensive screening 25.973 men would be screened and 508 (1,96%) men diagnosed compared to 12.986 men screened and 254 (1,96%) men diagnosed with the current situation. Finally in the high risk PWID population, with comprehensive screening 5.473 PWIDs would be screened and 714 (13,05%) PWIDs diagnosed compared to the current situation with 3.957 screened PWIDs and 516 (13,04%) diagnosed PWIDs.

After five screening rounds the number of diagnosed individuals with comprehensive screening would be 8.310 compared to 4.231 with the current situation in the general adult population. In the MSM population 2.273 compared to 1.364 infections would be diagnosed

with comprehensive screening and in the current situation respectively. Finally in the PWID population 1.629 and 1.492 individuals would be diagnosed with comprehensive screening and in the current situation respectively.

The number of individuals diagnosed after 1 screening round and cumulatively after 5 screening rounds with comprehensive screening and with the current situation are represented in Table 2.

The incremental cost per incremental QALY of comprehensive screening: The calculated ICERs after one and after five screening rounds with comprehensive screening versus the current situation are below 10.000€/QALY in the general population and the ED attendees (one screening round) and below 5.000€/QALY in the known risk populations MSMs and PWIDs. This suggests that comprehensive screening combined with HCV treatment is a cost-effective intervention compared to the current situation in the general adult population and ED attendees as well as in the populations with known increased risk for HCV infection (Table 3).

Sensitivity analysis: In all populations, cost-effectiveness was most sensitive to HCV prevalence, awareness of HCV positive status, treatment initiation and the acceptance of initial antibody test. In all estimates, the ICER remained lower than 10.000€/QALY.

Results of the probabilistic sensitivity analysis are presented in figure 3.

At the willingness to pay threshold of 10.000€/QALY, the probability of comprehensive screening and treatment being cost effective after one and five screening rounds was 81% and 84% respectively in the general population, 80% (first round) in ED attendees, 83% and 87% respectively in MSM and 79% and 82% respectively in PWIDs.

Scenario analysis : In the scenario analysis with the general population based on the results of the recent screening study (5) and an estimated awareness of HCV positivity of 70%, the calculated ICER for one screening round was 6.105€/QALY and for five screening rounds 6.150€/QALY. The calculated number of chronic HCV infected individuals detected was 913 for 716.071 individuals screened with comprehensive screening compared to 433 individuals for 340.134 individuals screened in the current situation during the first screening round. Cumulative number of individuals detected after five screening rounds was 4.324 individuals with comprehensive screening compared to 2.200 individuals in the current situation.

For an estimated prevalence of 0.15% and an estimated awareness of HCV positivity of 70%, the ICER for the first screening year was 10.647€/QALY and for five screening years 9.758€/QALY. The calculated number of chronic HCV infected individuals detected was 274 for 717.832 individuals screened with comprehensive screening compared to 130 individuals for 340.970 individual screened in the current situation during the first screening round. Cumulative number of individuals detected after five screening rounds was 1.540 individuals with comprehensive screening compared to 779 individuals in the current situation.

In the scenario analysis with the general population with an estimated cost for DAA treatment of 30.000€, the calculated ICERs for one and for five screening rounds were 3.987€/QALY and 4.048€/per QALY respectively.

Discussion

At this moment there is no HCV screening policy implemented in Belgium. Based on the number of performed HCV antibody tests, we can estimate that every year approximately 4% of the adult general population receives an HCV antibody test (12). In MSM and PWIDs this proportion is certainly higher as individuals with known HIV infection are screened for HCV (16). Also screening is proposed by centers engaged in harm reduction programs for PWIDs. We also estimated that at least 50% of the HCV infected individuals are already aware of their HCV positive status and those individuals will not enter the screening model. We evaluated the cost-effectiveness of comprehensive screening, proposing screening to all members of the target population, followed by treatment with DAAs.

With comprehensive screening, asymptomatic chronic HCV infected individuals can be diagnosed and treated.

Model results suggest that comprehensive screening could increase the number of detected and treated individuals and that this health strategy is cost-effective in the general adult population and ED attendees (one screening round) as well as in the risk populations MSM and PWIDs.

It should be noted that only direct costs related to HCV screening and treatment were considered. Screening therefore would be proposed during a contact with a health care professional for any other reason. Additional costs to identify high risk individuals and to invite them for screening were not included. Therefore, in this analysis, cost incurred for HCV antibody negative individual accepting screening is limited.

The United States Centers for Disease Control and Prevention recommends that adults born between 1945 and 1965 should be tested once. Few data are available concerning HCV prevalence in the Belgian baby boom population. Recently results of economic models in the general population have been published. A study in the US found that universal 1-time screening of adults was cost-effective compared with either no screening or screening of the baby boom birth cohort (29). A Canadian study concluded that one time screening was likely to be cost effective in the birth cohorts from people aged 25-64 or people aged 45-64 (30). Results of a Dutch study comparing screening and treatment to no intervention were less conclusive. However this study also included costs for nationwide awareness and case finding campaigns (31). Results of HCV prevalence studies in Belgium vary widely. Therefore we performed

a scenario analysis with an estimated HCV prevalence of 0,15% and only 30% of infected individuals being unaware of their HCV infection. In this scenario with comprehensive screening 717.832 individuals would be screened to detect 274 (0,04%) undiagnosed individuals during the first screening round. The calculated ICER was 10.647€/QALY. After completion of our analysis, results of a Belgian HCV prevalence study on residual sera became available. In this study among individuals of 20 years and older, estimated prevalence of chronic HCV infection was 0,13% (32).

Results from two Belgian HCV screening studies among patients admitted in Emergency Departments including patients born between 1945 and 1965 became recently available. Both studies were performed in the Dutch speaking part of Belgium. In a Belgian university hospital 1.106 patients admitted at the ED agreed for HCV screening and a HCV antibody blood test was performed. Positive HCV antibody prevalence was 1,9%. There was no positive correlation found between a positive HCV test and age (33).

A screening study in an ED department of a large non-university Belgian hospital evaluated HCV prevalence and the risk factors associated with HCV infection. Of 2.913 contacted patients, 2.330 patients agreed for screening, 12 patients presented with chronic HCV infection. None of these patients were in follow-up in a hepatology department. Results of the multiple logistic regression model showed that age (by gender), drug use, intravenous drug use and being born in a high endemic birth country were significant risk factors for HCV infection and the study outcome suggested that screening in drug users, immigrants from high-endemic countries and individuals born between 1948 and 1967 is recommended (5).

We included the ED population as a separate population in the analysis. ED could contribute to increase screening as those departments have access to a broad range of the Belgian population. If implemented in all Belgian EDs, a high proportion of individuals could be offered screening. In the Belgian prevalence study conducted in a non-university ED department, of the 2.913 patients invited for HCV screening, 2.330 (79,7%) patients accepted the screening offer (5). Therefore, the assumed proportion of 50% of ED attendees accepting the screening offer might be a conservative estimation.

A high HCV prevalence has been observed in ED departments in studies conducted in Germany and the United States (34,35). Both studies were conducted in an urban setting and it is uncertain to what extent these findings are generalizable to other ED. Therefore, we assumed the same HCV prevalence in the ED population as in the general population in Belgium.

The Belgian number of MSM is estimated at 106.336, based on the publication of Marcus et al. which was larger than 3% of the total male population. This could be an overestimation (17).

In the PWID population, HCV antibody testing is currently proposed by centers engaged in harm reduction programs. However, there is no general policy to screen or re-test this high-risk group in Belgium. HCV RNA test are only reimbursed once. This impedes screening efforts.

Our estimate of the proportion of PWIDs currently having access to HCV antibody testing is 47% based on the proportion of PWIDs engaged in harm reduction programs as screening is often only proposed in these programs (6). We assumed that the proportion of PWIDs accepting screening can attain 65% with comprehensive screening. In a recent screening study among PWIDs, all persons visiting a London Drug Treatment Unit were invited for screening and 28% declined the screening offer (36). Expanding harm reduction services to reach more PWID will furthermore decrease the risk of new infections (6).

In the relatively small target group of 10.100 PWIDs in Belgium, it is estimated that after 5 years comprehensive screening 1.629 individuals will be detected compared to 1.492 individuals with current screening or a difference of 137 detected individual. Results of a Belgian study with an HCV transmission model to track HCV incidence and prevalence among active PWID in Belgium indicates that treatment of > 10% of HCV infected PWIDs was needed to deplete the viral pool and prevent new infections (6). Results of other economic models in the PWID population are in agreement with our results (31,36).

This study was performed at the time that for HCV infected patients with early fibrosis stages, there were some reimbursement restrictions for DAA treatment. This is no longer the case as these restrictions disappeared in January 2019 and DAA treatment is available to all HCV patients. We assume a higher proportion of identified patients that will be treated with DAAs in the first year after diagnosis with comprehensive screening (85% of identified patients) compared to the current situation (70% of identified patients). In the DSA, treatment initiation was shown to be a parameter influencing the ICER and an increase of the proportion of patients with treatment initiation during the first year after diagnosis would increase the impact of comprehensive screening.

Our analysis has some limitations. A number of assumptions had to be made such as HCV prevalence or screening and treatment uptake and model results are based on these assumptions. The model assumes that the populations are stable and does not anticipate for an evolution of the number of PWIDs over time or for the effect of immigration.

Also, the treatment model does not exactly match with the screening model. The treatment model considered patients infected with genotype 1 HCV. Although this is the most prevalent strain among individuals in the target group, the potential benefits of screening and treatment in patients with non-genotype 1 infection is an important area of future research. The treatment model simulates the natural disease progression in individuals without

additional risk factors such as HIV co-infection, drug or alcohol use. Finally, it should be noted that this analysis is a cost-effectiveness analysis and the budget impact of comprehensive screening and treatment in the different target populations is not evaluated.

Conclusion

The results of this cost-effectiveness analysis, including only direct costs for HCV screening and treatment, suggest that public health efforts to implement HCV screening in the general adult population and ED attendees is a cost-effective health policy to detect and treat HCV infected individuals. Public efforts to screen high risk populations, PWID and MSM, is also cost-effective and efforts should continue to decrease the burden of chronic HCV infection in these populations.

Conflict of interest statement:

Gilead funded the development of the used models.

Lutgart Opstaele received funding for the production of the manuscripts from Gilead.

Doctor Bielen has received travel grants for international congresses from Abbvie, MSD and Gilead Sciences.

Doctor Bourgeois was member of advisory boards for Abbvie, Gilead, MSD, BMS and Janssen.

Professor Moreno has acted as consultant for Abbvie, Gilead and MSD.

Professor Nevens has received research grants from Roche, Astellas, Sandoz, BMS, CAF, MSD, TwinPharma, Ipsen and acted as consultant for Novartis, Gilead, Abbvie, BMS, MSD, CAF, Promethera Biosciences, Durect, Ferring, Gore, Cook Medical, TwinPharma, Biotest, Ipsen, Intercept.

Professor Robaeys has received research grants from AbbVie, Gilead, Janssen Pharmaceuticals, MSD, and has acted as a consultant/advisor for AbbVie, BMS, Gilead Sciences and MSD.

Professor Van Vlierberghe has acted as consultant for Gilead.

References

1. GERKENS S., THIRY N., HULSTAERT F., ROBAYS J. KCE 276As Naar een uitbreiding van de terugbetaling van de hepatitis C-behaneling? https://kce.fgov.be/nl/publications/KCE-Reports (accessed April 10, 2017).
2. CHEN S.L., MORGAN T.R. The natural history of hepatitis C virus (HCV) infection. *Int. J. Med. Sci.,* 2006, **3**(2) : 47-52.
3. WORLD HEALTH ORGANISATION. http://www.who.int/mediacentre/factsheets/fs164/en/ (accessed April 10, 2017).
4. POLARIS OBSERVATORY. http://polarisobservatory.org/polaris/dash.htm. http://polarisobservatory.org/polaris/dash.htm (accessed April 10, 2017).
5. BIELEN R., KREMER C., KOC O.M., BUSSCHOTS D., HENDRICKX D.M., VANELDEREN P. *et al.* Screening for hepatitis C at the emergency department: Should babyboomers also be screened in Belgium? *Liver Int.,* 2018.
6. MATHEI C., BOURGEOIS S., BLACH S., BRIXKO C., MULKAY J.P., RAZAVI H. *et al.* Mitigating the burden of hepatitis C virus among people who inject drugs in Belgium. *Acta Gastroenterol. Belg.,* 2016, **79**(2) : 227-32.
7. 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.
8. HOORNENBORG E., ACHTERBERGH R.C.A., SCHIM VAN DER LOEFF M.F., DAVIDOVICH U., HOGEWONING A., DE VRIES H.J.C. *et al.* MSM starting preexposure prophylaxis are at risk of hepatitis C virus infection. *Aids,* 2017, **31**(11) : 1603-10.
9. WETENSCHAPPELIJK INSTITUUT VOLKSGEZONDHEID. IPH/EPI REPORTS N° 2006 - 035 Boek V Medische Consumptie Gezondheidsenquête België 2004.
10. ORKIN C., FLANAGAN S., WALLIS E., IRELAND G., DHAIRYAWAN R., FOX J. *et al.* Incorporating HIV/hepatitis B virus/hepatitis C virus combined testing into routine blood tests in nine UK Emergency Departments: the "Going Viral" campaign. *HIV Med.,* 2016, **17**(3) : 222-30.
11. STATBEL. Structuur van de bevolking volgens leeftijd en geslacht België 2016. http://statbel.fgov.be/nl/statistieken/cijfers/bevolking/structuur/leeftijd geslacht/belgie/ (accessed March 27, 2017).
12. GERKENS S., MARTIN N., THIRY N., HULSTAERT F. KCE 173A Hepatitis C: Screening en preventie. https://kce.fgov.be/nl/publications/KCE-Reports (accessed April 10, 2017).
13. The Hepatitis Trust. The Uncomfortable Truth. Hepatitis C in England: The State of the Nation. 2013.
14. PUBLIC HEALTH ENGLAND. Hepatitis C in the UK: 2013 report. https://www.gov.uk/government/publications/hepatitis-c-in-the-uk (accessed April 10, 2017).
15. HARRIS M., WARD E., GORE C. Finding the undiagnosed: a qualitative exploration of hepatitis C diagnosis delay in the United Kingdom. *J. Viral Hepat.,* 2016, **23**(6) : 479-86.
16. WETENSCHAPPELIJK INSTITUUT VOLKSGEZONDHEID. Epidemiologie van AIDS en HIV-infectie in België, 2015.
17. MARCUS U., HICKSON F., WEATHERBURN P., SCHMIDT A.J. Estimating the size of the MSM populations for 38 European countries by calculating the survey-surveillance discrepancies (SSD) between self-reported new HIV diagnoses from the European MSM internet survey (EMIS) and surveillance-reported HIV diagnoses among MSM in 2009. *BMC Public Health,* 2013, **13** : 919.
18. 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.
19. GUNTER J., CALLENS S., DE WIT S., GOFFARD J.C., MOUTSCHEN M., DARCIS G. *et al.* Prevalence of non-infectious comorbidities in the HIV-positive population in Belgium: a multicenter, retrospective study. *Acta Clin. Belg.,* 2018, **73**(1) : 50-3.
20. GREBELY J., PAGE K., SACKS-DAVIS R., VAN DER LOEFF M.S., RICE T.M., BRUNEAU J. *et al.* The effects of female sex, viral genotype, and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection. *Hepatology,* 2014, **59**(1) : 109-20.
21. Public Health England Hepatitis C in the UK. 2015 report. https://www.gov.uk/government/publications/hepatitis-c-in-the-uk (accessed April 10, 2017).
22. GERKENS S., THIRY N., HULSTAERT F., ROBAYS J. KCE 276 Economic evaluation of novel Direct Acting Antiviral (DAA) treatment strategies for chronic hepatitis C. https://kce.fgov.be/nl/publications/KCE-Reports (accessed April 10, 2017).
23. NEVENS F., COLLE I., MICHIELSEN P., ROBAEYS G., MORENO C., CAEKELBERGH K. *et al.* Resource use and cost of hepatitis C-related care. *Eur. J. Gastroenterol. Hepatol.,* 2012, **24**(10) : 1191-8.
24. SCHWIERZ C., THIRY N., VAN DE SANDE S., GAMIL M., NEVENS F., COLLE I. *et al.* KCE 157A Economische evaluatie van antivirale behandeling van chronische hepatitis B in België – Deel 2. 2011. https://kce.fgov.be/nl/publicaties (accessed April 10, 2017).
25. CLEEMPUT I., NEYT M., VAN DE SANDE S., THIRY N. KCE 183A Belgische richtlijnen voor economische evaluaties en budget impact analyses: tweede editie. Health Technology Assessment (HTA). https://kce.fgov.be/nl/publications/KCE-Reports (accessed April 10, 2017).
26. MCDONALD S.A., HUTCHINSON S.J., PALMATEER N.E., ALLEN E., CAMERON S.O., GOLDBERG D.J. *et al.* Decrease in health-related quality of life associated with awareness of hepatitis C virus infection among people who inject drugs in Scotland. *J. Hepatol.,* 2013, **58**(3) : 460-6.
27. SINGER M.E., YOUNOSSI Z.M. Cost effectiveness of screening for hepatitis C virus in asymptomatic, average-risk adults. *Am. J. Med.,* 2001, **111**(8) : 614-21.
28. KIND P H.G., MACRAN S. UK Population Norms for EQ-5D. In: University of York CfHE, ed. Volume Discussion Paper 172, 1999.
29. ECKMAN M.H., WARD J.W., SHERMAN K.E. Cost Effectiveness of Universal Screening for HCV Infection in the Era of Direct-Acting, Pangenotypic Treatment Regimens. *Clin. Gastroenterol. Hepatol.,* 2018.

30. WONG W.W.L., ERMAN A., FELD J.J., KRAHN M. Model-based projection of health and economic effects of screening for hepatitis C in Canada. *CMAJ Open,* 2017, **5**(3) : E662-e72.
31. HELSPER C.W., JANSSEN M.P., VAN ESSEN G.A., CROES E.A., VAN DER VEEN C., DE WIT A.G. *et al.* Effectiveness and cost-effectiveness of nationwide campaigns for awareness and case finding of hepatitis C targeted at people who inject drugs and the general population in the Netherlands. *Int. J. Drug Policy,* 2017, **47** : 117-25.
32. LITZROTH A., SUIN V., WYNDHAM-THOMAS C., QUOILIN S., MUYLDERMANS G., VANWOLLEGHEM T. *et al.* Low hepatitis C prevalence in Belgium: implications for treatment reimbursement and scale up. *BMC Public Health,* 2019, **19**(1) : 39.
33. BOTTERMAN R., GLORIEUS E., LEFERE S., VERHELST X., VAN DE VOORDE P., HACHIMI IDRISSI S. *et al.* Do or don't: HCV screening in the Belgian Baby Boom Cohort. Belgian week of Gastroenterlogogy, 2017, A10.
34. VERMEHREN J., SCHLOSSER B., DOMKE D., ELANJIMATTOM S., MULLER C., HINTEREDER G. *et al.* High prevalence of anti-HCV antibodies in two metropolitan emergency departments in Germany: a prospective screening analysis of 28,809 patients. *PLoS One,* 2012, **7**(7) : e41206.
35. LYONS M.S., KUNNATHUR V.A., ROUSTER S.D., HART K.W., SPERLING M.I., FICHTENBAUM C.J. *et al.* Prevalence of Diagnosed and Undiagnosed Hepatitis C in a Midwestern Urban Emergency Department. *Clin. Infect. Dis.,* 2016, **62**(9) : 1066-71.
36. SELVAPATT N., WARD T., HARRISON L., LOMBARDINI J., THURSZ M., MCEWAN P. *et al.* The cost impact of outreach testing and treatment for hepatitis C in an urban Drug Treatment Unit. *Liver Int.,* 2017, **37**(3) : 345-53.