Clinical studies on hepatitis B, C, and E virus infection

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CHAPTER 7

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 (DAA's) is tolerable and effective but expensive. Our analysis projected the future HCV-related disease burden by applying different treatment scenarios in The Netherlands.

Methods
Using a modeling approach, the size of the HCV-viremic 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 viremic 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 is increased. Furthermore, the number of individuals with hepatocellular carcinoma and liver-related deaths are 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 ≥ 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.
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 ages\(^3\) and the infected population advances to late-stage liver disease.\(^4\) – \(^6\)

Recently, the World Health Organization (WHO) recognized 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 viremic. This corresponds to a viremic prevalence of 0.13% in the total Dutch population. The risk groups of individuals with a known viremic 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 to many other countries where HCV transmission among people who inject drugs (PWID) 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 is hidden to current screening practices ("hidden population").\(^16\)

With the availability of new powerful peginterferon-free treatment modalities in sight, treatment of HCV will be more effective and has fewer side effects. As a result, the barriers for starting treatment are expected to be lower and as a result more patients will be (successfully) 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 two-fold: The first aim was to estimate the future disease burden for The Netherlands using available data and expert opinion if the current treatment paradigm and cure would be continued.

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 countries around the world in a systematic manner, 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 international agencies’ reports. As described in detail in an earlier published study, 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 the liver disease stages (META VIR 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® optimization add-in, Frontline Systems’ Solver, was used to calculate the number, age and gender distribution of the annual acute infections. The model was validated in countries where annual HCC incidence and liver-related deaths were reported. The model was used to calculate the number, age and gender distribution of the annual acute HCV-infections, that progressed to chronic HCV-infection after accounting for spontaneous clearance of the virus (Figure 1). 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-viremic (ribonucleic acid (RNA) positive) cases. Non-HCV-viremic cases (those 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. 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 of cases, at each stage of the disease, was tracked by age and gender. Five-year age cohorts were used through 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 85 and older, was moved to the next age cohort to simulate aging.

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. There were no reliable age and gender distributions available for The Netherlands but the median age was reported at 54 years in 2006-2007, slightly younger than in the United States. In addition, United States and Dutch gender ratios were considered comparable, as well as the timing of the peak infections, so the Dutch age and gender distributions were established using the United States as an analog (Figure 2). Dutch population data were obtained by 5 year age and gender cohorts from the United Nations population database, which uses the data registered at the Dutch central bureau for statistics (Statnet). 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.

**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 600-700 new infections were reported per year (3.9-4.1 per 100,000 inhabitants). 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 under-estimation, but there are also patients tested more than once per year, which may compensate for this under-estimation. From 2005 to 2010 there were 700 to 900 diagnoses per year, and from 2011-2014 the number declined to 380 diagnoses per year. 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 viremia.

![Figure 1](image.png)

**Figure 1.** The flow of the HCV disease progression model
New HCV infections
The annual number of new cases (i.e. acute HCV-infections and new chronic HCV-infections due to immigration) did not remain 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 notified to be due to injecting drug use (IDU) and an earlier study performed in 1999-2001 showed that 6% of all new HCV cases were attributable to IDU. In line with these findings, cohort studies show a very low incidence. Therefore, in the model the annual number of new cases due to IDU was considered low. In The Netherlands, like in many other countries, transfusion of blood products is considered no longer 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 2011 onwards. Another group with high risk 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. The risk of re-infection is considered low among PWID but substantial among MSM in The Netherlands.

Table 1. HCV genotype distribution in The Netherlands, 2002–2005 [19]

<table>
<thead>
<tr>
<th>Genotype</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>14.8</td>
</tr>
<tr>
<td>1b</td>
<td>15.7</td>
</tr>
<tr>
<td>1 Other/NA</td>
<td>18.8</td>
</tr>
<tr>
<td>2</td>
<td>9.7</td>
</tr>
<tr>
<td>3</td>
<td>19.1</td>
</tr>
<tr>
<td>4</td>
<td>10.5</td>
</tr>
<tr>
<td>5</td>
<td>0.0</td>
</tr>
<tr>
<td>6</td>
<td>0.0</td>
</tr>
<tr>
<td>Other</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Figure 2. Prevalence of viremic HCV-infections by age and gender (2009)
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 or calculated using known numbers from Dutch national reports. Liver transplant data were available through the Eurotransplant Statistics Report Library and from the individual transplant centers in The Netherlands. In 2013, there were 142 liver transplants performed in The Netherlands. 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 centers in The Netherlands). The total number of cases was adjusted for aging, 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. Mortality rates were adjusted using standard mortality ratios among PWID and individuals having received blood products.

**Treated & Cured**
Analysis of ribavirin (RBV) units sold (for chronic or acute HCV-infection) were used to estimate the total number of treated HCV patients in The Netherlands. 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). 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 peg-IFN and RBV or triple therapy with peg-IFN, RBV 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 sustained viral response (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. Different new therapies considered were: DAA + peg-IFN + RBV, DAA + RBV (interferon-free) and all-oral DAA combinations with or without RBV. For the model, we assumed that all changes took effect immediately. The co-existence of multiple therapies was handled by modifying the average SVR.
Increased efficacy and treatment uptake

![Figure 3. Model inputs for the "Increased efficacy and treatment scenario", by calendar year)
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 peg-IFN/RBV. The definition of eligibility includes contra-indications to the drugs as well as patient’s preference. In this analysis, 60% of the patients were considered treatment eligible for standard-of-care (Figure 3.), being peg-IFN plus RBV for genotype 2 to 6 and peg-IFN plus RBV plus DAA for genotype 1. When peg-IFN could be eliminated, the eligibility was increased. We assumed that the increase in eligibility did 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. The latter 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 patients’ age and their stage of fibrosis (F4 (Child-Pugh A, B or C), F3, F2, or F1/F0). Review of treatment guidelines and interviews with the expert panel were used to identify both of these factors. Decompensated cirrhotic patients were considered ineligible for peg-IFN-containing therapies (irrespective of genotype). 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 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-viremic infections represented all current HCV-infections (acute and chronic HCV-infections). The term viremic 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. HCC referred to the total number of viremic HCV-related HCC cases, rather than new cases. Additionally, all reductions by disease stage were assumed to occur among the viremic 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. 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, we assumed in this scenario 650 newly diagnosed HCV infections annually and treatment of 880 HCV infections annually in The Netherlands. Treatment in this scenario was focused on patients of 15-69 years of age and with a METAVIR score of ≥ F3 assessed using FibroScan. In the light of a future high treatment rate, we considered patients with a fibrosis stage of ≥ F2 (according to METAVIR, measured using FibroScan) eligible for treatment in 2018, and patients with a fibrosis stage of ≥ F0/F1 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 FibroScan 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 90% across all genotypes. These rates were held constant through 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 with 10% across all genotypes to 970 individuals and the number of diagnoses was increased with 25% to 810 individuals annually. Treatment was open to individuals 15-69 years of age. In 2016, treatment uptake was increased to 1,210 individuals annually and diagnosis was increased to 890 individuals annually. Patients with fibrosis ≥F2 were considered eligible for treatment. In 2018, treatment uptake was increased to 1,700 individuals annually. Treatment was now also open for patients with fibrosis >F0/F1 and the eligible age range was increased up to 74 years. Treatment and diagnosis uptake were held constant from 2018 through 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: ≥F3, ≥F2, ≥F0/F1**

A fifth, sixth and seventh scenario were created to assess the impact of focused treatment of individuals with fibrosis ≥F3, ≥F2 and ≥F0/F1. Starting in 2015 treatment uptake was increased by 10% across all genotypes to 970 individuals and the number of diagnoses was increased to 25% to 810 individuals. In 2016, the treatment uptake increased 25% to 1,210 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 ≥F2 and ≥F0/F1 scenarios treatment uptake was increased by 40% to 1,700 individuals. In 2021, the number of diagnoses was kept constant at 890
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individuals. For the ≥F3 scenario 400 individuals were treated annually. For the ≥F2 scenario 530 individuals were treated as the treatment outpaced eligibility in 2020. For the ≥F0/F1 scenario 1,700 individuals were treated annually.

**Birth Cohort Effect**

The age distribution was determined as described above. The disease progression model was used to age the HCV-infected population after taking into account mortality and SVR. 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. The number of people that need to be screened to identify one viremic case was calculated by taking the inverse of the viremic HCV-prevalence. The number needed to screen to identify one new case was calculated as follows:

\[
\frac{1}{(HCV \text{ Viremic Prevalence} \times (1 - \% \text{ of HCV Population Already Diagnosed}))}
\]

**RESULTS**

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

**Base scenario**

Using historical data, it was estimated that there are around 19,200 individuals in The Netherlands with a viremic HCV infection in 2014. It was forecasted to decrease to 10,599 (45%) in 2030. The number of HCV-related HCC 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 viremic 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 2,413 fewer HCV-viremic individuals in 2030, a 23% reduction as compared to the base scenario. The number of HCV-related HCC cases and the number of liver-related deaths both decrease with 25% from the base scenario. This scenario would result in 463 cirrhosis cases being averted.
## Table 2. Model inputs and 2014 estimations

<table>
<thead>
<tr>
<th></th>
<th>Historical (min-max uncertainty interval)</th>
<th>Year (Reference)</th>
<th>2014 (95% uncertainty interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HCV-Infected Cases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Anti-HCV Cases</td>
<td>29,450 (9,400-49,530)¹</td>
<td>2009</td>
<td>26,010 (7,140-45,820)</td>
</tr>
<tr>
<td>Anti-HCV Prevalence</td>
<td>0.2% (0.1%-0.3%)¹</td>
<td></td>
<td>0.2% (0.0%-0.3%)</td>
</tr>
<tr>
<td>Number of Viremic Cases</td>
<td>21,800 (6,370-36,650)¹</td>
<td>2009</td>
<td>19,200 (4,740-35,480)²</td>
</tr>
<tr>
<td>Viremic Prevalence</td>
<td>0.13% (0.0%-0.2%)¹</td>
<td></td>
<td>0.12% (0.0%-0.2%)</td>
</tr>
<tr>
<td>Viremic Rate</td>
<td>74.0%³</td>
<td></td>
<td>74.0%</td>
</tr>
<tr>
<td><strong>HCV Diagnosed (Viremic)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viremic Diagnosed</td>
<td>10,470⁴</td>
<td>2013</td>
<td>10,200</td>
</tr>
<tr>
<td>Viremic Diagnosis Rate</td>
<td></td>
<td></td>
<td>51.1%</td>
</tr>
<tr>
<td>Annual Newly Diagnosed</td>
<td>650⁵</td>
<td>2013</td>
<td>650</td>
</tr>
<tr>
<td><strong>New Infections</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Infections</td>
<td></td>
<td></td>
<td>510⁶</td>
</tr>
<tr>
<td>New Infection Rate (per 100K)</td>
<td></td>
<td></td>
<td>3.0</td>
</tr>
<tr>
<td><strong>Treated</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number Treated</td>
<td>880⁷</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual Treatment Rate</td>
<td></td>
<td></td>
<td>4.5%</td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infected via IDU (%)</td>
<td>6.0%⁸</td>
<td>2000</td>
<td>614 (3.2%)³</td>
</tr>
<tr>
<td>Infected via blood transfusion (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹The reported prevalence of anti-HCV antibodies was 0.22% (28,100) in 15-79 year olds.² Prevalence in older and younger individuals was extrapolated resulting in an overall prevalence of 0.18% or 29,450 for all ages. The viremic rate was applied get both the viremic prevalence as well as the number of viremic cases. ³Model estimate after considering new infections and cured. ⁴Thomas et al⁵, ⁶Panel expert estimate – over the last 20 years, on average 600 individuals were newly diagnosed per year, the panel estimated 650 in 2013.⁷According 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). ⁸New viremic 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 12/1000⁹ 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. ⁹GIP databank⁴¹,⁴². ⁰EMCDDA – European Drug Report 2013. ¹¹Chaves et al⁴⁴.
Figure 4. Distribution of HCV-infected population by birth year cohort 2014

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

Figure 6. HCV disease burden over time, The Netherlands 1950-2030 (base scenario). Decompensated cirrhosis figures excluded those who received a liver transplant.
**Increased efficacy and treatment uptake**

With an aggressive treatment and diagnosis strategy, there will be 9,043 fewer HCV-viremic individuals in 2030, an 85% reduction as compared to the base scenario. The number of HCV-related HCC cases and the number of liver-related deaths in 2030 decrease with 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 9,334 fewer HCV-viremic individuals in 2030, an 88% reduction as compared to the base scenario. The number of HCV-related HCC cases and the number of liver-related deaths in 2030 decrease with 68% and 66% respectively from the base scenario. This scenario would result in 972 cirrhotic cases being averted.

**Focused treatment: ≥ F3**

There will be 1,610 more HCV-viremic individuals in 2030, a 15% increase as compared to the base scenario. The number of HCV-related HCC cases and the number of liver-related deaths in 2030 decrease with 57% and 60% respectively from the base scenario. This scenario would result in 825 cirrhotic cases being averted.

**Focused treatment: ≥ F2**

There will be 811 fewer HCV-viremic individuals in 2030, an 8% reduction as compared to the base scenario. The number of HCV-related HCC cases and the number of liver-related deaths in 2030 both decrease with 68% from the base scenario. This scenario would result in 965 cirrhotic cases being averted.

**Focused treatment: ≥ F0/F1**

There will be 8,999 fewer HCV-viremic individuals in 2030, an 85% reduction as compared to the base scenario. The number of HCV-related HCC cases and the number of liver-related deaths in 2030 decrease with 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 viremic HCV-infected population in 2014 was 51 years (birth year 1963). More than 50% of the viremic HCV-infected population was born between 1955–1969; over 80% were born between 1950–1979 (Figure 4). The highest prevalence of HCV-viremia is in the population born between 1960–1964 (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 within this age cohort (Table 4). It was assumed that 51% of the total HCV-viremic population has been diagnosed for all age groups.
Figure 7. HCV characteristics, by scenario, The Netherlands 2013-2030
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Table 3. Predicted number of viremic HCV-infections, cases with Hepatocellular carcinoma and liver-related deaths according to scenario from 2014 to 2030

<table>
<thead>
<tr>
<th>Scenario</th>
<th>HCV-Infections N</th>
<th>HCC N</th>
<th>LRD N</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014 (base)</td>
<td>19,200</td>
<td>110</td>
<td>102</td>
</tr>
<tr>
<td>Base scenario (% decrease*)</td>
<td>10,599 (45)</td>
<td>89 (19)</td>
<td>74 (27)</td>
</tr>
<tr>
<td>Increased efficacy only (% decrease*)</td>
<td>8,187 (57)</td>
<td>66 (40)</td>
<td>54 (47)</td>
</tr>
<tr>
<td>Compared to base scenario</td>
<td>-23%</td>
<td>-25%</td>
<td>-25%</td>
</tr>
<tr>
<td>Increased efficacy and treatment uptake (% decrease*)</td>
<td>1,556 (92)</td>
<td>30 (73)</td>
<td>25 (75)</td>
</tr>
<tr>
<td>Compared to base scenario</td>
<td>-85%</td>
<td>-67%</td>
<td>-65%</td>
</tr>
<tr>
<td>Screening and elimination (% decrease*)</td>
<td>1,265 (93)</td>
<td>31 (72)</td>
<td>26 (75)</td>
</tr>
<tr>
<td>Compared to base scenario</td>
<td>-88%</td>
<td>-68%</td>
<td>-66%</td>
</tr>
<tr>
<td>Focused treatment: ≥F3 (% decrease*)</td>
<td>12,210 (36)</td>
<td>33 (79)</td>
<td>30 (71)</td>
</tr>
<tr>
<td>Compared to base scenario</td>
<td>+15%</td>
<td>-57%</td>
<td>-60%</td>
</tr>
<tr>
<td>Focused treatment: ≥F2 (% decrease*)</td>
<td>9,788 (49)</td>
<td>28 (75)</td>
<td>24 (76)</td>
</tr>
<tr>
<td>Compared to base scenario</td>
<td>-8%</td>
<td>-68%</td>
<td>-68%</td>
</tr>
<tr>
<td>Focused treatment: ≥F0/F1 (% decrease*)</td>
<td>1,600 (92)</td>
<td>36 (76)</td>
<td>30 (71)</td>
</tr>
<tr>
<td>Compared to base scenario</td>
<td>-85%</td>
<td>-63%</td>
<td>-60%</td>
</tr>
</tbody>
</table>

* Decrease compared to base (from 2014 to 2030). Abbreviations: HCC: hepatocellular carcinoma, LRD: liver-related deaths

Table 4. HCV viremic prevalence according to screening by Birth Cohort

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Tests Required to Identify 1 Viremic Case</td>
<td>833</td>
<td>354</td>
<td>430</td>
<td>322</td>
</tr>
<tr>
<td>Tests Required to Identify 1 New Case</td>
<td>1706</td>
<td>725</td>
<td>880</td>
<td>659</td>
</tr>
</tbody>
</table>
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 HCC and/or liver-related death) on the key driver of uncertainty HCV prevalence (range 0.05 – 0.27 %). Since the model is based on 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 viremic HCV-infection is projected to decrease with 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 HCC is substantial. Treatment of HCV-infection in an early stage might prevent the occurrence of HCV-related mortality and HCC.

Of all scenarios, the “screening and elimination” scenario predicts the largest reduction of 88% in viremic 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 a only slightly smaller reduction in viremic HCV infection prevalence compared to the base scenario of 85%. If we focus on liver-related deaths and HCC, the “≥ F2 only model” provides the greatest decrease from the base scenario (both liver-related deaths and HCC 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 “> F0/F1 model” (68% for the “≥ F2 only model” versus 60 – 67% for the other three models). Besides this, the “F2 only model” predicts only a slight reduction in viremic HCV infection prevalence (8%) whereas the other three models predict a reduction 85–88% compared to the base scenario. All 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 viremic HCV-infection prevalence, HCC and liver-related deaths. However, due to the current high costs of treatment with DAAs it is very unlikely that this scenario would 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 1,700 individuals annually, and allowing treatment access to individuals regardless of fibrosis stage. Over the last years there have been about 1,000 (range: 880 – 1,130) treatments with peg-IFN and RBV (with or without DAAs) annually. Assuming that this number is
representative of the number of treatments for HCV, an increase from 1,000 to 1,700 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 have favourable improvements in end-stage liver disease, with maybe little 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 HCC. However, although reduced, these patients are still at risk of decompensation of liver cirrhosis and/or HCC. They are therefore advised to remain in long-term clinical care for monitoring progression of liver disease and/or development of HCC. In the current model these patients have not been considered as 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 HCC following SVR among patients with F0-1-2-3 is negligible. 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. Achieving 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 1960–1964 without prior assessment of HCV risk might be effective as our model suggests that one newly diagnosed viremic case may be found per 659 tests (compared to 1 out of 1,706 for the general population). This approach has been chosen in the USA and was described in 2012. 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. Next to this, it is difficult to suggest specific recommendations on birth cohort screening as the age and gender distribution of the viremic 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. However, the (cost-) effectiveness of these strategies relative to each other has not been studied yet, hampering efficient targeting of screening programmes. Moreover, there is no structural screening programme 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 health care professionals should be increased. Increasing knowledge of HCV-infection among health care professionals and the general population may also lower the barriers of testing and referring.\textsuperscript{58}

Next to migrants, two other groups require attention. The first group consists of people that already have been diagnosed with a viremic 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 (occasionally) 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 health care professionals, in particular general practitioners and public health workers. Innovative approaches such as internet-mediated blood screening services\textsuperscript{58} 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 viremic 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 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.\textsuperscript{59} Finally, FibroScan has been 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 way as FibroScan scores are only reliable in low (F0) and high (F4) ranges, but are not between META VIR scores F1 to F3. Also, FibroScan does not differentiate between META VIR 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 inputs 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 viremic 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 HCC is best achieved when using the “≥F2 fibrosis” strategy. The most realistic with reasonable reductions in HCV-prevalence, HCV-related death and HCC 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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