

## Chronic hepatitis C virus (HCV) burden in Rhode Island: modelling treatment scale-up and elimination

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### SUMMARY

We utilized a disease progression model to predict the number of viraemic infections, cirrhotic cases, and liver-related deaths in the state of Rhode Island (RI) under four treatment scenarios: (1) current HCV treatment paradigm (about 215 patients treated annually, Medicaid reimbursement criteria fibrosis stage  $\geq$  F3); (2) immediate scale-up of treatment (to 430 annually) and less restrictive Medicaid reimbursement criteria (fibrosis stage  $\geq$  F2); (3) immediate treatment scale-up and no fibrosis stage-specific Medicaid reimbursement criteria ( $\geq$  F0); (4) an ‘elimination’ scenario (i.e. a continued treatment scale-up needed to achieve  $>90\%$  reduction in viraemic cases by 2030). Under current treatment models, the number of cirrhotic cases and liver-related deaths will plateau and peak by 2030, respectively. Treatment scale-up with  $\geq$  F2 and  $\geq$  F0 fibrosis stage treatment criteria could reduce the number of cirrhotic cases by 21·7% and 10·0%, and the number of liver-related deaths by 19·3% and 7·4%, respectively by 2030. To achieve a  $>90\%$  reduction in viraemic cases by 2030, over 2000 persons will need to be treated annually by 2020. This strategy could reduce cirrhosis cases and liver-related deaths by 78·9% and 72·4%, respectively by 2030. Increased HCV treatment uptake is needed to substantially reduce the burden of HCV by 2030 in Rhode Island.

**Key words:** Disease burden, epidemiology, HCV, hepatitis C, modelling, treatment.

### INTRODUCTION

Chronic hepatitis C virus (HCV) infection is a rapidly growing public health problem in the United States. The consequences of chronic HCV infection are numerous, and include cirrhosis of the liver, liver cancer,

and death [1]. Over the past two decades, morbidity and mortality attributable to HCV infection has continued to increase in parallel with the ageing population (particularly people born between 1945 and 1965, popularly described as the ‘baby boomer’ generation) [2]. In the non-institutionalized civilian population in the United States, an estimated 2·7 million people ( $\sim 1\%$ ) are chronically infected with HCV [1]. Since 2006, mortality attributable to HCV infection has surpassed that of HIV/AIDS, and chronic liver disease (often HCV-related) is a leading cause of

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death [3]. More people in the United States are now dying of HCV than all other top 60 nationally notifiable infectious diseases combined [4]. Likewise, the number of HCV-associated advanced liver diseases has been on the rise in the United States and the trend is projected to continue [1, 5].

In the state of Rhode Island, it is estimated that between 1.2% and 1.7% of the adult population is chronically infected with HCV [6]. In addition to baby boomers (who account for the majority of people chronically living with HCV infection) younger populations, comprised mainly of people who inject drugs, account for an increasing number of incident HCV cases in New England [7, 8].

HCV treatment has evolved rapidly over recent years, particularly with the development of direct-acting antivirals [7]. However, economic and health-systems barriers have greatly limited uptake of more effective, safer therapies [9]. Under the current HCV treatment paradigm, the burden of HCV infection and its sequelae are expected to continue on an upward trend in the United States and other industrialized countries, particularly as the number of people with advanced HCV-related liver disease grows [10, 11]. Moreover, many current Medicaid reimbursement criteria (with various liver staging, substance use-related, and other restrictions) do not follow recommendations from professional organizations, such as the Infectious Diseases Society of America and the American Association for the Study of Liver Diseases [12]. Therefore, in order to ensure uptake of novel anti-HCV drugs, greatly decreased prices of therapy, and a change in HCV treatment policies, are needed.

In response to the high morbidity and mortality associated with HCV infection, we launched Rhode Island Defeats Hepatitis C ('RI Defeats Hep C'), a project dedicated to the elimination of HCV in Rhode Island. A key objective of RI Defeats Hep C is to identify the most effective HCV treatment and prevention policies that will lead to a substantial decrease, and eventual elimination, of chronic HCV infection in Rhode Island. To meet this objective, we carried out a mathematical modelling analysis of different treatment scenarios, using as a base case HCV treatment roll-out under the current Rhode Island Medicaid HCV treatment policies [12, 13].

## METHODS

To estimate the burden of chronic HCV infection in Rhode Island, we adapted an HCV disease

progression model, described in detail previously [5, 14]. Wherever possible, state-specific estimates were used to construct a model representing the adult population of Rhode Island. The model was designed to examine the effects of possible policy changes and interventions on the burden of HCV in the state. The aim of this study was to estimate the projected burden of the disease under different treatment scenarios, and also to demonstrate whether HCV disease burden can be reduced via change in relevant treatment scale-up and eligibility policies.

In brief, a computer-generated simulation model of HCV burden was used to investigate four possible treatment scenarios. The model was constructed in Microsoft Excel (Microsoft Corp., USA), and Monte Carlo and sensitivity analyses were done using Crystal Ball, an Excel add-in by Oracle. We used beta-Project Evaluation and Review Technique (PERT) distributions to model the uncertainty associated with the inputs. Tracking of the HCV-infected population started from 1950, and was calibrated to 2014; the model projected the outcomes up to 2030. The number of individuals infected with HCV prior to 1950, who are still alive, was expected to be negligible and to have minimal impact on the final analysis. The model population was tracked by 5-year age cohorts and by gender. To simulate ageing, each year one-fifth of the age group moved to the next age cohort, after accounting for age-specific mortality (see below). The distribution of HCV prevalence for the age and gender cohorts was assumed to be proportional to the US population [1], given that the age and gender structures in Rhode Island are very similar to the US average [6]. Incident cases were distributed in the different age and gender cohorts using distributions reported by the Centers for Disease Control and Prevention (CDC) between 1992 and 2007 [15–18]. We assumed that the incidence distribution from 2008 to 2030 remained stable and reflected that reported in 2007.

The disease progression modelling was carried out via multiplying the total number of cases at a particular stage of the disease by a progression rate to the next stage (see disease progression schematic, Supplementary Fig. S1). Subjects in a particular disease stage were handled as stocks, while yearly transitions from one health state to another were treated as flows. HCV disease progression rates are presented in Supplementary Tables S1 and S2), and were adapted from previously published studies [19–22] or back-calculated. As described previously [14], the number of reported cases of liver cancer and liver cancer deaths (by age and

gender) from the US Surveillance, Epidemiology, and End Results (SEER) database were used to back-calculate age- and gender-specific annual fibrosis progression rates (Supplementary Table S1). The transition rates shown in Supplementary Table S1 equate to  $\sim 16\%$  cirrhotic at 20 years, which is within the range of empirical estimates [23], and similar to that of a recently published modelling study that estimated a 12–14% cumulative cirrhosis progression rate at 20 years [24]. For persons acutely infected, we estimated the proportion that progressed to chronic infection, taking into account the spontaneous clearance of the virus based on previously published data [6, 25] (see Supplementary Table S2).

The model estimated the annual number of acute infections historically (from 1950) using a calibration procedure described previously [5]. In brief, national surveillance data [26] regarding the annual number of estimated total new infections was adjusted for the state's population relative to the US population in each year. These values reflect methods used by the CDC to estimate true incidence of acute HCV infection, given under-ascertainment of reported cases [27]. For 2010 onwards, we used national surveillance data and other previously published estimates [14, 28–30], and interpolated the number of acute infections in Rhode Island, assuming constant incidence over the simulation period. The prevalence of chronic HCV infection in a particular year was calculated by the sum of new infections (incidence) minus disease stage-specific mortality and cured cases leading up to that year. Finally, incidence was modified to match reported prevalence in 2014 in Rhode Island (see below). The final incidence values for each year, as well as the interpolated CDC surveillance estimates for Rhode Island, are shown in Supplementary Fig. S2).

To parameterize the model, data on Rhode Island-specific parameter estimates were abstracted from published reports and from other data sources [3, 6, 14]. The following parameters were quantified using state-specific data and are summarized in **Table 1**: the size of the HCV-infected population (both anti-HCV positive and viraemic infections), proportion medically eligible for HCV treatment, the state's HCV genotype distribution, and the number liver transplants annually. For example, chronic HCV prevalence was obtained from a Rhode Island study [6] that used a method similar to that employed in a recent analysis of national HCV prevalence [31]. In both studies, the HCV prevalence estimate from the National Health and Nutrition Examination

Survey (NHANES) was supplemented with data from grey literature and other sources to account for missed cases from under-represented populations and/or those purposely excluded from the NHANES (e.g. veterans, the homeless). The chronic HCV prevalence estimate obtained by Kinnard *et al.* was also adjusted to account for the fact that the racial composition of Rhode Island differs from that of the national average [6].

The following parameters were based on national data and interpolated to the Rhode Island population (0.33% of the US population in 2014): proportion previously diagnosed, number newly diagnosed per year, proportion of the diagnosed pool in each fibrosis liver disease stage, and the number of treated and cured patients per year [3, 20, 32–36]. For example, the annual number of treated and cured patients in Rhode Island between 2004 and 2007 was estimated from previously published national data [36], assuming a sustained virological response (SVR) of 55% for G1, 70% for G2 and G3, and 48% for G4, and a treatment completion rate of 80% [5]. The number of cured patients prior to 2002 was ignored and assumed not to have an effect on the primary results. The number of cured patients between 2008 and 2013 was extrapolated based on results of a previously published modelling study [36]. Only patients with fibrosis  $\geq F2$  and aged between 15 and 64 years were considered for treatment prior to 2014.

Background mortality rates by age and gender were adjusted for increased mortality in HCV-infected patients due to injection drug use and transfusion, as described in detail previously [37]. These rates were applied to all HCV-infected populations in the model. Separate mortality rates were defined for liver-related deaths in individuals with decompensated cirrhosis (diuretic sensitive and refractory ascites, variceal haemorrhage, and hepatic encephalopathy), hepatocellular carcinoma (HCC), and those who required liver transplantation (sources and rates shown in Supplementary Table S2).

Following model calibration, we probed the model with four treatment scenarios, resulting in future projections of HCV disease burden. The base-case scenario describes the extant HCV treatment paradigm, in which about 215 patients are treated annually, with a restriction to patients in fibrosis stage  $\geq F3$  (based on current Rhode Island Medicaid reimbursement criteria) [12]. Second, we analysed two treatment scale-up scenarios. The first describes an immediate scale-up of treatment to 430 patients annually, and a

Table 1. Summary parameters for Rhode Island HCV burden model, base case (2014)

Variable	Base estimate	Low	High	Source
HCV Ab+ positive (prevalence)	19 632 (2.0%)	16 603 (1.7%)	22 660 (2.3%)	[6]
Chronic infections (prevalence)	14 527 (1.5%)	12 286 (1.2%)	16 768 (1.7%)	[6]
Annual number of new infections	86	–	400	[14, 28–30]
Spontaneous clearance rate	18%	15%	45%	[25]
Previously diagnosed	49%	–	75%	[32, 33]
Newly diagnosed (number per year)	360	65	654	[3]
Proportion of diagnosed pool in F0	15%	13%	17%	[20, 34]
Proportion medically eligible for treatment	95%	–	–	L. Taylor, pers. comm.
Age range for treatment	18–70	–	–	L. Taylor, pers. comm.
Treatment restriction	≥F3	–	–	[45]
Treated patients (number per year)*	215	–	322	[5, 36]
Genotype distribution				[38]
G1a	46.2%	–	–	
G1b	26.3%	–	–	
G2	10.7%	–	–	
G3	8.9%	–	–	
G4	6.3%	–	–	
Other	1.6%	–	–	
Average SVR*				[39]
G1a	90%	–	–	
G1b	90%	–	–	
G2	90%	–	–	
G3	75%	–	–	
G4	90%	–	–	
Other	90%	–	–	
Number of liver transplants (annually)	10	–	–	R. Saidi, pers. comm.

HCV, Hepatitis C virus; SVR, sustained virological response; pers. comm., personal communication.

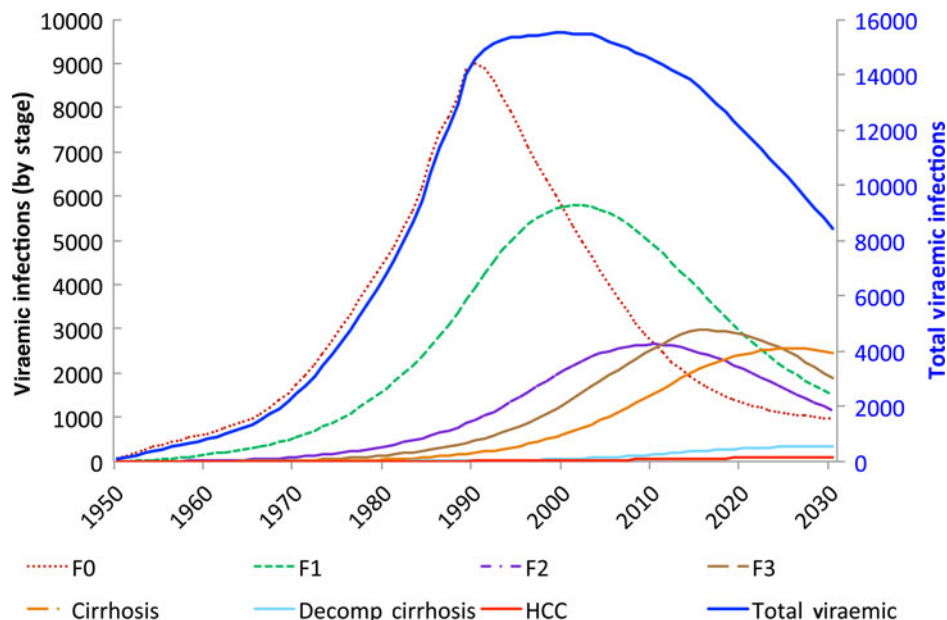
\* Average SVR increases to 90% for all genotypes in 2015.

less restrictive Medicaid treatment authorization and reimbursement criteria (fibrosis stage  $\geq$ F2); the other treatment scale-up scenario describes an immediate treatment scale-up to 430 patients annually and no fibrosis stage-specific Medicaid reimbursement criteria ( $\geq$ F0). Finally, there is an elimination scenario, in which the number of patients treated annually is determined based on a continued treatment scale-up needed to achieve >90% reduction in viraemic cases by 2030. In the elimination scenario, there is no treatment criteria based on liver fibrosis stage. In both scenarios in which there is no fibrosis-stage criteria, treatment is independent of an individual's disease stage (i.e. treatment is allocated randomly throughout the population).

The number of persons in each liver fibrosis stage (including the number of cirrhotic patients), and the number of deaths from liver-related and all causes in the HCV-infected population was estimated for the base case and each treatment scenario, using the HCV disease progression framework described above and previously [6, 14]. The average SVR rates for each genotype

(assuming direct-acting antiviral therapy) were based on previously published data [39], and are shown in Table 1.

Finally, we carried out a sensitivity analysis and estimated the 95% uncertainty interval for chronic HCV prevalence, number of cirrhotic cases, as well as overall and liver-related mortality in the base-case scenario. Monte Carlo simulations were conducted to examine the effect of variability in estimated HCV incidence and other factors. We conducted Monte Carlo analyses in which input parameters were randomly sampled from beta-PERT distributions. Specifically, for each model input that was considered as having uncertainty, a beta-PERT distribution was developed with a minimum and maximum value defined by the low and high ranges shown in Table 1 and Supplementary Table S2, and a likeliest value given by that used in the primary base-case analysis. As an example a beta-PERT distribution is shown in Supplementary Figure S3. As shown, we focused our sensitivity analysis on parameters for which there was greater uncertainty (e.g. HCV incidence,



**Fig. 1.** Estimated burden of chronic HCV infection in Rhode Island, 1950–2030: total viraemic infections (dark blue) and by liver disease stage. HCC, Hepatocellular carcinoma.

number newly diagnosed per year, liver-related deaths, etc.) Finally, to further examine the impact of uncertainty regarding specific variables (e.g. disease progression rates), we conducted a series of one-way sensitivity analyses, using the same methodology described above but sampling from only one beta-PERT distribution for each analysis.

## RESULTS

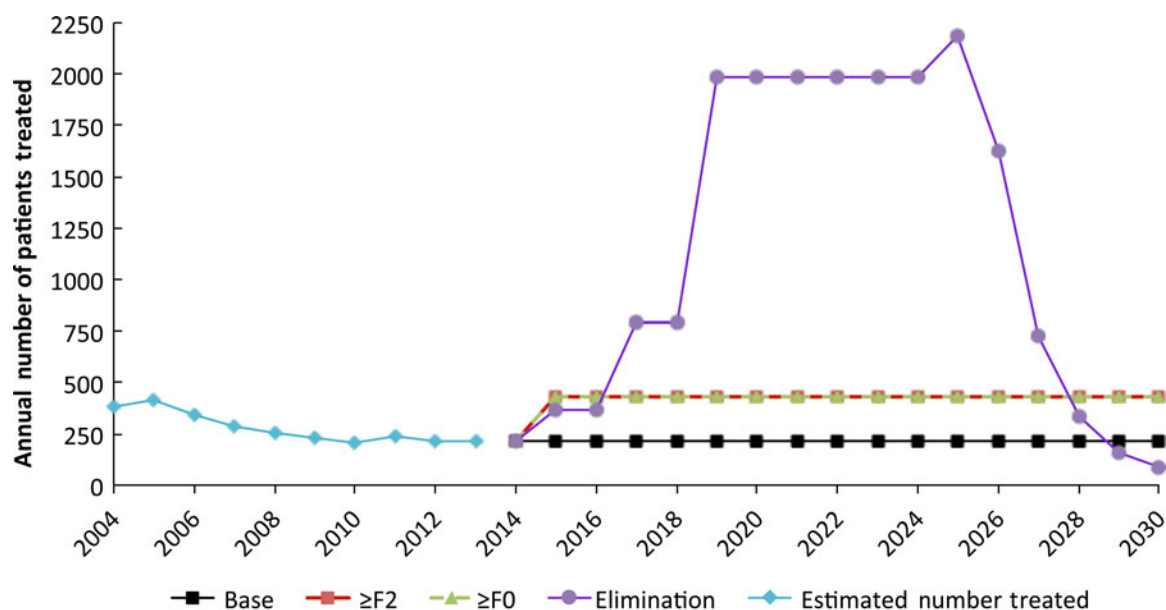
The peak prevalence of chronic HCV infection in Rhode Island was estimated to occur in 1999, with 15 500 viraemic cases (Fig. 1). The estimated number of new infections per year (which was estimated to peak in 1989) is shown in Supplementary Figure S1. The number of HCV-infected individuals with fibrosis stage F0 has been declining since 1990, while those in fibrosis stage F2 likely peaked in 2010 (Fig. 1). Assuming the current treatment paradigm continues, this number is expected to drop below 10 000 viraemic cases by the year 2030. However, the number of HCV-infected persons with decompensated cirrhosis and HCC in the Rhode Island population is expected to continue to rise as the baby-boomer generation ages (see Fig. 1). In the base-case scenario, the proportion of the diagnosed pool in F0 is estimated to increase from 15% in 2014 to 90% by 2025.

The annual number of patients treated in the base case and various treatment scale-up scenarios is

shown in Figure 2. In the elimination scenario, the number of patients treated was back-calculated to result in <1000 viraemic cases (i.e. a  $\geq 90\%$  reduction) by 2030. As shown, achieving elimination by 2030 requires a rapid and substantial scale-up in treatment, to over 2000 patients treated annually by 2020.

The estimated total number of viraemic infections and cirrhotic cases under each scenario is shown in Figures 3 and 4, respectively. Immediate treatment scale-up with  $\geq F2$  and  $\geq F0$  fibrosis stage treatment criteria could reduce the total number of viraemic cases in 2030 by 17.3% and 19.6%, respectively (Fig. 3). In contrast, a greater reduction in cirrhotic cases was observed when treatment was restricted to persons in liver disease stage  $\geq F2$  (21.7% vs. 10.0% reduction for the  $\geq F0$  scenario in 2030, respectively). As expected, the largest reduction in total cases and cirrhotic patients was observed in the elimination scenario (93.9% and 78.9%, respectively).

Under the present treatment paradigm, the rates of all-cause and liver-related deaths are expected to continue to increase and peak by 2030 (Figs 5 and 6, respectively). Under the elimination scenario (i.e.  $\geq 90\%$  reduction in viraemic cases), projected mortality associated with any cause, as well as mortality from liver-related conditions, is expected to fall through to 2030 (Figs 5 and 6). This treatment strategy could reduce liver-related deaths by 72.4% in 2030 compared to the base scenario. Reductions in



**Fig. 2.** Annual number of patients treated in the base-case and treatment scale-up scenarios, Rhode Island, 2004–2030. The annual number of treated patients between 2004 and 2013 was estimated from national data [36], and interpolated to the Rhode Island population.

mortality were also observed in the treatment scale-up scenarios. As shown in Figures 5 and 6, assuming the same number of persons are treated annually, restricting treatment eligibility to  $\geq F2$  produced greater reductions in all-cause and liver-related deaths compared to the  $\geq F0$  scenario.

The results of the one-way sensitivity analyses are summarized in a tornado diagram (see Supplementary Fig. S4). As shown, the model was most sensitive to the number of incident cases. Estimated chronic HCV prevalence in 2030 was also sensitive to changes in disease progression rates, including the rate at which individuals transition from mild to moderate fibrosis.

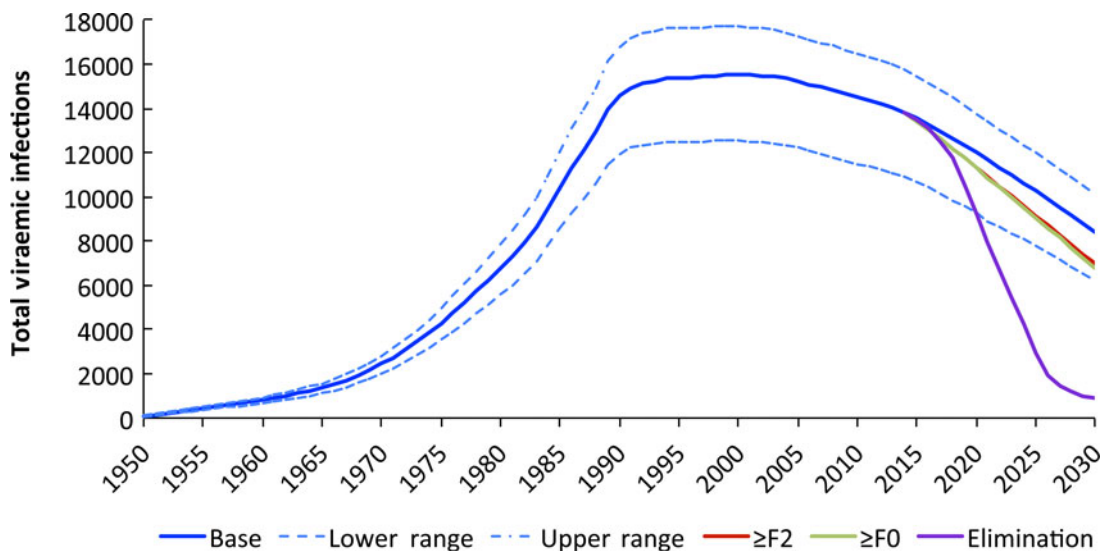
## DISCUSSION

The results from our mathematical modelling study show that HCV-related morbidity and mortality can be reduced significantly in Rhode Island if an aggressive treatment strategy is implemented over the next decade. In contrast, if the current rate of HCV treatment continues, the number of liver-related deaths will continue to increase until at least 2030. A treatment scenario in which the number of patients treated annually is increased to 430 reduces the burden of advanced liver disease and related deaths in Rhode Island, although the estimates fall within the uncertainty interval of the base-case scenario. However, our model suggests that HCV elimination (i.e. <1000

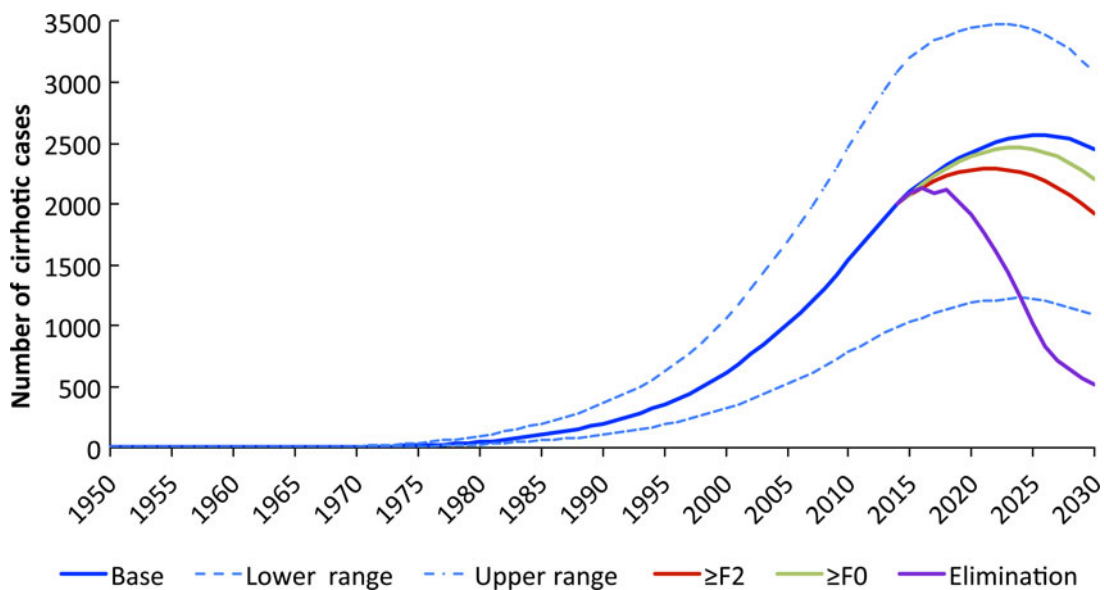
chronic HCV cases by 2030) is the best approach and notably falls outside the uncertainty interval. Reducing viraemic cases by 90% is possible if treatment is scaled up immediately and continuously, to ~2000 persons annually, by 2020.

Our results are in accordance with a recently published national study that found a marked scale-up of treatment is needed to reduce future HCV disease burden [39]. In that study, it was projected that treating all diagnosed patients in the United States would reduce HCV-related disease burden to <1400 cases in 50 years, although such a strategy would be extraordinarily expensive. The authors also found that treating 5% of all diagnosed patients annually, irrespective of disease stage, would produce substantial public health benefit and would be much more affordable. These findings are similar to our results, in that substantial reductions in chronic HCV prevalence will likely require immediate and ongoing treatment of a significant proportion of the population over the next decade.

A comparison of model outputs from scenarios in which treatment is capped (but restricted to individuals with liver disease stage  $\geq F2$  and  $\geq F0$ ), shows that, although the estimated number of viraemic infections in 2030 was similar, a greater reduction in cirrhotic cases was observed when treatment was restricted to persons in liver disease stage  $\geq F2$ . More advanced HCV disease stages have a higher



**Fig. 3.** Estimated number of total viraemic infections in Rhode Island, 1950–2030: base-case and treatment scale-up scenarios. Results of the Monte Carlo sensitivity analysis (95% uncertainty interval, base case) are shown by dashed blue lines. The 95% uncertainty interval at 2030 is 6260–10 490 total viraemic infections.

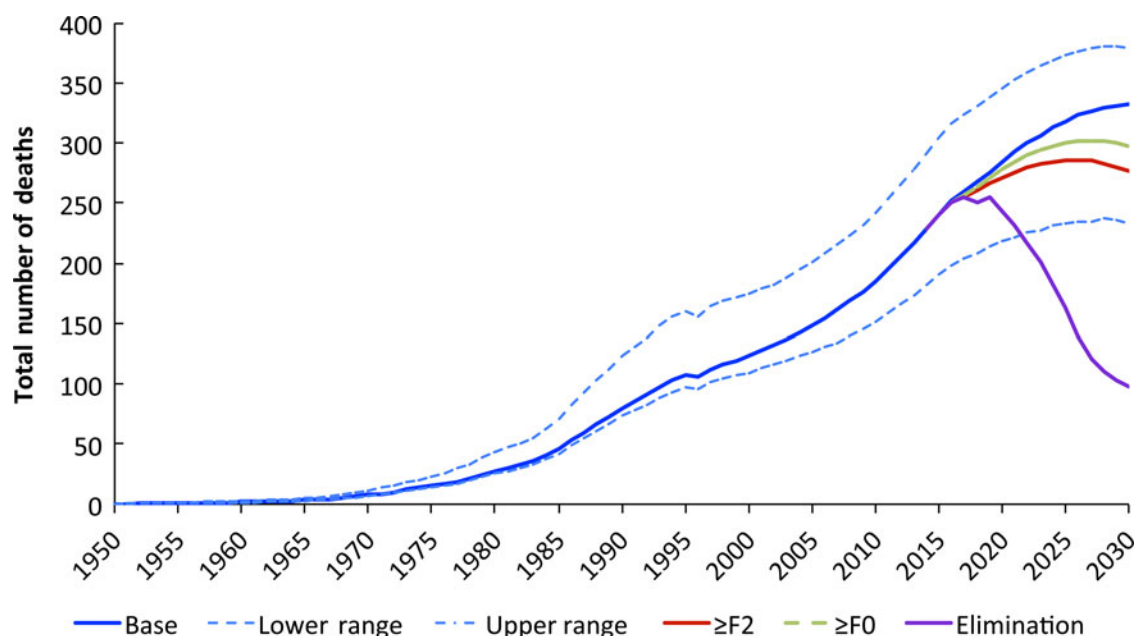


**Fig. 4.** Estimated number of cirrhotic cases in Rhode Island, 1950–2030: base-case and treatment scale-up scenarios. Results of the Monte Carlo sensitivity analysis (95% uncertainty interval, base case) are shown by dashed blue lines. The 95% uncertainty interval at 2030 is 1085–3092 cirrhotic cases.

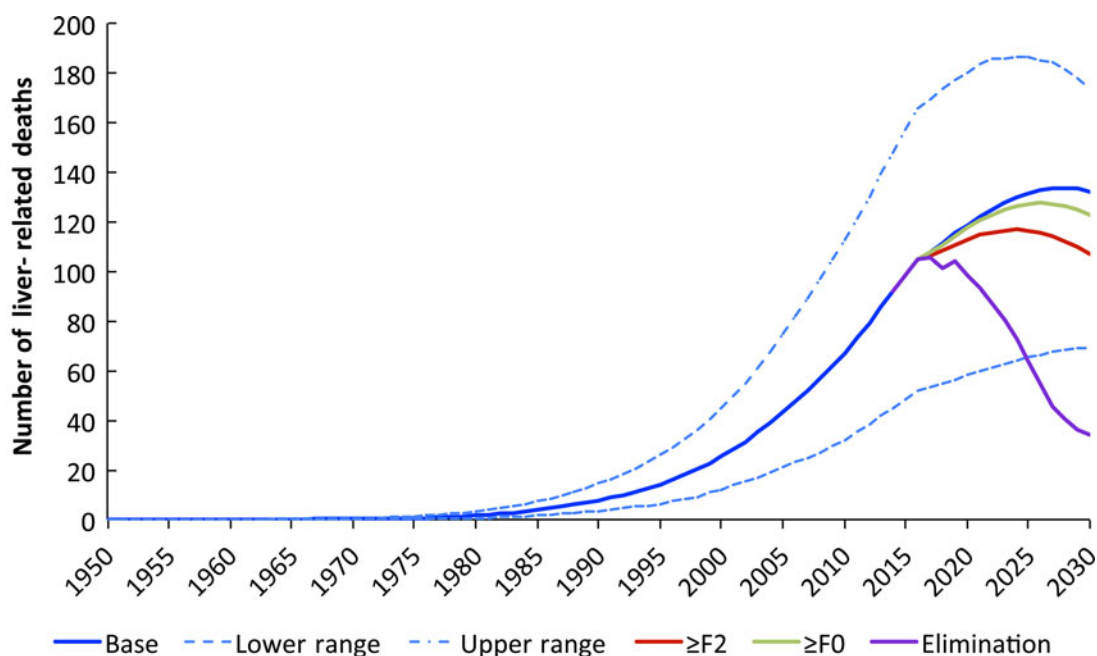
probability of progression; as such, the model confirms that restricting treatment to these patients has a larger impact on rates of cirrhosis and liver-related mortality in the population. However, our results further imply that a significant proportion of persons in lower fibrosis disease stages will eventually progress to F2. This is in agreement with a study demonstrating substantial natural progression in liver

fibrosis from stage F0/F1 to higher stages [40]. Thus, if achieving >90% reduction in viraemic cases is the goal, a rapid expansion of treatment eligibility to all patients (regardless of disease stage) is recommended.

This study has a number of important limitations. First, in our primary analysis, we assumed a constant incidence of new infections over the modelled time period (2015–2030) in all scenarios. Recent studies



**Fig. 5.** Estimated number of deaths from any cause in the viraemic HCV population, Rhode Island, 1950–2030: base-case and treatment scale-up scenarios. Results of the Monte Carlo sensitivity analysis (95% uncertainty interval, base case) are shown by dashed blue lines. The 95% uncertainty interval at 2030 is 237–381 deaths.



**Fig. 6.** Estimated number of liver-related deaths in the viraemic HCV population, Rhode Island, 1950–2030: base-case and treatment scale-up scenarios. Results of the Monte Carlo sensitivity analysis (95% uncertainty interval, base case) are shown by dashed blue lines. The 95% uncertainty interval at 2030 is 69–177 liver-related deaths.

have identified an increasing number of acute HCV infections in young people who inject drugs in the United States and in New England [8, 41, 42]. Thus, the number of new infections in Rhode Island may

be greater than we estimated, and could continue to increase over time. In addition to the removal of restrictions on HCV treatment eligibility for people who inject drugs [12], the expansion of additional



prevention and harm reduction interventions, including needle-and-syringe programmes, is recommended. Similarly, we did not consider treatment as prevention (i.e. the impact of curing HCV in transmitters on HCV incidence and prevalence).

Second, we were not able to obtain specific estimates for the number of treated patients from Rhode Island Medicaid, private insurance companies, or from the Veterans Affairs system. Therefore, the estimated number of treated patients may be inaccurate.

Third, because mortality rates were modelled based on age, gender, injection drug use, and liver-related deaths without accounting for deaths from other risk factors, our model may underestimate the true HCV-related mortality. Under-reporting of mortality rates from HCV has been noted in previous studies, where researchers found under-documentation of HCV infection on death certificates [43]. We attempted to account for this uncertainty by conducting sensitivity analyses in which the likelihood of death at each HCV disease stage was varied.

Fourth, our model assumed the same rate of spontaneous clearance for all HCV-infected individuals. Recent work has shown that the rate of spontaneous clearance may be as high as 50% in persons with re-infection [44]. Future work will seek to incorporate differential rates of spontaneous clearance based on re-infection status and other risk factors.

Fifth, as with all modelling studies, our findings are only as valid as the available data and assumptions. Given that HCV surveillance (including case notification) and the dissemination of information regarding HCV treatment uptake is limited in Rhode Island [45], data exclusively representative of the state's population were frequently unavailable. As such, a limitation of our study is the use of national estimates from which state-specific figures were interpolated, since actual values for the population under study were unavailable in Rhode Island. Wherever possible, modelling parameter estimates were derived from published literature of Rhode Island-specific data [6]. However, we note that national estimates have been validated and utilized successfully in prior modelling studies [5, 14, 46]. This limitation demonstrates the urgent need to improve HCV surveillance capacity and to increase research and treatment evaluation infrastructure in Rhode Island.

Sixth, with the discovery of more potent anti-HCV medications in the future, the SVR rates specified in the input parameters might be different from present-day estimates. This may alter the true progression and

prevalence estimates, particularly for later years of the simulation.

Seventh, the model utilized in this analysis is a progression model in which costs of treatment were not estimated. Therefore, we were unable to determine the budgetary implications of the simulated treatment scale-up strategies. Recent research has shown that treating HCV infection at early fibrosis stages is cost-effective (at a standard cut-off of <\$10 000 per quality-adjusted life-year gained), but that such strategies incur substantial upfront investment [47]. Future work will investigate the cost-effectiveness of various treatment strategies in Rhode Island.

A final limitation of our study is the assumption that sufficient numbers of patients will be screened and diagnosed in order to achieve the modelled treatment targets: this is particularly an issue under the elimination scenario (>90% reduction in viraemic cases). Generally, as treatment rate ramps up, it may become more difficult to find untreated patients. Low-threshold, community-based HCV screening programmes with reflexive RNA confirmatory testing are needed to ensure a sufficient number of individuals are eligible for treatment.

In sum, our analysis demonstrates that achieving a substantial reduction in the disease burden of HCV in Rhode Island will necessitate treating ~2000 patients annually by 2020. However, there is a need to enhance HCV surveillance in Rhode Island and to increase clinical infrastructure and provider capacity to meet the demands of treatment scale-up. If the current paradigm of treating a much smaller number of patients with F2 liver staging and above is sustained, it will take a much longer period to eliminate HCV infection in Rhode Island, with total mortality increasing until at least 2030.

## SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit <http://dx.doi.org/10.1017/S0950268816001722>.

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## DECLARATION OF INTEREST

The Center for Disease Analysis has received research funding from public and private sources (Gilead Sciences, Boehringer Ingelheim and AbbVie), but its projects are limited to basic epidemiology and modeling research. H. Razavi and D. Razavi-Shearer are employees of The Center for Disease Analysis but did not receive remuneration for this work. All other authors declare no conflicts of interest.

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