ORIGINAL ARTICLE

Impact of improved treatment on disease burden of chronic hepatitis C in New Zealand

Edward Gane, Catherine Stedman, Cheryl Brunton, Sarah Radke, Charles Henderson, Chris Estes, Homie Razavi

Abstract

Background Chronic hepatitis C is an important cause of liver failure, liver cancer and liver-related deaths in New Zealand. Although these complications can be prevented by HCV eradication, current treatment uptake is <1% per annum. We describe the burden of HCV infection and estimate the effect of four different treatment strategies to reduce HCV-related morbidity and mortality.

Methods Baseline model parameters were based upon literature review and expert consensus, focusing on New Zealand data. Four scenarios were modelled: Scenario 1 estimated the impact of increased treatment efficacy, while Scenario 2 estimated the effect of increased treatment efficacy and gradual increases in numbers treated. Scenarios 3 and 4 estimated the impact of deferred introduction of new DAAs for either 1 or 2 years.

Results Prevalence of HCV infection peaked in 2010 (50,480 cases). Peak prevalence of cirrhosis and HCC will occur after 2030. Scenario 2 resulted in sizeable decreases in HCV-related morbidity and mortality. The impact of Scenario 1 was smaller. Deferring funding for new DAA treatments for a further 1 or 2 years resulted in an 18-36% increase in liver-related deaths in 2030.

Conclusions While prevalence of chronic HCV infection may have peaked, disease burden continues to grow. Increased treatment uptake and efficacy combined with efforts to reduce disease transmission, will help prevent advanced liver disease and deaths.

About 2% of the world's population (almost 80 million people) has been infected with the hepatitis C virus (HCV).[1] Almost 30 years after the first notified case of post-transfusion non-A, non-B hepatitis, the exact prevalence of chronic HCV infection in New Zealand remains unknown because most cases remain undiagnosed and only acute infection is notifiable. However, the epidemiology of HCV is assumed to be similar to that in Australia, which has obtained accurate HCV prevalence data through high diagnosis rates and compulsory notification of prevalent, as well as incident cases (270,000 identified cases, prevalence 1.28%). The same rate in New Zealand would equate to approximately 54,000 people living with past or present HCV infection. From laboratory data, it is estimated less than one half of HCV-infected New Zealanders have been diagnosed and less than 10 per cent have accessed treatment of whom only half have been cured (Gane E, personal communication, 2014).

In many developed countries, the incidence of HCV infection was high during the 1960s, 70s and 80s, secondary to the rise in injecting drug use (IDU) over those decades. Since 2000, the incidence of HCV infection in Australia has dropped by more than 50% reflecting both a reduction in IDU and safer injecting practices.[2,3] Epidemiologic studies have identified that most chronic infections are now in the 40-to-60-year age group.

In the USA, the total size of the HCV-infected population has been stable since 2000[4] and this may also be the case in New Zealand. However, the very low rates of treatment uptake and an aging cohort effect will result in a steady increase in the proportion with established cirrhosis and numbers with the complications of HCV-related liver failure and hepatocellular carcinoma.[5–7] This will be associated with an increase in both liver-related mortality and demand for liver transplantation. A recent pharmacoeconomic analysis has costed the future

health burden of the current HCV epidemic in New Zealand at more than 0.5 billion dollars over the next 20 years.[8]

Eradication of HCV infection will halt liver disease progression and prevent liver-related complications. However, the poor efficacy and tolerability of current interferon-based (IFN) therapies have limited treatment uptake. Real world studies report that more than half of all patients with chronic HCV infection are either IFN-ineligible or intolerant.[9] Reduction of the projected future health burden associated with chronic hepatitis C will require widespread access to new regimens with better efficacy and less side effects.

Direct acting antiviral agents (DAAs) provide new opportunities for treatment of HCV whilst reducing the need for both interferon and ribavirin. Two combination DAA regimens are approaching approval for treatment of patients infected with HCV genotype 1 (G1): ledipasvir and sofosbuvir, and ABT-450, ombitasvir, and dasabuvir, with ribavirin.[10–13]

These new regimens have certainly raised the bar for future DAA development to at least 95% sustained virologic response (SVR) with only 12 weeks of treatment. Current Phase II studies combining three or more next generation DAAs are looking at reducing duration to as short as only 4 weeks (see clinicaltrials.gov NCT02133131 and NCT02175966), and also providing a one-size-fits-all regimen for all HCV genotypes.[14] It is expected that within the next 5 years, highly effective and well tolerated all-oral DAA regimens will be available and affordable for most patients living with HCV infection

This current study estimates the impact of increased treatment uptake and efficacy on the projected health burden from liver-related complications in New Zealanders with chronic HCV infection and also estimates the impact of delaying any access to new therapies for 1 or 2 years.

Methods

As previously described,[7,15,16] country-specific inputs were used to construct a disease progression model in Microsoft Excel software (Redmond, WA, USA) to quantify the HCV-infected population from 2013-2030. Uncertainty and sensitivity analyses were completed using Crystal Ball, an Excel add-in by Oracle. Beta-PERT distributions were used to model uncertainty associated with all inputs. Sensitivity analysis was used to identify the uncertainties that had the largest impact on peak prevalence in 2030. Monte-Carlo simulation was used to determine the 95% uncertainty intervals for prevalence.

The following model parameters were used:

Total population

Population data were organised by sex, 5-year age groups, and year (1950–2030) and obtained from the United Nations population database.[17]

Total infected

In New Zealand, the viraemic prevalent HCV infected population was estimated at 50,000 individuals in 2013 (Table 1).[18] A viraemic rate of 74.6% was assumed (Table 1).[19] The age and sex distribution of the infected population was based on demographic data collected through March 2014 from over 1000 clients with HCV attending a HCV clinic (Figure 1) (Personal communication, Brunton C, 2014). Christchurch Hepatitis C Community Clinic data, 2014. Razavi H, editor. 2014. 5-6-2014). The genotype distribution of the prevalent population was based upon distribution in more than 2000 individual results from a reference laboratory G1=56%, G2=8%, G3=35%, G4=0.5%, G6=1%.

http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2014/vol-127-no-1407/6390

Table 1. Model inputs and 2013 estimates

	Historical	Year	2013 (Est.)
HCV Infected Cases	66,980 (36,240 - 96,630)	2013	66,980
Anti-HCV Prevalence	1.5% (0.8% - 2.1%)		1.5%
Total Viremic Cases	50,000 (27,050 - 72,130)	2013	50,000
Viremic Prevalence	1.1% (0.6% - 1.6%)		1.1%
Viremic Rate	74.6%		
HCV Diagnosed (Viremic)	20,000	2013	20,000
Viremic Diagnosis Rate	40%		40.0%
Annual Newly Diagnosed	910	2013	910
New Infections			1,020
New Infection Rate (per 100K)			22.6
Treated			
Number Treated	900	2011	900
Annual Treatment Rate	1.8%		1.8%
Risk Factors			
Number of Active IDU with HCV			10,100
Percent Active IDU			20.2%
Previous Blood Transfusion			1,790
Percent Previous Blood Transfusic			3.6%

Figure 1. Age and gender distribution of anti-HCV prevalence, New Zealand, 2013
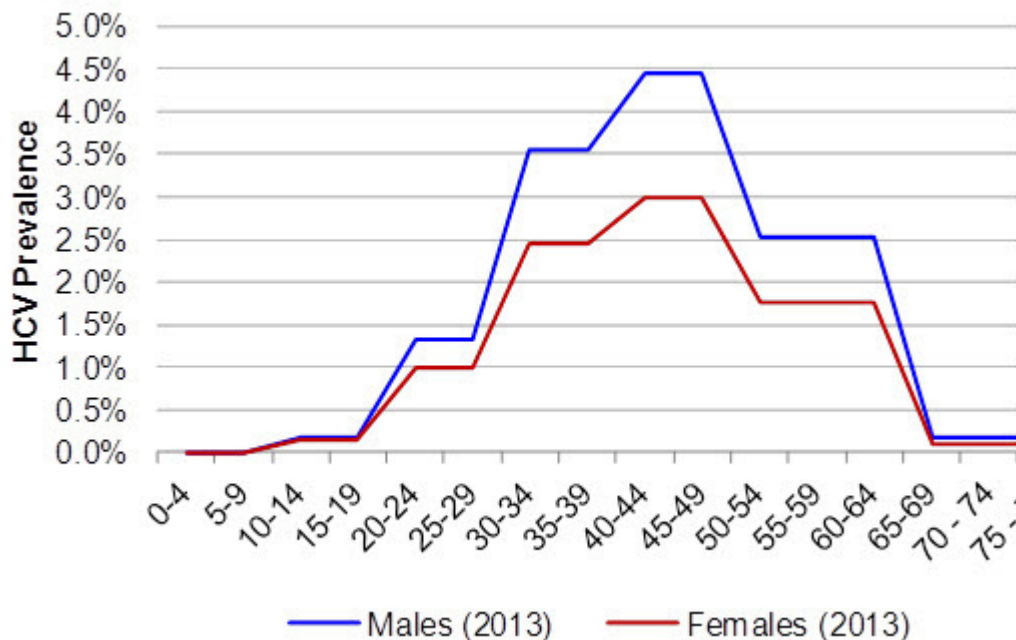
Transition probabilities

Age and sex specific transition probabilities were used to progress patients annually through each disease state, as described in earlier work.[7]

New cases

Historical changes in incidence were estimated based on expert consensus, previous New Zealand HCV modelling[20] and notification data.

It was estimated that the incidence of HCV infection peaked in 1980, and has since decreased. In 2014, it is estimated that 1,020 new infections occurred in New Zealand.

Treated patients

In 2013, it is estimated that 900 patients were treated in New Zealand, based on expert consensus and IMS Health (NZ) Ltd data for standard units of Peg-IFN sold in New Zealand, with a multiplier to account for under-reporting. The New Zealand genotype distribution was used to estimate the average number of weeks of treatment per patient with 85% compliance/persistence.

Liver transplants

In 2013, there were 36 liver transplants performed in New Zealand of which 24 were in adults. Thirteen transplants were attributable to HCV (54% of all adult transplants). The total number of annual liver transplants was available from transplant registry reports for the years 1997 to 2013.[21] The proportion of all liver transplants attributable to HCV was reported as 37% of all transplants.

Hepatocellular carcinoma

The best indicator of the increasing health burden related to chronic HCV infection is the incidence of HCV-related hepatocellular carcinoma (HCC). The best estimate for HCC incidence in New Zealand is the number referred to the National Hepatoma Service at Auckland City Hospital. This number has increased by more than 10% each year –from 55 cases in 2003, to 110 cases in 2008 and 205 cases in 2013. This observed increase matches the base case model outputs (Figure 2).

The major contributor to this rising HCC incidence in New Zealand is now chronic HCV infection. In 2003, there were nine new cases of HCV-related HCC, increasing to 21 in 2008 and 75 in 2013. Of these, the proportion in whom the diagnosis of HCV was known prior to presentation with HCC has increased steadily from only 33% in 2003 to 38% in 2008 and 53% in 2013. These figures would suggest that overall, less than 50% of the HCV-infected population in New Zealand is aware of their HCV status.

Diagnosed patients

Based on expert consensus, it was assumed that 40% of the HCV-viraemic population in New Zealand in 2013 was previously diagnosed. Based on the ratio of newly to previously diagnosed HCV infection in Australia, it was estimated that 910 cases were newly diagnosed in New Zealand in 2013.[19,22]

Mortality & risk factors

Background mortality rate by year, age group and sex was calculated using the Berkeley Human Mortality database.[23] Based on expert consensus, it was estimated that approximately 1% of the New Zealand population were active IDU and 30% were infected with HCV. Based on these data, it was estimated that 20.2% of the total infected population are active IDU while notification data show that 82.8% of those with incident HCV infection report a history of IDU.[24] Increased mortality among active IDU was estimated using a standard mortality ratio (SMR) of 10.0 for individuals between the 15 and 44 years of age.[25-30] A national study reported that 3.8% of the viraemic population was infected through transfusion.[20] An SMR of 1.5 was applied for all age groups in this population.[31]

Figure 2. Base case model outputs
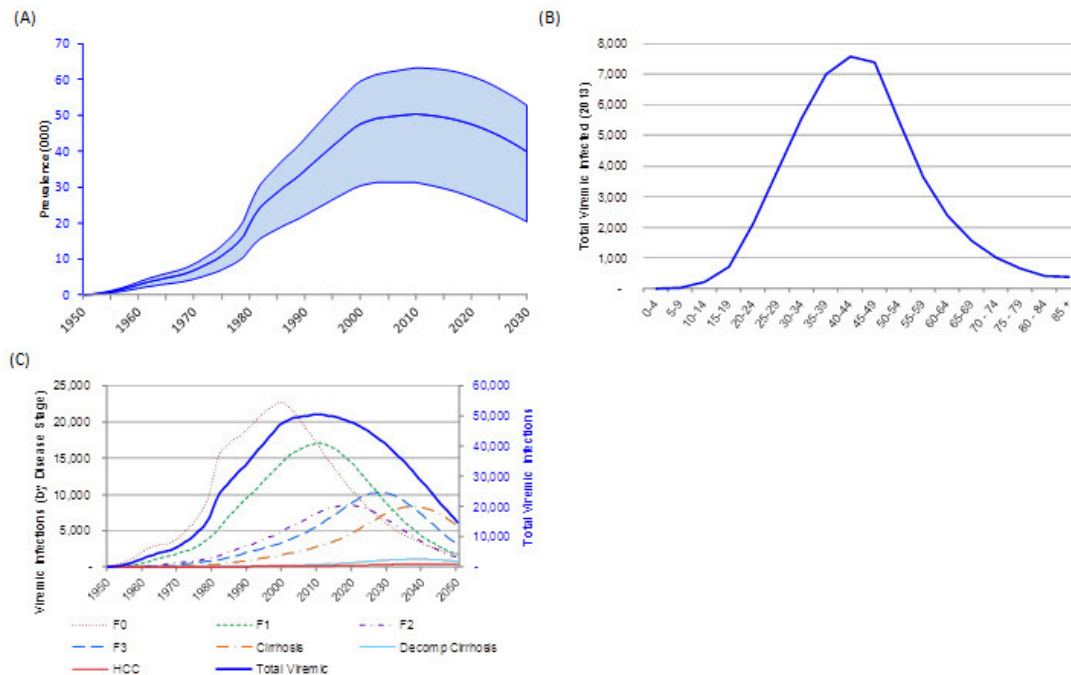
(A) Total viraemic cases, by year, 2013-2030; shaded areas represent interquartile range (B) Total viraemic cases, by age, 2013; (C) Number of viraemic cases, in total, and by disease stage, 1950-2030

Four model scenarios were explored

For the base case, it was assumed that all patients aged 15–59 years are considered for treatment with no restrictions based on fibrosis stage, and that 60% of potential patients in New Zealand were eligible and willing to complete treatment (Figure 3). It was also assumed that average SVR rates were 60% (G1), 80% (G2), 65% (G3) and 50% (G4). A treated population of 900 patients annually was modelled. It was further assumed that patients with decompensated cirrhosis, HCC, or transplant eligibility are not eligible for treatment until 2016.

- **Scenario 1: Increased SVR only**

  SVR and treatment eligibility rates gradually increased to 90% (all genotypes) by 2016. 2013 values for annual treated and newly diagnosed populations were held constant. Treatment restriction based on fibrosis stage (≥F3) was implemented during 2015-2017 in order to focus treatment on individuals with the most advanced liver disease. Beginning in 2018, fibrosis restrictions were removed (Figure 3).

- **Scenario 2: Increased SVR and increased annual treated population (Elimination Strategy)**

  This scenario included the same SVR and fibrosis restriction changes as Scenario 1. In addition, the annual number of treated patients was gradually increased to 4,040 by 2020. Beginning in 2016, treatment was expanded to include individuals up to 74 years old (Figure 3).

- **Scenario 3: Access to DAA therapy deferred for 1 year (Elimination [1-year delay] Strategy)**

  Scenario 2 was altered to estimate the impact of delaying access to new IFN-free DAA therapies to all patients, irrespective of stage of liver disease, for 1 year.
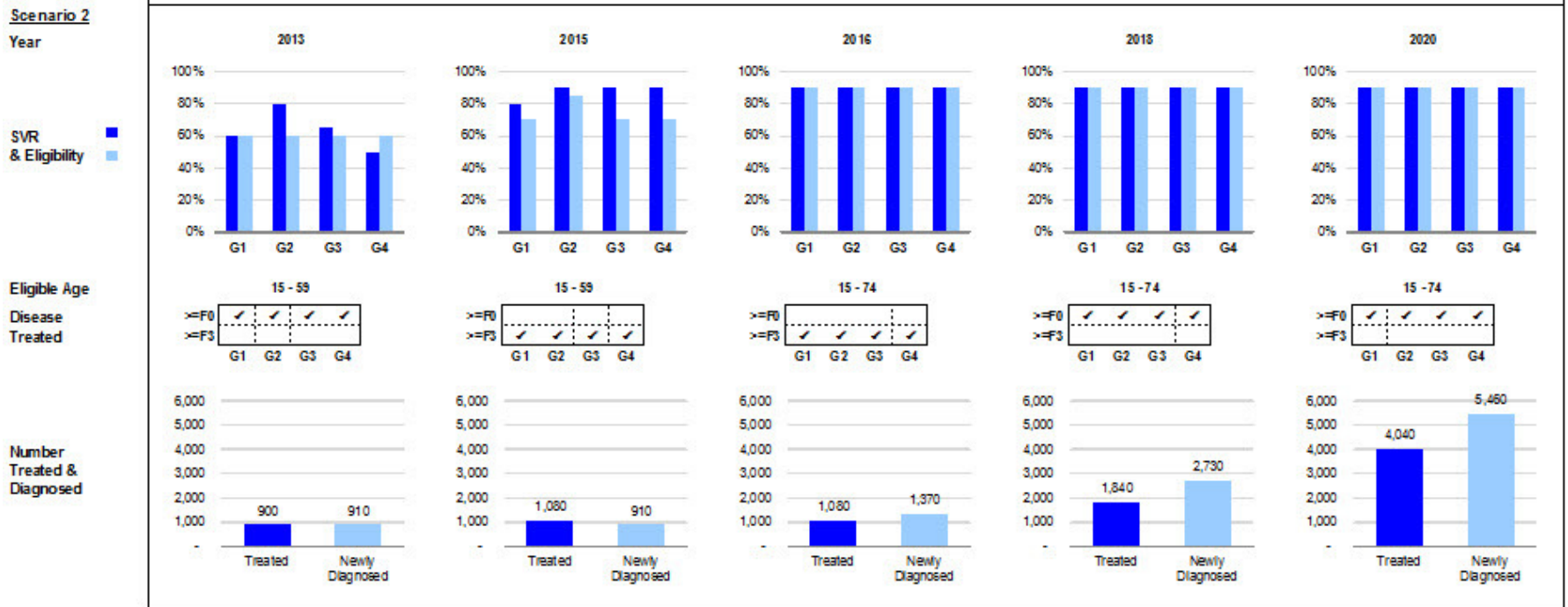
- **Scenario 4: Access to DAA therapy deferred for 2 years (Elimination [2-year delay] Strategy)**

  Scenario 2 was altered to estimate the impact of delaying access to new IFN-free DAA therapies to all patients, irrespective of stage of liver disease, for 1 year.

Figure 3. Model inputs for Base Case, Scenario 1 and Scenario 2

Fig 3, continued

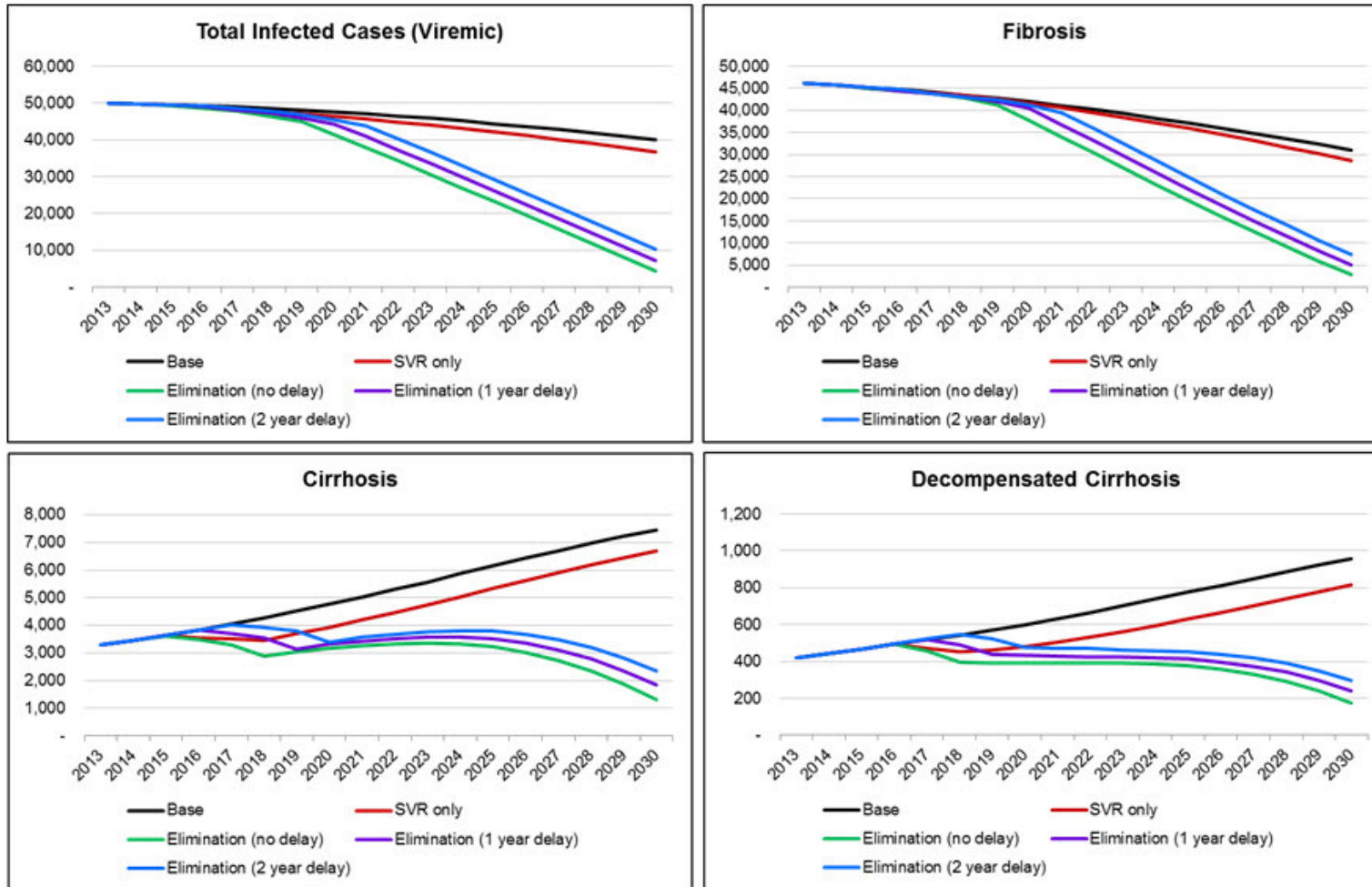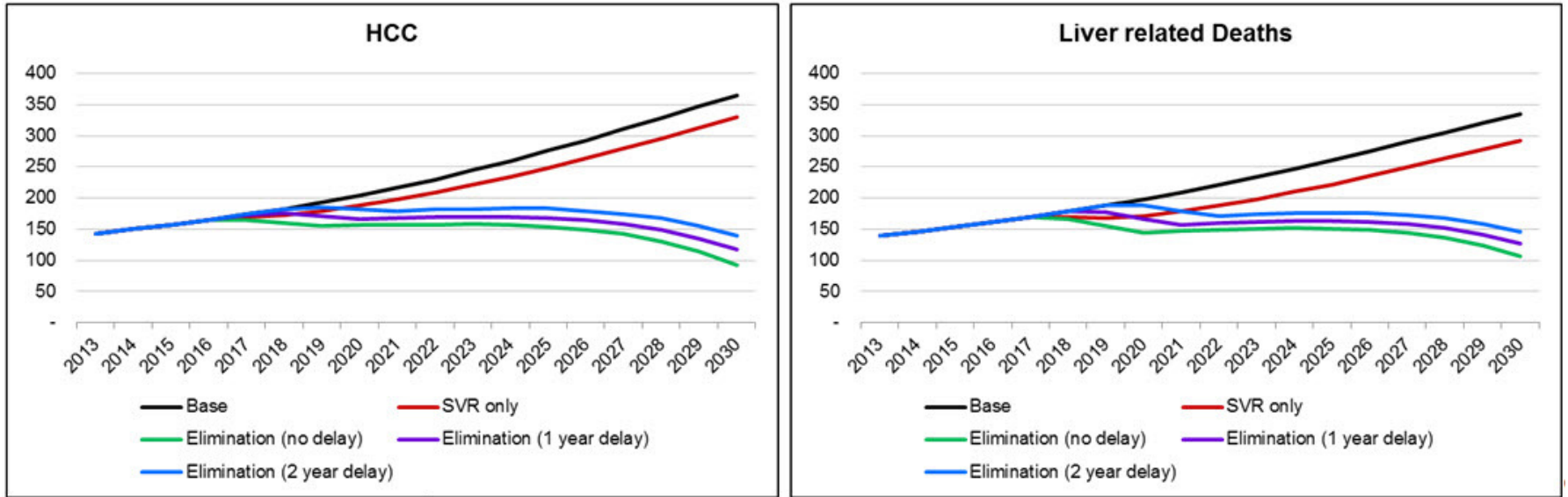**Figure 4. Morbidity and mortality by scenario—New Zealand, 2013–2030**

Fig 4, continued

Results

Base case

The base case estimated 50,000 (30,440–63,130) infected individuals in 2013 (Figure 2A); their median age was 42 years (Figure 2B). Prevalence peaked at 50,480 patients in 2010, and declined to 39,950 by 2030. This model predicted an estimated 340 HCV-related deaths in 2030 compared to 140 deaths in 2013 (Figure 4). In 2013, 8% of viraemic cases are estimated to have compensated cirrhosis or more advanced liver disease (decompensated cirrhosis, HCC, or transplant), while this proportion will increase to 21% in 2030.

Scenario 1: Increased SVR only (SVR Strategy)

In this scenario, cumulative HCV-related mortality during the years 2013-2030 decreased by 11% (440 deaths averted) compared to the base case (Figure 4). HCC cases in 2030 decreased by 10% (35 cases), and the number of patients progressing to decompensation decreased by 15% (144 cases). The total infected population declined by 3,262 (8%) by 2030, compared to the base case

Scenario 2: Increased SVR and increased annual treated population (Elimination Strategy)
In this scenario, cumulative HCV-related mortality during 2013-2030 decreased by 35% (1,387 deaths averted) compared with the base case (Figure 4). The number of HCC cases in 2030 decreased by 75% (272 cases) and the number of patients progressing to decompensation decreased by 82% (784 cases). The total infected population decreased by 89% (35,526 cases) by 2030 compared to the base case.

Scenario 3: Access to DAA therapy deferred for 1 year: Elimination (1-year delay) strategy

In this scenario, cumulative HCV-related mortality was increased by 7% (195 extra deaths, the total number of HCC cases in 2030 increased by 26% (24 additional cases) and the total number of patients progressing to decompensation increased by 37% (65 additional cases) compared to the number predicted if the Elimination strategy was introduced in 2014 (Figure 4).

With this 1-year delay scenario, the size of infected population was 7287 in 2030, an increase of 2889 (62% increase) compared to the number predicted if the Elimination strategy was introduced in 2014.

Scenario 4: Access to DAA therapy deferred for 2 years: Elimination (2-year delay) strategy

In this scenario, cumulative HCV-related mortality was increased by 14% (377 extra deaths), the total number of HCC cases in 2030 increased by 50% (47 additional cases), and the total number of patients progressing to decompensation increased by 72% (124 additional cases), compared with outcomes if the Elimination strategy had been introduced in 2014 (Figure 4).

In this 2-year delay scenario, the size of the infected population in 2030 was 10,182, which was an increase of 5784 (132%) compared to the infected population size if DAA therapy had been introduced in 2014.

Discussion

Although the HCV-infected population in New Zealand has probably been relatively stable since 2000, the numbers with cirrhosis have doubled over the last decade, because of an aging cohort effect and very low rate of treatment uptake. The numbers presenting with life-threatening complications of decompensation and liver cancer are projected to treble over the next two decades. However, end-stage liver disease in a patient with chronic HCV infection can be prevented or even reversed by eradicating HCV with antiviral therapy. On a population scale, improvement in both treatment uptake and treatment effectiveness, along with ongoing measures to prevent new infections (such as needle exchange services), should reduce the future health burden from the epidemic of HCV infection.

This study modelled the impact of four different scenarios most likely to reflect PHARMAC responses to the introduction of the new IFN-free, DAA regimens. In the first scenario, the

new DAA regimens with SVR rates >90% are made available, but due to high cost, their funding is limited to patients with more advanced liver disease. Consequently, in this scenario the total numbers of patients treated will be similar to current levels but cure rates will be almost double, resulting in a small but significant reduction in the projected increase in liver-related complications. However, with this approach, the HCV-related health burden from HCV and related costs will continue to increase for the next two decades.

In the second scenario, access to the new DAAs is widened to include all stages of liver disease. The availability of more effective, better tolerated therapy will drive a rapid increase in treatment uptake, because there will be no more IFN-ineligible patients (those with contraindications to, or intolerance of IFN). Given that only 1.8% of diagnosed patients are currently treated per annum, a four-fold increase in treatment numbers adopted for this scenario would seem attainable.

The capacity of current treatment services would be boosted by replacing the complex 48 week boceprevir-triple therapy with IFN and RBV-free DAA regimens of very short duration (maximum durations 8–12 weeks), without any need for on-treatment viral load or safety monitoring . However, such increases in treatment numbers will rapidly exhaust the relatively small numbers already diagnosed with HCV, so broadening of access criteria to include all stages of liver disease, and increased HCV diagnosis would also be necessary. The latter would be achievable through improved community awareness and targeted testing programmes, which the current Government-funded National Hepatitis C Action Plan could address.

Finally, we included two additional scenarios in the model to estimate the impact of delaying funding the new DAA therapies for all patients, including cirrhotics, for either 1 or 2 years. These scenarios would reflect a potential PHARMAC decision to wait until there is increased competition from multiple manufacturers of new DAA therapies, which could drive down costs of treatment. However, such a strategy would come at a real human cost, resulting in an additional 377 preventable deaths.

This study estimated that immediate funding of IFN-free, DAA regimens for patients with established HCV cirrhosis would significantly reduce the life-threatening complications of hepatic decompensation and hepatocellular carcinoma, thereby dramatically reducing both liver-related mortality and demand for liver transplantation in New Zealand within the next decade. Widening of access to include all patients with all fibrosis stages could eliminate chronic HCV infection in this country within the next 20 years.

There are a number of limitations with this study. The lack of recent studies quantifying the total HCV-infected population in New Zealand means that our estimates are based on largely historical prevalence studies and expert opinion rather than large community-based seroprevalence studies. In addition, rates of SVR for current and future treatment protocols were based on clinical data from registration studies from centres experienced in treating patients and managing adverse events. SVR rates with DAAs in the real world could be lower than those published in journals if non-adherence is a significant occurrence outside the strict supervision provided during clinical trials.[32] There is variance in HCV prevalence estimates and the relative impact of each scenario may be more or less pronounced if true prevalence is higher or lower than the estimated values.[15]

Another limitation of this study is that modelled increases in treatment rate, diagnosis rate, eligibility and SVR were all assumed to take effect immediately. Adoption of new therapies

and strategies at the national level is more likely to take several years as new treatment guidelines are developed and as PHARMAC funding decisions are made. However, analyses examining the impact of accelerating or delaying increases in SVR or treatment consistently demonstrated that the desired outcomes were more likely to be achieved when the strategies were implemented earlier.

A final limitation is that disease progression was no longer followed when patients were cured. Among cured patients, risks for advanced liver disease and related mortality can remain, but at markedly lower rates.[33] Therefore, the model could overestimate the impact of curing patients on total HCV liver-related morbidity and mortality. Any underestimation is likely to be minimal as most reduction in HCV morbidity and mortality came from prevention of HCV progression in earlier disease stages where progression to more advanced liver disease is unlikely.

In conclusion, although the number of HCV infections in New Zealand is expected to decline over the next 15 years, HCV-related morbidity and mortality from cirrhosis and its complications will increase steadily. Reducing future HCV disease burden is possible with a two-pronged effort, through increased detection of undiagnosed New Zealanders living with HCV and increased treatment uptake, with new DAA regimens. Immediate funding of IFN-free, DAA regimens for patients with established HCV cirrhosis would dramatically reduce both liver-related mortality and the demand for liver transplantation in this country within a decade.

When combined with widening of access to treatment to include all patients, regardless of fibrosis stage, ongoing prevention efforts, targeted testing and treatment programmes in populations at high risk of infection, such as people who inject drugs and prisoners (so-called "treatment as prevention" strategy), these DAA regimens could eventually eliminate HCV infection in New Zealand within our lifetime.[34]

Competing interests: Nil.

Author information: Edward Gane, Professor of Medicine, University of Auckland, Auckland, NZ; Catherine Stedman Associate Professor of Medicine, University of Otago, Christchurch, NZ; Cheryl Brunton, Public Health Physician, University of Otago, Christchurch, NZ; Sarah Radke, Epidemiologist, Institute of Environmental Science and Research, Wallaceville, NZ; Charles Henderson, National Manager, New Zealand Needle Exchange Programme, Christchurch, NZ; Chris Estes, Center for Disease Analysis, Louisville, Colorado, USA; Homie Razavi, Center for Disease Analysis, Louisville, Colorado, USA

Correspondence: Professor Edward Gane, New Zealand Liver Transplant Unit, 15th Floor Support Building, Auckland City Hospital, Grafton, Auckland, New Zealand. edgane@adhb.govt.nz

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