

The estimated future disease burden of hepatitis C virus in the Netherlands with different treatment paradigms

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ABSTRACT

Background & Aims: Prevalence of hepatitis C virus (HCV) infection in the Netherlands is low (anti-HCV prevalence 0.22%). All-oral treatment with direct-acting antivirals (DAAs) is tolerable and effective but expensive. Our analysis projected the future HCV-related disease burden in the Netherlands by applying different treatment scenarios.

Methods: Using a modelling approach, the size of the HCV-viraemic population in the Netherlands in 2014 was estimated using available data and expert consensus. The base scenario (based on the current Dutch situation) and different treatment scenarios (with increased efficacy, treatment uptake, and diagnoses) were modelled and the future HCV disease burden was predicted for each scenario.

Results: The estimated number of individuals with viraemic HCV infection in the Netherlands in 2014 was 19,200 (prevalence 0.12%). By 2030, this number is projected to decrease by 45% in the base scenario and by 85% if the number of treated patients increases. Furthermore, the number of individuals with hepatocellular carcinoma and liver-related deaths is estimated to decrease by 19% and 27%, respectively, in the base scenario, but may both be further decreased by 68% when focusing on treatment of HCV patients with a fibrosis stage of \geq F2.

Conclusions: A substantial reduction in HCV-related disease burden is possible with increases in treatment uptake as the efficacy of current therapies is high. Further reduction of HCV-related disease burden may be achieved through increases in diagnosis and preventative measures. These results might inform the further development of effective disease management strategies in the Netherlands.

KEYWORDS

HCV disease burden, HCV epidemiology, HCV treatment, prediction model, the Netherlands

INTRODUCTION

Chronic hepatitis C virus (HCV) infection is a major cause of chronic liver disease. It causes liver fibrosis and may ultimately lead to liver cirrhosis, hepatocellular carcinoma and death.¹ It has been estimated that there are around 80 million people worldwide with chronic HCV infection.² There is a large geographical variation in prevalence of HCV infection and in many countries the epidemiology of HCV infection is not well known. At the same time, HCV-related mortality continues to increase as the infected population ages³ and the infected population advances

to late-stage liver disease.^{4,6} Recently, the World Health Organisation (WHO) recognised viral hepatitis as a global public health problem,⁷ and asked countries to develop comprehensive national viral hepatitis strategies.⁸

In the Netherlands, estimates on antibody prevalence of HCV infection vary from 0.1 to 0.6%.⁹⁻¹³ The most recent and reliable nationwide estimate was 0.22% (0.07%-0.37%) in Dutch habitants aged 15-79 years in 2009, incorporating prevalence data among different subpopulations,⁹ corresponding with about 28,000 adult individuals ever infected with HCV. Assuming a spontaneous clearance rate of 26%,¹⁴ around 20,000 of them are or have been viraemic. This corresponds to a viraemic prevalence of 0.13% in the total Dutch population. The risk groups of individuals with a known viraemic HCV infection (relatively many (ex-)drug users) are different from the groups of individuals currently at risk of a new HCV infection (strikingly almost no drug users, but mainly HIV-positive men who have sex with men). This situation is different in the Netherlands compared with many other countries where HCV transmission among people who inject drugs is ongoing. Importantly, the undiagnosed population might be substantial due to the symptom-free course in approximately 80% of cases.¹⁵ A study from the southern region of the Netherlands indicated that 66% of HCV infections are hidden to current screening practices ('hidden population').¹⁶

With the availability of new powerful peginterferon-free treatment modalities in sight, treatment of HCV will become more effective and have fewer side effects. As a result, the barriers for starting treatment are expected to be lower and more patients will be treated. Following the recommendations of the WHO, it is important to develop a strategy to diagnose the 'hidden' HCV-infected population in the Netherlands in order to be able to benefit from the treatment advances. However, reliable data on epidemiology and understanding of disease dynamics and barriers to HCV screening and treatment are needed before robust plans can be made.

The aim of this study was twofold:

- The first aim was to estimate the future disease burden for the Netherlands using available data and expert opinion for if the current treatment paradigm and cure rates were to continue.
- The second aim was to show the impact of different intervention strategies on the future disease burden. Extreme strategies were considered to illustrate the potential range of outcomes. The reality may fall within one of these strategies. The focus of this analysis was not prescriptive, stating what should be done to reduce HCV infection disease burden. Instead, the focus was descriptive, showing the impact on disease burden if certain assumptions can be met. Cost-effectiveness analyses were not considered.

This study is part of a larger project to quantify HCV epidemiology in a systematic manner in countries around the world, and for which the same prediction model has been used.^{2,6,17} In our report we focus on the situation in the Netherlands.

METHODS

Baseline population characteristics

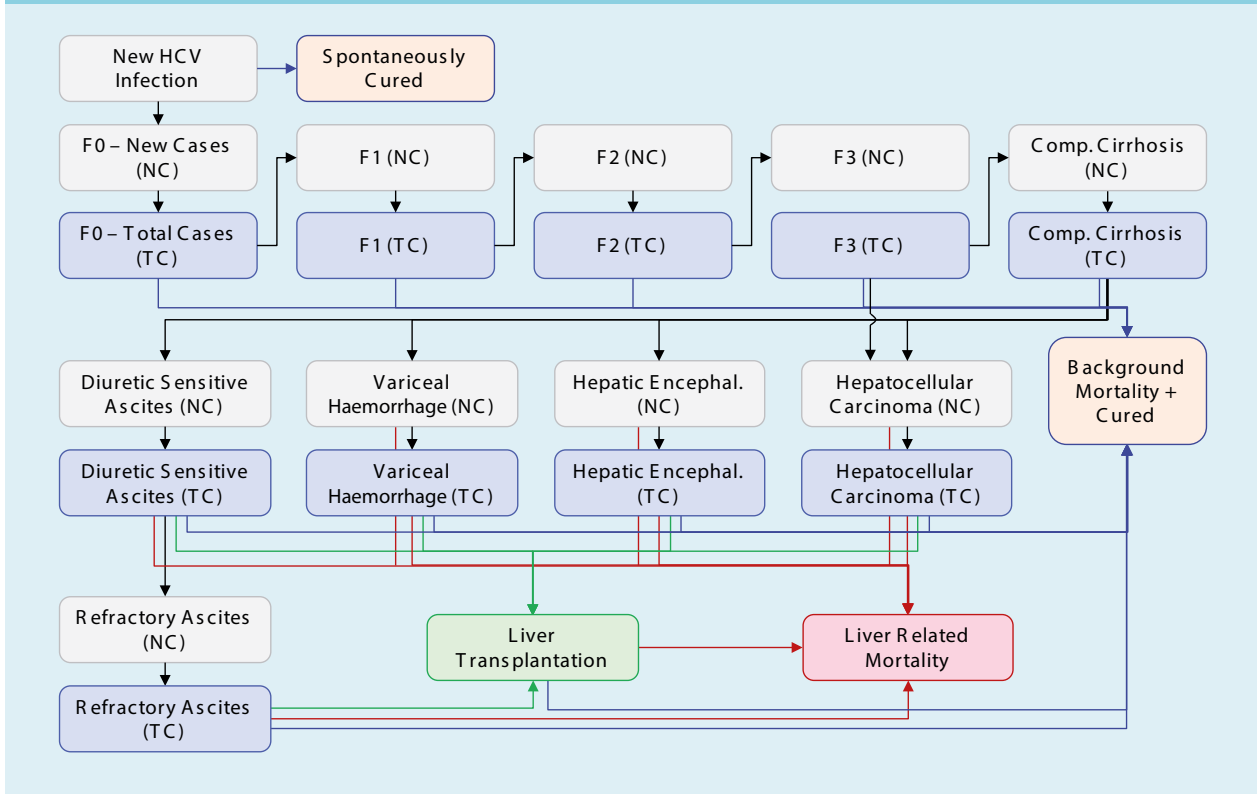
Inputs

A systematic review of the literature was conducted to identify studies reporting the total number of HCV cases diagnosed, treated and cured in the Netherlands. Indexed articles were found by searching PubMed and Embase. The review encompassed all studies between January 1990 and July 2013. Non-indexed sources were identified through Ministry of Health websites and reports from international agencies. As described in detail in an earlier published study,¹⁸ this literature search was combined with face-to-face discussions with a panel of experts (consisting of epidemiologists, hepatologists, infectious disease specialists, public health professionals and virologists) to gather epidemiological data and consensus estimates. The obtained data were used to estimate the historical number of new HCV infections per calendar year.

Model

A disease progression model was constructed in Microsoft Excel® (Microsoft Corp., Redmond, WA) to quantify the size of the HCV-infected population by liver disease stages (METAVIR score F0-F4), from 1950-2030. The model was set up for sensitivity and Monte Carlo analysis using Crystal Ball®, an Excel® add-in by Oracle®. Beta-PERT distributions were used for all uncertain inputs. The Excel® optimisation add-in, Frontline Systems' Solver, was used to calculate the number, age and gender distribution of the annual acute HCV infections which progressed to chronic HCV infection after accounting for spontaneous clearance of the virus (*figure 1*).⁶ The model was validated in countries where annual hepatocellular carcinoma incidence and liver-related deaths were reported.^{6,17} The progression of these new cases was followed along with all chronic infections from prior years. Unless specified, the scope of the model was limited to HCV-viraemic (ribonucleic acid (RNA) positive) cases. Non-HCV-viraemic cases (those patients who spontaneously cleared the virus or were treated and cured) were not considered even though they would test positive to HCV antibodies and may still progress to more advanced stages of liver disease despite viral clearance.¹⁹ In addition, re-infections following spontaneously or treatment-induced clearance were not considered as it was not possible to add this factor to the prediction model we used. The total number

Figure 1. The flow of the HCV disease progression model



of cases, at each stage of the disease, was tracked by age and gender. Five-year age cohorts were used up to age 84; those aged 85 and older were treated as one cohort. Each year, one fifth of the population in each age group, except for those 85 and older, was moved to the next age cohort to simulate ageing.

Estimation of chronic and new HCV infections

Prevalence of HCV infections

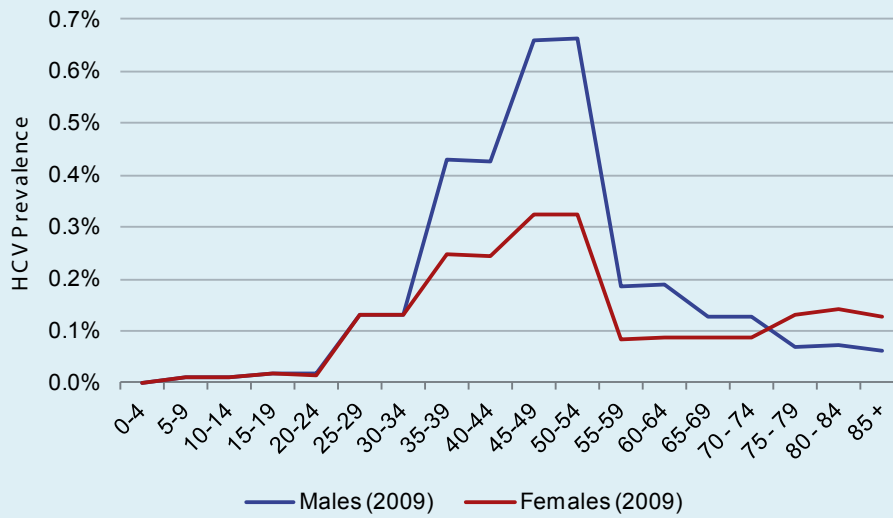
Available data were used to estimate the number of adults living with an HCV-RNA positive infection in the Netherlands. The paper we used for estimating anti-HCV-antibody prevalence was chosen because it was the most recent estimate and had the best representation of the overall population in the Netherlands.⁹ There were no reliable age and gender distributions available for the Netherlands but the median age was reported at 54 years in 2006-2007,¹⁰ slightly younger than in the United States.²⁰ In addition, United States and Dutch gender ratios were considered comparable, as well as the timing of the peak infections,^{9,20,21} so the Dutch age and gender distributions were established using the United States as an analogue (figure 2). Dutch population data were obtained by five-year age and gender cohorts from the United Nations population database, which uses the data registered at the Dutch central bureau for statistics (Statnet).²² The genotype

distribution (table 1) was established using data from an analysis of patient data collected between 2002 and 2005 from 53 hospitals in 11 of the 12 Dutch provinces.²³

Diagnosed HCV infections

The annual number of newly diagnosed HCV cases ranged from 400 to 800 according to the expert panel. This range was based on different recent and less recent reports. One of these data sources is the compulsory reporting system for new HCV infections from 1999 to 2003, in which 600 to 700 new infections were reported per year (3.9-4.1 per 100,000 inhabitants).²⁴ Another data source is the information system of Dutch microbiology laboratories reporting the number of positive HCV tests per year. Not all laboratories participate, giving an underestimation, but there are also patients tested more than once per year, which may compensate for this underestimation. From 2005 to 2010 there were 700 to 900 diagnoses per year, and from 2011 to 2014 the number declined to 380 diagnoses per year.²⁵ By 2013, it was estimated that 12,000 individuals were diagnosed (an average of 600 newly diagnosed cases per year over 20 years). In 2013, based on estimations of the expert panel in combination with data in the literature, it was estimated that 650 individuals were newly diagnosed with HCV viraemia.

Figure 2. Prevalence of viraemic HCV infections by age and gender (2009)



New HCV infections

The annual number of new cases (i.e. acute HCV infections and new chronic HCV infections due to immigration) has not remained stable since 1950. Thus, an annual relative incidence value was used to describe the change in the number of new infections over time. Relative incidence was set to 1 in 1950 and based on discussion with the expert panel, taking into account the risk factors common in the Netherlands over time (nosocomial infections before 1992, injection drug use, etc.), it was estimated that the number of new infections peaked in 1989 and gradually declined thereafter. In 2013, 62 new cases of acute HCV infection were notified to the National Institute of Public Health and the Environment (RIVM). Of these cases only two were reported to be due to injecting drug use²⁶ and an earlier study performed in 1999 to 2001 showed that 6% of all new HCV cases were attributable to injecting drug use.²⁴ In line with these findings, cohort studies show a very low incidence.²⁷ Therefore, in the model the annual number of new cases due to injecting drug use was considered low. In the Netherlands, as in many other countries, transfusion of blood products has not been considered a risk factor for new HCV infections since 1992, as donor blood screening started in 1991. A linear declining rate was applied to get the percentage of total infections attributed to transfusion to zero by 2030. The annual number of new cases due to immigration was calculated by gathering net annual immigration, by country of origin and the corresponding anti-HCV prevalence in the country of origin. Based on the immigration data the numbers increase from 1995 until 2011, and then stay constant from 2011 onwards (see notes in *table 2* for more details).² Another group with a high risk

Table 1. HCV genotype distribution in the Netherlands, 2002-2005¹⁹

Genotype	%
1a	14.8
1b	15.7
1 Other/NA	18.8
2	9.7
3	19.1
4	10.5
5	0.0
6	0.0
Other	1.1

of a new HCV infection is the group of HIV-positive men who have sex with men (MSM). Of the 362 newly reported HCV infections in 2013, 155 were among HIV-positive MSM.²⁸ The risk of re-infection is considered low among people who inject drugs²⁹ but substantial among MSM³⁰ in the Netherlands. However, in the model we used, it was not possible to consider re-infections.

The model calculated the annual number of all-cause and liver-related deaths and the cured cases as described below.

Progression rates

Disease progression by age and sex was simulated by multiplying the total number of cases at a particular stage of the disease by a progression rate to the next stage. The rates were gathered from previous studies^{5,12,31-37} or

Table 2. Model inputs and 2014 estimations

	Historical (min-max uncertainty interval)	Year (Reference)	2014 (95% uncertainty interval)
HCV-infected cases			
Number of anti-HCV cases	29,450 (9400-49,530) ¹	2009	26,010 ² (7,140-45,820)
Anti-HCV prevalence	0.2% (0.1%-0.3%) ¹		0.2% (0.0%-0.3%)
Number of viraemic cases	21,800 (6370-36,650) ¹	2009	19,200 (4740-35,480) ²
Viraemic prevalence	0.13% (0.0%-0.2%) ¹		0.12% (0.0%-0.2%)
Viraemic rate	74.0% ³		74.0%
HCV diagnosed (viraemic)			
Viraemic diagnosed	10,470 ⁴	2013	10,200
Viraemic diagnosis rate			51.1%
Annual newly diagnosed	650 ⁵	2013	650
New infections			
New infections			510 ⁶
New infection rate (per 100K)			3.0
Treated			
Number treated			880 ⁷
Annual treatment rate			4.5%
Risk factors			
Infected via injecting drug use (%)			4090 (21.3%) ⁸
Infected via blood transfusion (%)	6.0% ⁹	2000	614 (3.2%)

¹The reported prevalence of anti-HCV antibodies was 0.22% (28,100) in 15-79 year olds.⁹ Prevalence in older and younger individuals was extrapolated resulting in an overall prevalence of 0.18% or 29,450 for all ages. The viraemic rate was applied to both the viraemic prevalence as well as the number of viraemic cases. ²Model estimate after considering new infections and cured. ³Thomas et al.¹⁵ ⁴Panel expert estimate – over the last 20 years, on average 600 individuals were newly diagnosed per year, the panel estimated 650 in 2013. ⁵According to laboratory reports, 679 cases were newly diagnosed in 2011 and 500 cases in 2012. In 2013, it was estimated that 650 HCV infections were newly diagnosed (expert panel together with literature findings). ⁶New viraemic infections estimated using the following data: 6 among IDU, 354 among immigrants (used Statistics Netherlands to calculate net immigrants in 2011 (n = 35,131) with an average prevalence of 1.01%; the average prevalence included an adjustment for a lower HCV prevalence among younger immigrants), 155 among HIV+ MSM (incidence rate of 12/1000 (from Van den Berg et al.²⁷) applied to 12,880 HIV+ MSM who are HCV negative of a total of 14,000 HIV+ MSM of whom 8% is already HIV/HCV co-infected), 6 nosocomial infections (range 4-8). This adds up to a total of 521 new infections. ⁷GIPdatabank^{41,42}. ⁸EMCDDA – European Drug Report 2013.⁹ Chaves et al.²⁴

calculated using known numbers from Dutch national reports. Liver transplant data were available through the Eurotransplant Statistics Report Library and from the individual transplant centres in the Netherlands. In 2013, there were 142 liver transplants performed in the Netherlands.³⁸ Of all liver transplants 12% are attributable to HCV infection each year (a frequency of 11-13% over the past 12 years, based on personal communication with the three transplant centres in the Netherlands). The total number of cases was adjusted for ageing, all-cause mortality and proportion of cured HCV infections in any given year.

All-cause mortality

The all-cause mortality rates by age and gender were gathered from the Human Mortality Database.³⁹ Mortality rates were adjusted using standard mortality ratios among

people who inject drugs and individuals who have received blood products.⁴⁰

Treated and cured

Analysis of ribavirin units sold (for chronic or acute HCV infection) was used to estimate the total number of treated HCV patients in the Netherlands.^{41,42} In 2013, this number was 880. It was assumed that the number of treated patients stayed constant after this last reported year (2013). It was also assumed that the number of treated patients for each genotype was proportional to the genotype distribution of the HCV-infected population.

The annual number of cured patients was estimated using the average sustained viral response (SVR) rate of the different treatments in a given year (SVR rates were based on available literature).⁴³⁻⁴⁵ A separate SVR was used for the major genotypes, as shown in *figure 3*. A weighted

average of different treatment options in a given year was considered (dual therapy with peginterferon and ribavirin or triple therapy with peginterferon, ribavirin and a direct-acting antiviral (DAA)).

The number of cured patients from all genotypes was summed by stage of the disease and we assumed that the numbers were equally distributed among eligible age cohorts.

Treatment protocols and strategies

The model interface allowed for changing assumptions for the number of patients treated, the proportion of cases eligible for treatment, the reduction in treatment restrictions, the average SVR rate by genotype, the number of newly diagnosed individuals and the number of new infections at five different points in time. The year in which these changes were observed was also an input field. The different new therapies considered were: DAA + peginterferon + ribavirin, DAA + ribavirin (interferon-free) and all-oral DAA combinations with or without ribavirin. For the model, we assumed that all changes took effect immediately. The co-existence of multiple therapies was handled by modifying the average SVR.

The pool of patients who could be treated was impacted by explicit or implicit treatment protocols. According to the literature, approximately 40-60% of HCV patients are eligible for peginterferon /ribavirin.⁴³⁻⁴⁵ The definition of eligibility includes contraindications to the drugs as well as patient preference. In this analysis, 60% of the patients were considered eligible for standard-of-care treatment (figure 3), being peginterferon + ribavirin for genotype 2 to 6 and peginterferon + ribavirin + DAA for genotype 1.

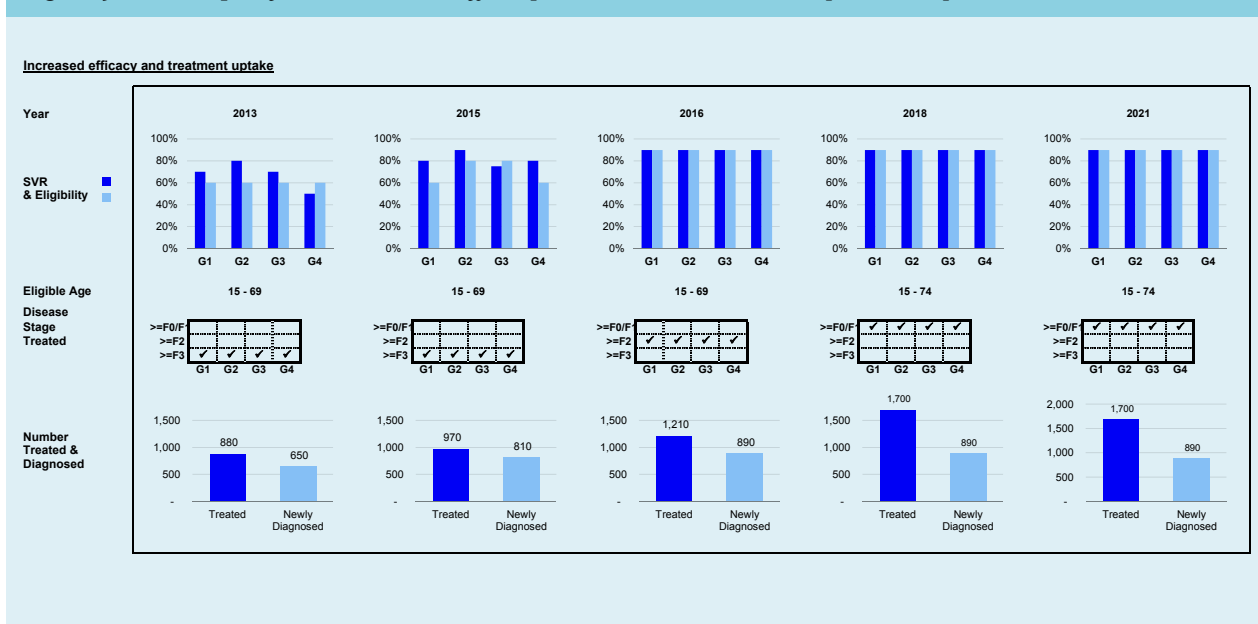
When peginterferon could be eliminated, the eligibility was increased. We assumed that the increase in eligibility would not directly increase the number of patients treated in the future. However, we assumed that it did increase the pool of diagnosed and eligible patients who could be drawn upon. Any changes in treatment were implemented using a separate input.

The future number of treated patients was capped by (I) the number already diagnosed, (II) number eligible, and (III) unrestricted cases, related to implicit (defined by physicians' practice) and/or explicit (defined by treatment guidelines) restrictions. These restrictions could be modified by changing the upper and lower end of patient age and their stage of fibrosis (F4 (Child-Pugh A, B or C), F3, F2, or F1/F0). Review of the treatment guidelines and interviews with the expert panel were used to identify both of these factors. Decompensated cirrhotic patients were considered ineligible for peginterferon-containing therapies (irrespective of genotype). The fibrosis stages eligible for treatment are shown in figure 3. When the number of treated patients was greater than those diagnosed, eligible and unrestricted, the number of newly diagnosed cases was increased or the treatment restrictions were loosened. The focus of the analysis was to highlight how many cases have to be diagnosed to achieve a treatment strategy rather than to forecast the screening capacity.

Scenarios

Multiple treatment strategies were considered and are described below: base scenario, increased efficacy only, increased efficacy and treatment uptake, screening and

Figure 3. Model inputs for the 'Increased efficacy and treatment scenario', by calendar year



elimination, and focused treatment of individuals with different fibrosis stages. Scenario inputs, including SVR, fibrosis stage and medical eligibility, divided by genotype and year, are shown in *figure 3*. The numbers of treated and diagnosed patients necessary to achieve the desired scenario outputs are also shown.

In all instances, HCV-viraemic infections represented all current HCV infections (acute and chronic HCV infections). The term viraemic was used throughout this study to highlight the presence of HCV-RNA. The term incidence was used for new HCV infections per calendar year and not newly diagnosed. Hepatocellular carcinoma referred to the total number of viraemic HCV-related hepatocellular carcinoma cases, rather than new cases. Additionally, all reductions by disease stage were assumed to occur among the viraemic HCV-infected population. The effects of non-HCV-related liver disease were not considered in this analysis.

Base scenario

The base scenario was defined as the scenario where all assumptions (the number of acute cases, treated patients, percentage of patients eligible for treatment, treatment restrictions, the number of newly diagnosed and the average SVR by genotype) remained the same as in 2013-2014. The base scenario was previously described in detail, together with other countries,^{17,46} and was assumed to be the most conservative scenario. Even more conservative scenarios are possible (e.g., stop treating HCV-infected patients completely), but those were deemed to be unlikely.

As described above, in this scenario we assumed 650 newly diagnosed HCV infections annually and treatment of 880 HCV infections annually in the Netherlands. Treatment in this scenario was focused on patients aged 15-69 years and with a METAVIR score of $\geq F_3$ assessed using FibroScan. In the light of a future high treatment rate, we considered patients with a fibrosis stage of $\geq F_2$ (according to METAVIR, measured using FibroScan) eligible for treatment in 2018, and patients with a fibrosis stage of $\geq F_0/F_1$ eligible for treatment in 2021. We assumed SVR rates of 70% for genotype (G) 1 and G3, 80% for genotype 2 (G2) and 50% for genotype 4 (G4). We used fibrosis scores obtained using FibroScans because that is the most common mode of fibrosis assessment at the moment.

Increased efficacy only

A second scenario was developed to assess the impact of improved treatment efficacy without changes in the number of treated or diagnosed patients. Treatment age and fibrosis staging eligible for treatment, as presented in the base scenario, was held constant. In 2015, it was projected that SVR could increase to 80% for G1 and G4, 90% for G2 and 75% for G3. In 2016, SVR was estimated

at 90% across all genotypes. These rates were held constant through to 2030.

Increased efficacy and treatment uptake

A third scenario was created to assess the actions necessary to eliminate chronic HCV infection by 2030. Beginning in 2015, treatment uptake was increased by 10% across all genotypes to 970 individuals and the number of diagnoses was increased by 25% to 810 individuals annually. Treatment was open to individuals aged 15 to 69 years. In 2016, treatment uptake was increased to 1210 individuals annually and diagnosis was increased to 890 individuals annually. Patients with fibrosis $\geq F_2$ were considered eligible for treatment. In 2018, treatment uptake was increased to 1700 individuals annually. Treatment was now also open for patients with fibrosis $> F_0/F_1$ and the eligible age range was increased up to 74 years. Treatment and diagnosis uptake were held constant from 2018 through to 2030. In 2021, all patients, regardless of fibrosis staging, were eligible for treatment.

Screening and elimination

A fourth scenario was created to assess the response of increased treatment and the corresponding required increase in screening (and diagnoses) to keep up with treatment. In addition, it was assumed that preventive measures will be taken to reduce the number of new infections by 40% over six years.

Focused treatment: $\geq F_3$, $\geq F_2$, $\geq F_0/F_1$

A fifth, sixth and seventh scenario were created to assess the impact of focused treatment of individuals with fibrosis $\geq F_3$, $\geq F_2$ and $\geq F_0/F_1$. Starting in 2015 treatment uptake was increased by 10% across all genotypes to 970 individuals and the number of diagnoses was increased by 25% to 810 individuals. In 2016, the treatment uptake increased by 25% to 1210 individuals and the diagnosis rate increased 10% to 890 individuals annually. By 2018, the eligible age range was increased to 74 years while treatment was increased by 40% to 700 individuals, as in this year treatment exceeded eligible individuals. For the $\geq F_2$ and $\geq F_0/F_1$ scenarios treatment uptake was increased by 40% to 1700 individuals. In 2021, the number of diagnoses was kept constant at 890 individuals. For the $\geq F_3$ scenario 400 individuals were treated annually. For the $\geq F_2$ scenario 530 individuals were treated as the treatment outpaced eligibility in 2020. For the $\geq F_0/F_1$ scenario 1700 individuals were treated annually.

Birth cohort effect

The age distribution was determined as described above.^{10,17} The disease progression model was used to age the HCV-infected population after taking into account mortality and SVR.²⁴ For this analysis, the median age

in each five-year age cohort was selected and converted to a birth year. A range of birth years were selected which accounted for approximately 75% (or more) of the total HCV-infected population using the 2014 HCV population distribution.⁴ The number of people that need to be screened to identify one viraemic case was calculated by taking the inverse of the viraemic HCV prevalence. The number needed to screen to identify one new case was calculated as follows:

$$\frac{1}{(\text{HCV viraemic prevalence} * (1 - \% \text{ of HCV population already diagnosed}))}$$

RESULTS

The results of the literature review and expert opinion, including estimates of HCV antibody and HCV viraemia prevalence, diagnosis, as well as annual treatment and liver transplants are summarised in *table 2*.

Base scenario

Using historical data,⁹ it was estimated that there were around 19,200 individuals in the Netherlands with a viraemic HCV infection in 2014. This was forecasted

to decrease to 10,599 (45%) in 2030. The number of HCV-related hepatocellular carcinoma cases in 2014 was estimated at 110, and it was forecasted to decrease by 19% by 2030. The number of liver-related deaths in chronic HCV patients was forecasted to decrease 27% from a base of 102. *Figure 2* shows the age and gender distribution of the HCV-infected population in 2009 while *figure 4* shows the projected age distribution in 2014. *Figure 5* shows the number of viraemic HCV infections over time in the Netherlands from 1950 to 2030 and *figure 6* shows the projected HCV disease burden for this period.

Other scenarios

The results of the analyses for HCV morbidity and mortality, by scenario, are summarised in *figure 7* and the percent change from the base scenario can be found in *figure 8*. *Table 3* compares the change in HCV disease burden in 2014-2030 by scenario.

Increased efficacy only

There will be 2413 fewer HCV-viraemic individuals in 2030, a 23% reduction as compared with the base scenario. The number of HCV-related hepatocellular carcinoma cases and the number of liver-related deaths both decrease by 25% from the base scenario. This scenario would result in 463 cirrhosis cases being averted.

Figure 4. Distribution of HCV-infected population by birth year cohort 2014

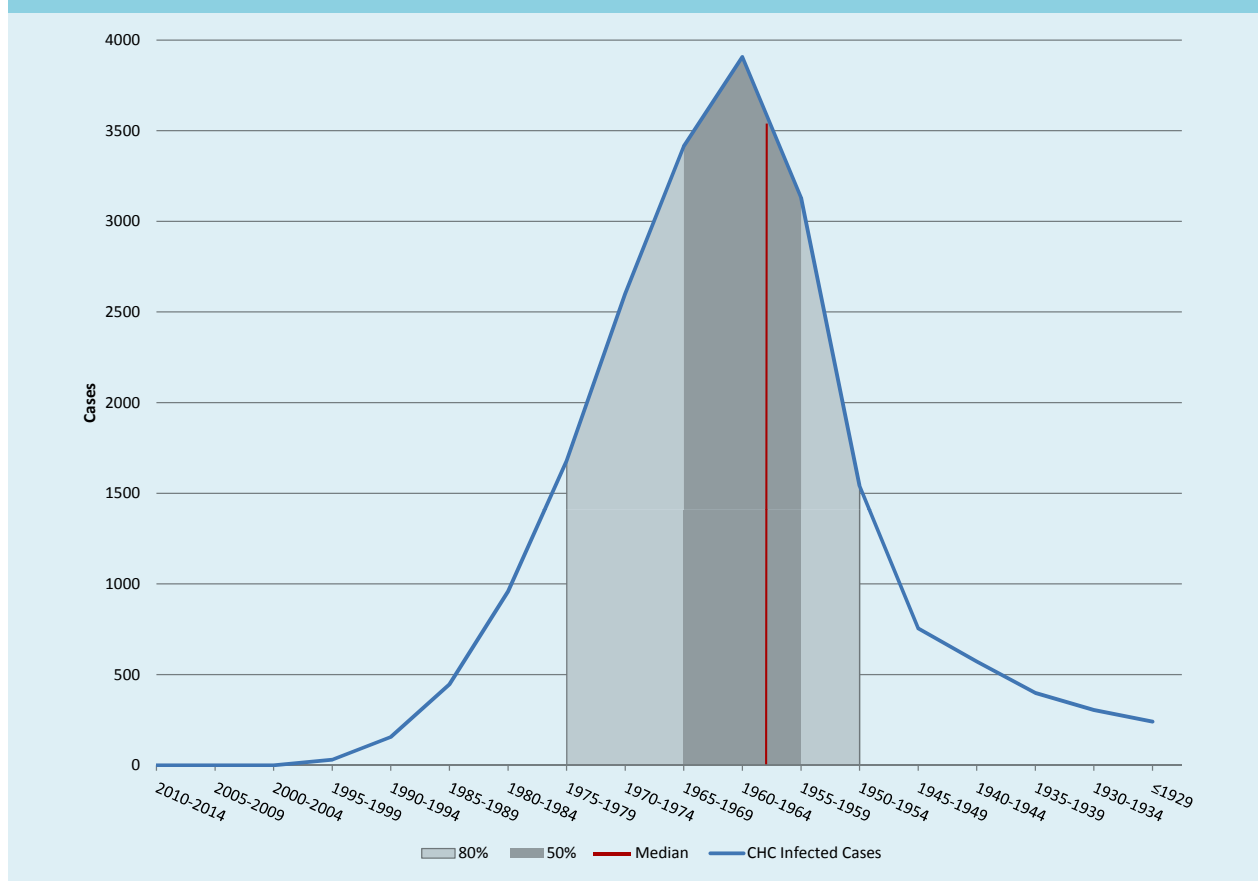


Figure 5. The number of viraemic HCV infections over time, the Netherlands 1950-2030 (base scenario)

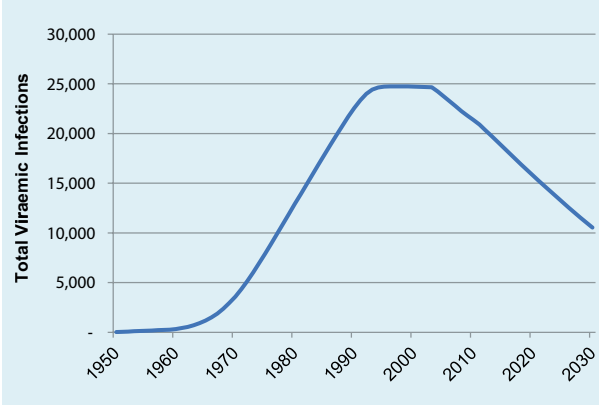
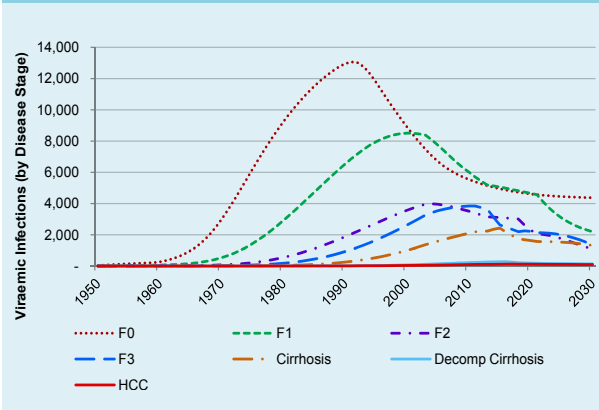


Figure 6. HCV disease burden over time, the Netherlands 1950-2030 (base scenario)



Increased efficacy and treatment uptake

With an aggressive treatment and diagnosis strategy, there will be 9043 fewer HCV-viraemic individuals in 2030, an 85% reduction as compared with the base scenario. The number of HCV-related hepatocellular carcinoma cases and the number of liver-related deaths in 2030 decrease by 67% and 65%, respectively, from the base scenario. This scenario would result in 964 cirrhotic cases being averted.

Screening and elimination

With a screening and elimination strategy, there will be 9334 fewer HCV-viraemic individuals in 2030, an 88% reduction as compared with the base scenario. The number of HCV-related hepatocellular carcinoma cases and the number of liver-related deaths in 2030 decrease by 68%

Figure 7. HCV characteristics, by scenario, the Netherlands 2013-2030

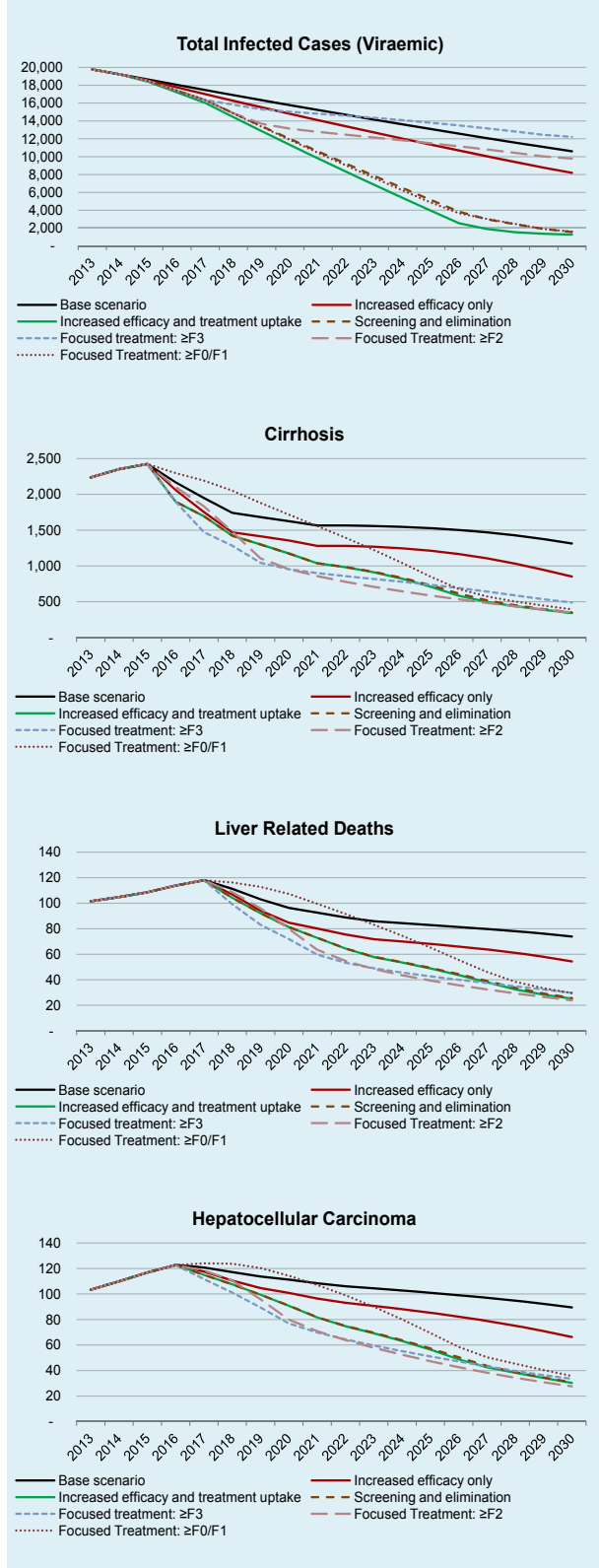
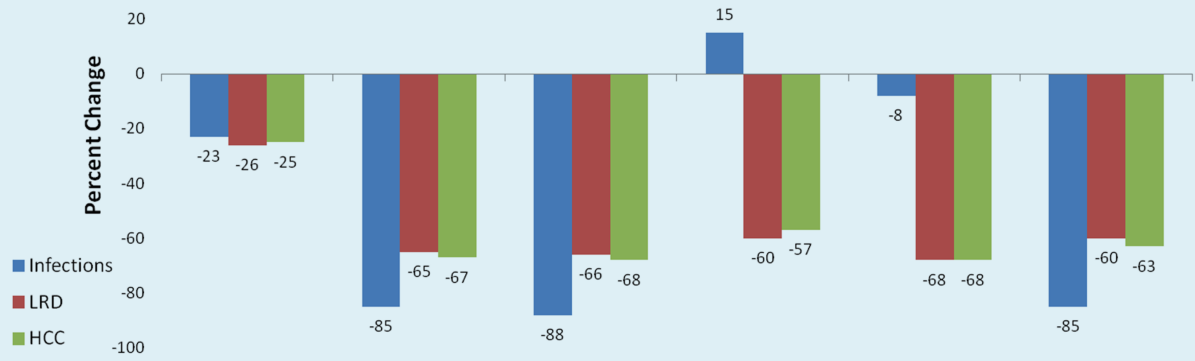


Figure 8. Percent change from the base scenario to 2030 with treatment by scenario

Scenario	Increased efficacy only	Increased efficacy and treatment uptake	Screening and elimination	Focused treatment: $\geq F_3$	Focused treatment: $\geq F_2$	Focused treatment: $\geq F_0/F_1$
Maximum Treated	880	1700	1700	1210	1700	1700
Max Year	-	2018-2027	2018-2026	2016-2017	2018-2019	2018-2026
2030 Treated	880	410	270	370	390	420



HCC =hepatocellular carcinoma; LRD = liver-related death.

Table 3. Predicted number of viraemic HCV infections, cases with hepatocellular carcinoma and liver-related deaths according to scenario from 2014 to 2030

Scenario	HCV infections N	HCC N	LRD N
2014 (base)	19,200	110	102
Base scenario N (% decrease*)	10,599 (45)	89 (19)	74 (27)
Increased efficacy only N (% decrease*) Compared with base scenario	8187 (57) - 23%	66 (40) - 25%	54 (47) - 25%
Increased efficacy and treatment uptake N (% decrease*) Compared with base scenario	1556 (92) - 85%	30 (73) - 67%	25 (75) - 65%
Screening and elimination N (% decrease*) Compared with base scenario	1265 (93) - 88%	31 (72) - 68%	26 (75) - 66%
Focused treatment: $\geq F_3$ N (% decrease*) Compared with base scenario	12,210 (36) +15%	33 (79) - 57%	30 (71) - 60%
Focused treatment: $\geq F_2$ N (% decrease*) Compared with base scenario	9788 (49) - 8%	28 (75) - 68%	24 (76) - 68%
Focused treatment: $\geq F_0/F_1$ N (% decrease*) Compared with base scenario	1600 (92) - 85%	36 (76) - 63%	30 (71) - 60%

*Decrease compared with base (from 2014 to 2030). HCC = hepatocellular carcinoma; LRD = liver-related deaths.

and 66% respectively from the base scenario. This scenario would result in 972 cirrhotic cases being averted.

Focused treatment: $\geq F_3$

There will be 1610 more HCV-viraemic individuals in 2030, a 15% increase as compared with the base scenario. The number of HCV-related hepatocellular carcinoma cases and the number of liver-related deaths

in 2030 decrease by 57% and 60%, respectively, from the base scenario. This scenario would result in 825 cirrhotic cases being averted.

Focused treatment: $\geq F_2$

There will be 811 fewer HCV-viraemic individuals in 2030, an 8% reduction as compared with the base scenario. The number of HCV-related hepatocellular carcinoma

Table 4. HCV viraemic prevalence according to screening by birth cohort

	General	1955-1969	1950-1979	1960-1964
HCV prevalence	0.12%	0.28%	0.23%	0.31%
Tests required to identify 1 viraemic case	833	354	430	322
Tests required to identify 1 new case	1706	725	880	659

cases and the number of liver-related deaths in 2030 both decrease by 68% from the base scenario. This scenario would result in 965 cirrhotic cases being averted.

Focused treatment: $\geq F_0/F_1$

There will be 8999 fewer HCV-viraemic individuals in 2030, an 85% reduction as compared with the base scenario. The number of HCV-related hepatocellular carcinoma cases and the number of liver-related deaths in 2030 decrease by 63% and 60% respectively from the base scenario. This scenario would result in 921 cirrhotic cases being averted.

Birth cohort

The median age of the viraemic HCV-infected population in 2014 was 51 years (birth year 1963). More than 50% of the viraemic HCV-infected population was born between 1955 and 1969; over 80% were born between 1950 and 1979 (*figure 4*). The highest prevalence of HCV viraemia is in the population born between 1960 and 1964 (0.31%). By focusing screening on this birth cohort it is estimated that one case can be newly diagnosed for every 659 screened (after taking into consideration those already diagnosed), if participation rates are equal among HCV-infected and uninfected individuals within this age cohort (*table 4*). It was assumed that 51% of the total HCV-viraemic population have been diagnosed for all age groups.

Sensitivity analysis

A sensitivity analysis was conducted to assess the effect of variations in different input and outcome parameters (new infections 2014, treatment 2014, fibrosis stage, progression to hepatocellular carcinoma and/or liver-related death) on the key driver of uncertainty in HCV prevalence (range 0.05-0.27%).⁹ Since the model is based on the incidence of HCV, the number of new HCV infections required to match the reported prevalence was calculated in the model. The top driver reflecting the uncertainty in HCV prevalence is new HCV infections. This has a direct impact on the forecasted population by disease stage, mortality and disease progression. The impact of all other assumptions was small.

DISCUSSION

Under the current treatment structure, the base scenario, the prevalence of viraemic HCV infection is projected to decrease by 45% over the next 15 years. This sharp decline is likely attributed to successful treatment of HCV infection and lower mortality among the ageing population, in combination with low incidence of new HCV infections. Although transmission of HCV in the Netherlands is low, HCV-related mortality and occurrence of hepatocellular carcinoma is substantial. Treatment of HCV infection in an early stage might prevent the occurrence of HCV-related mortality and hepatocellular carcinoma.

Of all scenarios, the 'screening and elimination' scenario predicts the largest reduction of 88% in viraemic HCV infection prevalence in the Netherlands. This scenario is probably not the most feasible scenario as it requires screening and prevention programs to achieve the inputs required. A more realistic scenario would be the 'increased efficacy and treatment uptake' scenario, in which a phased increase of treatment uptake is calculated based upon genotype and fibrosis stage. This scenario predicts only a slightly smaller reduction in viraemic HCV infection prevalence compared with the base scenario of 85%.

If we focus on liver-related deaths and hepatocellular carcinoma, the ' $\geq F_2$ only model' provides the greatest decrease from the base scenario (both liver-related deaths and hepatocellular carcinoma 68%). However, the decrease in this model is only slightly greater than the decrease predicted by the 'screening and elimination model', the 'increased efficacy and treatment uptake model' and the '> F_0/F_1 model' (68% for the ' $\geq F_2$ only model' versus 60 to 67% for the other three models). Besides this, the ' F_2 only model' predicts only a slight reduction in viraemic HCV infection prevalence (8%) whereas the other three models predict a reduction of 85 to 88% compared with the base scenario.

Taken together, it seems that the 'increased efficacy and treatment uptake' scenario is the most feasible scenario in the current Dutch situation, which also predicts substantial reductions in viraemic HCV infection prevalence, hepatocellular carcinoma and liver-related

deaths. However, due to the current high costs of treatment with DAAs it is very unlikely that this scenario will be adopted in the near future. Lower prices of DAAs are necessary to make this scenario, in which a substantial decrease of prevalent HCV infections can be achieved, more realistic.

Most of the described models require an increase in treatment uptake to 1700 individuals annually and allowing treatment access to individuals regardless of fibrosis stage. Over the last years there have been about 1000 (range: 880-1130) treatments with peginterferon and ribavirin (with or without DAAs) annually.^{41,42} Assuming that this number is representative of the number of treatments for HCV, an increase from 1000 to 1700 treatments annually may be feasible with the current capacity in the Netherlands as new therapies have a shorter duration and less side effects. Next to this, it should be noted that the increase in treatment uptake per year is only required for the first eight years. After this initial investment, the yearly treatment drops significantly to 270 patients treated yearly by 2030.

Increases in SVR have the potential to result in favourable improvements in end-stage liver disease, with maybe few changes in the ultimate treatment rates. With the new treatment regimens with low side effects, treatment uptake is likely to increase, and with the high SVR rates, the need for retreatment will be low. It is known that curing HCV infection in liver cirrhosis patients reduces complications of cirrhosis and risk of hepatocellular carcinoma.⁴⁷ However, although reduced, these patients are still at risk of decompensation of liver cirrhosis and/or hepatocellular carcinoma. They are therefore advised to remain in long-term clinical care for monitoring progression of liver disease and/or development of hepatocellular carcinoma. In the current model these patients were not considered as a continued burden of HCV infection after SVR. From this point of view, it might be worthwhile to treat patients before the stage of cirrhosis, as the risk of hepatocellular carcinoma following SVR among patients with Fo-I-2-3 is negligible.⁴⁸ This higher treatment rate (with high SVR rates) for patients with a lower fibrosis stage may have favourable improvements in end-stage liver disease with no changes in the eventual treatment rates and could prevent ongoing transmission.^{47,49} This might save future costs for follow-up of chronic liver disease (cirrhosis) and long-term hepatocellular carcinoma monitoring. Next to this, achievement of SVR after treatment of chronic HCV reduces non-liver related mortality and hepatic and extra-hepatic manifestations of HCV infection, and improves quality of life. These are all factors in reducing healthcare costs related to HCV infection.⁵⁰

Achievement of our described strategy to treat more HCV patients is dependent upon the detection of people with

HCV infection, thus reinforcing the need for increased awareness and intensified screening among risk groups and professionals.

One might consider a risk-group approach. Alternatively, focusing on a birth cohort of 1960-to 1964 without prior assessment of HCV risk might be effective as our model suggests that one newly diagnosed viraemic case may be found per 659 tests, compared with 1 out of 1706 for the general population. This approach was chosen in the USA and was described in 2012.⁵¹ However, the effectiveness and cost-effectiveness of a birth cohort screening strategy or a modified birth cohort screening strategy in which additional risk-based screening criteria are used, need to be determined. Also, it is difficult to suggest specific recommendations on birth cohort screening as the age and gender distribution of the viraemic HCV-infected population in the Netherlands is not well known.

For first-generation migrants born in countries where HCV infection is endemic, and other difficult-to-reach risk groups for HCV, various pilot screening projects have been performed in recent years, using different screening strategies.⁵²⁻⁵⁷ However, the costs and effectiveness of these strategies relative to each other has not been studied yet, hampering efficient targeting of screening programs. Moreover, there is no structural screening program for migrant groups in place and combining HCV screening with screening for other infections might be considered. We suggest that cost-effectiveness analyses of screening strategies targeted at first-generation migrants should be performed and awareness among risk groups as well as healthcare professionals should be increased. Increasing knowledge of HCV infection among healthcare professionals and the general population may also lower the barriers of testing and referring.⁵⁸

Besides migrants, two other groups require attention. The first group consists of people who have already been diagnosed with a viraemic infection in the past (e.g. HCV-infected blood donors) but have been lost to follow-up in clinical care. The feasibility to retrieve these individuals should be investigated. The second group is more difficult to find because it is hidden in society: individuals that have injected drugs in the past, acquired a tattoo in an endemic region, or received a blood transfusion before 1992. For this group, again, awareness should be increased for both the individuals themselves and the healthcare professionals, in particular general practitioners and public health workers. Innovative approaches such as internet-mediated blood screening services⁵⁸ might be considered. There are some factors that limit the value of the described outcomes of the prediction models. First, many parameters that were used as input are based on assumptions or data of less recent years. These data include the current and future number of diagnosed and treated viraemic HCV

infections, and the distribution of genotype, fibrosis stage, age and gender of treated and untreated patients. Retrieving actual figures on the different parameters in the Netherlands is very difficult, as there is no national registry of HCV patients in place. The sensitivity analysis that was conducted with the key driver of uncertainty in HCV prevalence was in turn driven by uncertainty in the number of new HCV infections. The impact of all other assumptions was small. Second, parameters were not specified per risk group. These groups, however, have different characteristics, including the proportion diagnosed, genotypes, treatment rates and treatment outcome, influencing the outcome of the models. Third, factors such as sex differences and HIV infection, and their impact on clearance and HCV disease progression, have not been taken into account. Fourth, in this analysis it was assumed that the number of new infections and re-infections remained constant in all scenarios described. While disease progression models can predict disease burden, they are less accurate for estimating future prevalence as they do not explicitly model HCV transmission nor include the possibility of re-infection following successful therapy.³⁹ Finally, FibroScan was used for assessing the fibrosis score as a selection criterion for treatment and defining the different groups for the models. This might not be the most accurate method as FibroScan scores are only reliable in low (F0) and high (F4) ranges, but are not between METAVIR scores F1 to F3. Also, FibroScan does not differentiate between METAVIR scores F2 and F3. Fibrosis staging in this range should be done using a liver biopsy. These limitations may lead to incorrect inputs and estimations, leading in turn to incorrect predictions. Over time, the input of the models may have to be adjusted and updated, and linked with transmission models to achieve correct predictions. In conclusion, the largest decrease in viraemic HCV infections in the Netherlands may be achieved by applying the ‘elimination’ strategy. Preventing progression of HCV-related liver disease leading to HCV-related death and hepatocellular carcinoma is best achieved when using the ‘≥ F2 fibrosis’ strategy. The most realistic scenario with reasonable reductions in HCV prevalence, HCV-related death and hepatocellular carcinoma would be the ‘increased efficacy and treatment uptake’ strategy with a phased increase of treatment uptake. To be able to achieve these future goals, diagnosis of people with HCV infections in the Netherlands who may benefit from treatment should be increased. Prevalence data and knowledge regarding facilitating and impeding factors for HCV screening are needed for the largest risk groups separately (including the different migrant groups). Awareness among risk groups and professionals as well as the general population should be increased whereas

barriers on different levels (practical, psychological) should be lowered.

A coordinated national strategy and sufficient financial means to support it are needed to achieve these goals. The presented models on the future disease burden might inform our national strategy.

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REFERENCES

- Saito I, Miyamura T, Ohbayashi A, et al. Hepatitis C virus infection is associated with the development of hepatocellular carcinoma. *Proc Natl Acad Sci USA*. 1990;87:6547-9.
- Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. *J Hepatol*. 2014;61:S45-57.
- Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2095-128.
- Wedemeyer H, Duberg AS, Buti M, et al. Strategies to manage hepatitis C virus (HCV) disease burden. *J Viral Hepat*. 2014;21 Suppl 1:60-89.
- Deuffic-Burban S, Deltenre P, Buti M, et al. Predicted effects of treatment for HCV infection vary among European countries. *Gastroenterology*. 2012;143:974-85.
- Razavi H, Waked I, Sarrazin C, et al. The present and future disease burden of hepatitis C virus (HCV) infection with today's treatment paradigm. *J Viral Hepat*. 2014;21 Suppl 1:34-59.
- World Health Organization. Global policy report on the prevention and control of viral hepatitis. Jan 2013. Available from URL: http://apps.who.int/iris/bitstream/10665/85397/1/9789241564632_eng.pdf.
- World Health Organization. World health assembly adopts resolution on hepatitis. May 24, 2014. Available from URL: http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R6-eng.pdf.
- Vriend HJ, Van Veen MG, Prins M, Urbanus AT, Boot HJ, Op de Coul EL. Hepatitis C virus prevalence in The Netherlands: migrants account for most infections. *Epidemiol Infect*. 2013;141:1310-7.
- Vriend HJ, Op de Coul EL, van de Laar TJ, Urbanus AT, van der Klis FR, Boot HJ. Hepatitis C virus seroprevalence in The Netherlands. *Eur J Public Health*. 2012;22:819-21.
- Slavenburg S, Verduyn-Lunel FM, Hermsen JT, Melchers WJ, te Morsche RH, Drenth JP. Prevalence of hepatitis C in the general population in the Netherlands. *Neth J Med*. 2008;66:13-7.
- Veldhuijzen IK, Conyn-van Spaendonck MAE, Dorigo-Zetsma JW. Seroprevalentie van hepatitis B en C in de Nederlandse bevolking. *Infectieziekten Bull*. 1999;10:182-4.
- Baaten GG, Sonder GJ, Dukers NH, Coutinho RA, Van den Hoek JA. Population-based study on the seroprevalence of hepatitis A, B, and C virus infection in Amsterdam, 2004. *J Med Virol*. 2007;79:1802-10.
- Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. *J Viral Hepat*. 2006;13:34-41.
- Thomas DL, Seeff LB. Natural history of hepatitis C. *Clin Liver Dis*. 2005;9:383-98.
- Vermeiren AP, Dukers-Muijers NH, Van Loo IH, et al. Identification of hidden key hepatitis C populations: an evaluation of screening practices using mixed epidemiological methods. *PLoS One*. 2012;7:e51194.
- Hatzakis A, Chulanov VP, Gadano AC. The present and future disease burden of hepatitis C virus (HCV) with today's treatment paradigm – volume 2. *J Viral Hepat*. 2015;22 Suppl 1:26-45.
- Saraswat V, Norris S, de Knecht RJ, et al. Historical epidemiology of hepatitis C virus (HCV) in select countries – volume 2. *J Viral Hepat*. 2015;22 Suppl 1:6-25.
- Aleman S, Rahbin N, Weiland O, et al. A risk for hepatocellular carcinoma persists long-term after sustained virologic response in patients with hepatitis C-associated liver cirrhosis. *Clin Infect Dis*. 2013;57:230-6.
- Denniston MM, Jiles RB, Drobeniuc J, et al. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. *Ann Intern Med*. 2014;160:293-30.
- Armstrong GL, Alter MJ, McQuillan GM, Margolis HS. The past incidence of hepatitis C virus infection: implications for the future burden of chronic liver disease in the United States. *Hepatology*. 2000;31:777-82.
- United Nations. World population prospects: The 2010 revision – Population database. 2011; Available from URL: <https://esa.un.org/unpd/wpp/index.htm>.
- De Vries MJ, Te Rijdt B, Van Nieuwkerk CM. Genotype distribution amongst hepatitis C patients in The Netherlands. *Neth J Med*. 2006;64:109-13.
- Chaves S, Widdowson MA, Bosman A. Surveillance of HCV infection in the Netherlands. *Euro Surveill*. 2003;8:108-13.
- Virologische Weekstaten 2005-2010 and 2011-2015. http://www.rivm.nl/Onderwerpen/V/Virologische_weekstaten
- Van Aar F, Koedijk FDH, Van den Broek IVF, et al. Seksuele overdraagbare aandoeningen, waaronder HIV, in Nederland in 2013. *Infectieziekten Bulletin*. 2013; October.
- Van den Berg CH, Smit C, Bakker M, et al. Major decline of hepatitis C virus incidence rate over two decades in a cohort of drug users. *Eur J Epidemiol*. 2007;22:183-93.
- Vanhommerig JW, Stolte IG, Lambers FA, et al. Stabilizing incidence of hepatitis C infection among men who have sex with men in Amsterdam. *J Acquir Immune Defic Syndr*. 2014;66:e111-5.
- Grady BP, Vanhommerig JW, Schinkel J, et al. Low incidence of reinfection with the hepatitis C virus following treatment in active drug users in Amsterdam. *Eur J Gastroenterol Hepatol*. 2012;24:1302-7.
- Lambers FA, Prins M, Thomas X, et al.; MOSAIC (MSM Observational Study of Acute Infection with hepatitis C) study group. Alarming incidence of hepatitis C virus re-infection after treatment of sexually acquired acute hepatitis C virus infection in HIV-infected MSM. *AIDS*. 2011;25:F21-7.
- Razavi H, Elkhoury AC, Elbasha E, et al. Chronic hepatitis C virus (HCV) disease burden and cost in the United States. *Hepatology*. 2013;57:2164-70.
- Alter MJ, Margolis HS, Krawczynski K, et al. The natural history of community-acquired hepatitis C in the United States. The Sentinel Counties Chronic non-A, non-B Hepatitis Study Team. *N Engl J Med*. 1992;327:1899-905.
- Villano SA, Vlahov D, Nelson KE, Cohn S, Thomas DL. Persistence of viremia and the importance of long-term follow-up after acute hepatitis C infection. *Hepatology*. 1999;29:908-14.
- Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: A meta-analysis and meta-regression. *Hepatology*. 2008;48:418-31.
- Bennett WC, Inoue Y, Beck JR, Wong JB, Pauker SG, Davis GL. Estimates of the cost-effectiveness of a single course of interferon-alpha 2b in patients with histologically mild chronic hepatitis C. *Ann Intern Med*. 1997;127:855-65.
- Bernfort L, Sennfalt K, Reichard O. Cost-effectiveness of peginterferon alfa-2b in combination with ribavirin as initial treatment for chronic hepatitis C in Sweden. *Scand J Infect Dis*. 2006;38:497-505.
- 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;30:1318-24.
- Eurotransplant. Eurotransplant Statistics - 2013. Jan 8, 2014. Available from: URL: www.eurotransplant.org/cms/mediaobject.php?file=year_20131.pdf.
- Human Mortality Database. University of California, Berkeley, Max Planck Institute for Demographic Research. Jun 14, 2013. Available from: URL: www.mortality.org.
- Kershenobich D, Razavi HA, Cooper CL, et al. Applying a system approach to forecast the total hepatitis C virus-infected population size: Model validation using US data. *Liver Int*. 2011;31 Suppl 2:4-17.
- GIPdatabank. Aantal gebruikers 2009-2013 voor ATC-subgroep J05AB04: Ribavirine. Mar 7 2014; Available from: URL: www.gipdatabank.nl/databank.asp.
- GIPdatabank. Aantal gebruikers 2008-2012 voor ATC-subgroep J05AB04: Ribavirine. Nov 27 2013; Available from: URL: www.gipdatabank.nl/databank.asp.
- Evon DM, Verma A, Dougherty KA, et al. High deferral rates and poorer treatment outcomes for HCV patients with psychiatric and substance use comorbidities. *Dig Dis Sci*. 2007;52:3251-8.
- Morrill JA, Shrestha M, Grant RW. Barriers to the treatment of hepatitis C. Patient, provider, and system factors. *J Gen Intern Med*. 2005;20:754-8.
- North CS, Hong BA, Adewuyi SA, et al. Hepatitis C treatment and SVR: the gap between clinical trials and real-world treatment aspirations. *Gen Hosp Psychiatry*. 2013;35:122-8.

46. Gane E, Keršenobich D, Sequin-Devaux M, et al. Strategies to manage hepatitis C virus (HCV) infection disease burden – volume 2. *J Viral Hepat.* 2015;22 Suppl 1:47-73.
47. Van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA.* 2012;308:2584-93.
48. Martin NK, Foster GR, Vilar J, et al. HCV treatment rates and sustained viral response among people who inject drugs in seven UK sites: real world results and modelling of treatment impact. *J Viral Hepat.* 2014; Epub ahead of print.
49. De Vos AS, Prins M, Kretzschmar ME. Hepatitis C virus treatment as prevention among injecting drug users: who should we cure first? *Addiction* 2015; Epub ahead of print.
50. Lee MH, Yang HI, Lu SN, et al; R.E.V.E.A.L.-HCV Study Group. Chronic hepatitis C virus infection increases mortality from hepatic and extrahepatic diseases: a community-based long-term prospective study. *J Infect Dis.* 2012;206:469-77.
51. Smith BD, Morgan RL, Beckett GA, et al; Centers for Disease Control and Prevention. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. *MMWR Recomm Rep.* 2012;61:1-32. Erratum in: *MMWR Recomm Rep.* 2012;61:886.
52. Zuure FR, Bouman J, Martens M, et al. Screening for hepatitis B and C in first-generation Egyptian migrants living in the Netherlands. *Liver Int.* 2013;33:727-738.
53. Richter C, Beest GT, Sancak I, et al. Hepatitis B prevalence in the Turkish population of Arnhem: implications for national screening policy? *Epidemiol Infect.* 2012;140:724-730.
54. Richter C, Ter Beest G, Gisolf EH, et al. Screening for chronic hepatitis B and C in migrants from Afghanistan, Iran, Iraq, the former Soviet Republics, and Vietnam in the Arnhem region, The Netherlands. *Epidemiol Infect.* 2014;142:2140-6.
55. Zuure FR, Davidovich U, Coutinho RA, et al. Using mass media and the Internet as tools to diagnose hepatitis C infections in the general population. *Am J Prev Med.* 2011;40:345-52.
56. Helsper CW, Van Essen GA, Bonten MJ, De Wit NJ. A support programme for primary care leads to substantial improvements in the effectiveness of a public hepatitis C campaign. *Family Pract.* 2010;27:328-32.
57. Grintjes K, Dofferhoff ASM, Stelma F, et al. Hepatitis C detection among migrants in Nijmegen, The Netherlands. *Tijdschr Infect.* 2014;9:126-33.
58. Zuure FR, Heijman T, Urbanus AT, Prins M, Kok G, Davidovich U. Reasons for compliance or noncompliance with advice to test for hepatitis C via an internet-mediated blood screening service: a qualitative study. *BMC Public Health.* 2011;11:293.
59. Hickman M, Martin N, Vickerman P, Hutchison S. Strategies to reduce HCV disease burden and HCV transmission need different models, as what works for end-stage liver disease may not work for HCV prevalence: a comment on the results presented in *JVH Special Issue.* *J Viral Hepat.* 2014;21:e167-8.