

ANALYSIS OF HEPATITIS C VIRUS (HCV) EPIDEMIOLOGY AMONG YOUNG  
PRESCRIPTION OPIOD USERS IN RHODE ISLAND, AND MODELLING OF HCV  
TREATMENT SCALE-UP.

By

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Thesis

Submitted in partial fulfillment of the requirements for the degree of Master of Science in  
the Department of Epidemiology in the School of Public Health at  
Brown University

PROVIDENCE, RHODE ISLAND

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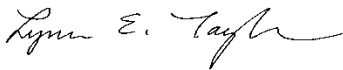
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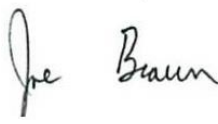
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- **Soipe, A.I.**, Taylor, L.E., Abioye, A.I., Green, T.C., Hadland, S.E., Marshall, B.D.L. Prevalence of hepatitis C screening, testing, and care experience among young adults who use prescription opioids non-medically in Rhode Island. *Submitted, In Review 2017.*
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- Abioye A.I, **Soipe A.I.**, Salako A.A, Odesanya M.O, Okuneye T.A, Abioye A.I, Ismail K.A, Omotayo M.O. Are there differences in disease progression and mortality among male and female HIV patients on antiretroviral therapy? A meta-analysis of observational cohorts. *AIDS Care.* 2015, Dec; 27(2): 1468-1486. *Cited in PubMed; PMID: 26695132.*
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- Oshikoya, K.A., Senbanjo, I.O., & **Soipe, A.I.** Ability of medical students to calculate drug doses in children after their pediatric attachment. *Pharmacy practice.* 2008, Dec; 6(4): 191 - 196. *Cited in PubMed; PMID: 25157293.*
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## STATEMENT ON CONTRIBUTION TO PUBLISHED WORK

Ayorinde Soipe interpreted the analysis output of published works, wrote the first draft of the manuscripts, updated the manuscripts with co-authors' comments, and responded to reviewers' comments during review by journals.

Hepatitis C virus (HCV) infection leads to a number of clinical conditions including acute hepatitis, chronic hepatitis, cirrhosis of the liver, and liver cancer (1). HCV belongs to the *Hepacivirus* genus of viruses, under a family of viruses known as *Flaviviridae* (2). Six distinct HCV genotypes are presently identified: genotypes 1 to 6. Genotype 1 is the most prevalent worldwide, accounting for 46.2% of all HCV cases globally, while genotype 3 accounts for 30.1% of all HCV cases globally (3). The largest proportions of genotypes 4 and 5 have been mapped to low-income countries (3). In the United States (US), approximately 70% of chronic HCV infections are caused by genotype 1, 15 to 20% by genotype 2, 10 to 12% genotype 3, 1% genotype 4, and less than 1% genotype 5 or 6 (4).

The replicative process of the virus occurs in the cytosol of the host liver cell. Upon successful replication and release into the bloodstream, the virus is most commonly spread through percutaneous exposure to infectious blood, for example through sharing of unsterilized infected needles (5). In addition to parenteral means, sexual mode of HCV transmission has been documented to occur primarily in HIV co-infected men who have sex with men (6, 7). Data from under-resourced countries indicate iatrogenic cause as a common means of HCV transmission in such settings (8).

The incidence of both acute and chronic HCV infection rose dramatically in the US through the 1970s and 1980s, and chronic HCV prevalence is particularly high among individuals born between 1945 and 1965 popularly described as the “baby boomers” (9, 10). Persons born between this time period account for approximately 75% of all HCV infections in the US (10). The morbidity and mortality attributed to HCV infection have also been significantly higher among this demographic (11). The disproportionately high burden of chronic HCV infection among “baby boomers” has been suggested to result from infections acquired between the 1960s and 1980s,

following the use of medical equipment or procedures before universal precautions and infection control procedures were adopted (12). Instances of transfusing HCV-infected blood to patients prior to the introduction of mandatory screening of blood for HCV in 1992 also played an additional role in the spread of the infection to other population demographics (13).

Beginning in the early 2000's, a bimodal age distribution in the prevalence of HCV infection began to appear in the US (14). A newer HCV-infected cohort has since been described, which mainly comprised of young persons who inject drugs (PWIDs). The evolving demographic led to a re-emergence of incident HCV infection epidemic in several US regions (15). The rapid increase in new HCV infections among PWIDs has been attributed to the ongoing opioid crisis across the US (16). A significant number of acute HCV infection acquisition among young drug users was fueled by this nationwide opioid crisis. This cohort of HCV-infected persons has attracted public health attention because injection drug use and syringe sharing behavior increase the risk of HCV transmission among young adult drug users (17), thus perpetuating the spread of the infection.

As concerns continue to grow regarding the need to curb further spread of HCV infection among PWIDs, numerous studies have shown the effectiveness of HCV treatment as a viable means for HCV prevention among PWIDs (18). Therefore, early testing and treatment of HCV ought to be encouraged because early detection and treatment of HCV among young persons will reduce HCV transmission to other young individuals (19, 20).

Up until a few years ago, the treatment regimen for HCV was mainly based on the use of two medications: pegylated interferon and ribavirin (21). These medications have been associated with severe side effects including hematological, systemic, and psychiatric adverse effects (22, 23). However, there have been advances in terms of medications available to treat HCV with the

approval of direct acting antivirals (DAAs) by the Food and Drug Administration. A major milestone was the approval of the first DAA to be used without interferon in December 2013 (24). DAAs achieve high sustained viral response (SVR) rates in persons with HCV infection (25). SVR is achieved when there are undetectable HCV-RNA at the end of therapy and this describes a state of HCV cure (26). In addition, DAAs facilitate shorter treatment duration thus lowering cost per cure (27). By extension, the treatment effects achieved by DAAs reduce the risk for hepatocellular carcinoma, liver-related mortality, and overall mortality (28). The antiviral activity of these agents is via the inhibition of vital enzymes involved in the replicative process of the virus (29).

DAAs have varying levels of antiviral activity against HCV genotypes. Patients infected with HCV genotype 3 are the least responsive to both DAAs and the older HCV treatment regimen (30, 31). The pan-genomic properties of the newer DAAs however, allow for simpler, shorter, less toxic, and broad treatment of HCV genotypes (25). Despite the scientific breakthrough in HCV treatment, several barriers limit access to the novel medications, thereby hindering efforts to achieve cure. These barriers can be categorized as patient-level barriers (for example poor knowledge and inaccurate perceptions about HCV), system-level barriers (for example limited reimbursements available to HCV care providers), and provider-level barriers (for example lack of provider knowledge of prescribing HCV treatment) (32-34).

In sum, the burden of HCV infection has attracted much attention on a national and global level. More people in the U.S. are now dying of HCV than all other top 60 infectious diseases combined (35). This observation underscores the need to aspire towards attaining a scenario where HCV infection spread is substantially curbed, and the virus eventually eliminated. To tackle the re-emerging HCV epidemic partly fueled by the nationwide prescription opioid crisis, it is

important to find, evaluate, and treat HCV-infected PWIDs. Treating PWIDs in the early stages of liver disease is effective and saves cost (36).

To this end, this thesis is a two-part analysis of HCV epidemiology in Rhode Island. The first examines HCV testing and care experience among young adults who use prescription opioids non-medically, amidst the current opioid and overdose crisis in Rhode Island. It describes the prevalence of HCV screening, confirmatory testing, and referral to care among young adults who use prescription opioids non-medically. The second part of this thesis presents strategies that can be employed in preventing further spread of the disease and eventually eliminating the disease in Rhode Island. A mathematical modeling approach was used to describe the amount of scale up in HCV treatment needed to achieve a substantial reduction in the burden of chronic HCV infection. Both studies underscore the fact that, with the discovery of highly effective anti-HCV medications, it is possible to achieve HCV elimination by instituting policy changes targeted at the barriers limiting access to the medications.

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# **Prevalence of hepatitis C screening, testing, and care experiences among young adults who use prescription opioids non-medically in Rhode Island.**

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## ABSTRACT

**Background:** Even though young adult non-medical prescription opioid (NMPO) users are at high risk of injection drug use initiation and subsequent hepatitis C virus (HCV) seroconversion, HCV screening, confirmatory testing, and care experiences are understudied among this population. We sought to examine the prevalence of self-reported HCV screening, testing, and care experience among young adult NMPO users in Rhode Island.

**Methods:** Two hundred young adults, aged 18-29 years, with NMPO use history in the past 30 days were recruited into The Rhode Island Young Adult Prescription Drug Study (RAPiDS), conducted between January 2015 and February 2016. An interviewer-administered questionnaire was used to collect information on sociodemographic factors, drug use patterns, sexual activity, family environment, and mental health. The outcomes of interest were self-reported histories of HCV screening, confirmatory testing, and HCV care. Bivariate associations were examined with Pearson  $\chi^2$  test, and modified Poisson regression models were constructed for multivariable analyses.

**Results:** Among 196 eligible participants, the mean age was 24.5 years (SD=3.2), and 67.7% (n=130) were male. Over three in four (n=154, 78.6%) had previously screened for HCV. Of these participants, 18 (11.7%) reported receiving a positive screening test result. Among participants who had positive screening test, 13 (72.2%) reported receiving confirmatory blood tests, two-thirds (n=12, 66.7%) were referred for specialty hepatitis care, half (n=9, 50%) reported receiving education about living with hepatitis, and only 3 (16.7%) reported being told by a doctor that they no longer had HCV. In multivariable models, a history of HCV screening was positively associated with injection drug use (adjusted prevalence ratio (APR): 1.19; 95% confidence interval (C.I): 1.05 – 1.33) and history of hospitalization for psychiatric illness (APR: 1.23; 95% C.I: 1.09 –

1.39). Younger participants (18-23 years) were less likely to have been screened (APR: 0.69; 95% C.I: 0.57-0.85).

**Discussion:** Although 3 in 4 young adults who use prescription opioids non-medically had been screened for hepatitis C, post-screening diagnostic testing, support, and referral to care were inadequate. Establishing case management programs for HCV positive young adult drug users is recommended to improve follow-up care.

**Keywords:** hepatitis C virus; non-medical prescription opioid use; testing; referral; linkage to care; follow-up; young adult

## 1. INTRODUCTION

The majority of persons chronically infected with hepatitis C virus (HCV) come from a cohort born between 1945 and 1965, popularly described as “baby boomers” (1). As this population ages, deaths due to HCV in the United States (US) have surpassed deaths due to all top 60 infectious diseases combined (2). Furthermore, the number of HCV-associated liver diseases has been on the rise in the US and in other jurisdictions, and this trend is projected to continue (3-7).

Despite these trends, young people who use drugs represent an increasing fraction of the overall HCV-infected population (8). This changing demographic has led to a re-emerging epidemic of incident HCV infection (9-11). Prior to 2005, the overall incidence of acute hepatitis C continued to drop across the US (12). This pattern was reversed, notably between 2010 and 2014, reflecting significant increases in the number of incident HCV infections (12), particularly among young people (13).

Further, studies have reported increases in new HCV infections specifically among individuals who are less than 30 years old (8, 13, 14). For example, in Wisconsin and Massachusetts, though the rate of overall newly reported HCV infection cases continued to drop prior to 2007, this trend was reversed by 2010 and 2011 respectively (15, 16). In addition, newly reported and confirmed cases of HCV infection increased significantly in the 15-24 year age group (17, 18). Similarly, other national studies have reported increases in the incidence of acute hepatitis C infection occurring among young individuals between 2006 and 2012 (19). Furthermore, recent studies have projected a rise in HCV infection among young adults (17, 20).

With the changing epidemiology of HCV infection, the role of illicit drug use in HCV infection transmission among young adults has become an issue of public health concern. Most

concerning is the role of non-medical prescription opioid (NMPO) use, and more importantly, opioid injection which is widespread across the US (8). NMPO use has been shown to drive transitions to injection drug use and syringe sharing behavior (21, 22), which in turn increases the risk of HCV transmission among young adult drug users. In a report, 75% of acute hepatitis C infection reported among young individuals involved persons who inject drugs (PWIDs), and 75% of the PWIDs abused prescription opioids(19).

Unfortunately, despite these trends, HCV testing and care among young adult drug users are low (23-25). Access to HCV testing and treatment are commonly hindered by barriers including psychiatric illness, discrimination from healthcare personnel, economic barriers, lack of health insurance, and limited knowledge about HCV (24, 26-30). Testing for HCV among this population should be encouraged because early detection and treatment of HCV among young persons will reduce HCV transmission to other young individuals. Specifically, studies have shown the effectiveness of HCV treatment as a viable means for HCV prevention among PWIDs (31-33).

Previous studies have shown HCV treatment to be feasible and effective in people who use drugs (34-36). However, only a few studies have examined HCV care experiences among young adult NMPO users. In this study, we examined the prevalence of self-reported HCV screening, testing, and HCV care experiences, among young adults who use prescription opioids non-medically in Rhode Island.

## **2. METHODS**

### **2.1 Study population and design**

The Rhode Island Young Adults Prescription Drug Study (RAPiDS) recruited young adults NMPO users (aged 18 to 29 years). Participant's age was verified with government issued ID. The study design and population have been described elsewhere (30, 37). In brief, using a cross-sectional design, young drug users who had used opioids non-medically within 30 days prior to interview were recruited between January 2015 and February 2016. NMPO use was defined as intentional use as not directed by a licensed medical provider (38). To confirm recent NMPO use, participants were shown a card containing pictures of prescription opioids (the Substance Abuse and Mental Health Services Administration's [SAMHSA's] "pill card a"). Other eligibility criteria for this study included the ability to speak and write English, ability to provide informed consent, and ability to prove Rhode Island residency.

### **2.2 Sample recruitment and procedures**

Recruitment and survey administration occurred in two stages. First, potentially eligible participants e-mailed or called a toll-free study hotline, at which point the study coordinator reviewed eligibility criteria. If eligible, the study coordinator scheduled an interview in a public location (e.g., library, community center) chosen by the participant, or at Brown University's Survey Research Center. Each participant received \$25 to compensate for his or her time. The study was approved by the Institutional Review Board of Brown University.

Prior to questionnaire administration, trained interviewers reviewed the purpose of the study with the participants and conducted consenting procedures. The questionnaire included sections on sociodemographic factors, housing, employment and income, pain, drug use (including injection drug use), the family environment (including questions about growing up experience), mental health, health care access and treatment, and overdose.

For this study, we excluded 4 (2.0%) persons of the 200 RAPIDS participants who did not respond to the primary outcome of interest (i.e., self-reported history of HCV screening), leaving an eligible sample of  $n=196$ .

## **2.3 Measures**

We assessed the prevalence of HCV screening, testing, and HCV care experiences, and also obtained information on HCV testing barriers and HCV risk behaviors. The primary outcome for this analysis was, “Have you ever been tested for hepatitis C?” (yes vs. no). Sociodemographic factors considered in the analysis include age (categorized as 18 – 23 years vs 24 – 29 years), and sex at birth (male vs female). Age distribution of the respondents was dichotomized as  $<24$  years vs  $\geq 24$  years based on similar categorization employed in previous studies in young drug users (17, 39). Barriers to testing that were studied included health insurance status, an experience of discrimination from the healthcare community, comorbid psychiatric illness including depression, and access to drug addiction treatment services (29). Specifically, barriers to testing were assessed by asking the questions “Have you felt discriminated against by the medical community?”, “Have you ever been hospitalized for a mental illness or depression?”, “Have you ever tried to enroll in a drug treatment program but were unable to?”, and “Do you currently have health insurance?”

(all response options yes vs no). The following questions were used to assess HCV risk behaviors: “Have you ever used a needle to chip, fix, muscle, or inject drugs even once?”, “Have you ever snorted or sniffed any of the drugs on card A?” (referring to a card containing photographs of prescription opioids), and “Have you ever been homeless?” (all response options yes vs no).

Among participants who were screened for HCV and reported a positive test history, the proportion who reported cure was assessed by asking “Have you since been told by a doctor that you no longer have hepatitis C?” (yes vs no). Also, we assessed support services and care offered to participants reporting positive screening tests by asking “When you tested positive for hepatitis C, what support or resources were offered to you?” (respondents checked all that apply). The knowledge level of participants with positive test history as it relates to living with HCV infection, and protecting others from the infection was assessed by asking respondents to choose how much they agree or disagree with the questions: “I know how to stay healthy while living with hepatitis C” and “I know how to protect others from getting hepatitis C” (responses categorized as agree vs. disagree).

## **2.4 Statistical analysis**

Means and standard deviations were calculated for normally distributed continuous variables, while medians and interquartile ranges were calculated for non-normal continuous measures. Bivariable associations between a prior history of HCV screening and participant characteristics, barriers to testing, as well as HCV risk behaviors, were examined using Pearson’s  $\chi^2$  test, and Fisher’s exact test for cell counts  $<5$ .

Thereafter, modified Poisson regression was used to determine the independent correlates of prior HCV screening. This modeling approach was utilized to obtain prevalence ratios for the relatively common primary outcome of interest. Variables with  $p \leq 0.20$  from bivariable analysis were included in the initial multivariable model (40), and the model was subsequently reduced using a backward selection procedure based on the quasi information criterion (QIC; model 1). To achieve a more parsimonious model, only variables that attained statistical significance at the 0.05 significance level were retained in the final model (model 2). To prevent over-fitting the model, collinearity between explanatory variables was assessed using phi correlation procedure. Prevalence ratios and confidence intervals were obtained for the models. Statistical analysis was done using SAS software version 9.4 (SAS Institute, Cary, NC), and all  $p$ -values are two-sided.

### **3. RESULTS**

Among the eligible analytic sample of  $n=196$ , the mean age was 24.5 years ( $SD=3.2$ ), and 130 (67.7%) were male (see Table 1). Among eligible participants, 154 (78.6%) reported ever being screened for HCV. HCV screening history differed by age group, with a higher proportion of respondents 24-29 years reporting being screened (89.5%) compared to those under age 24 (59.7%). Other participant characteristics associated with HCV screening included a history of been hospitalized for psychiatric illness, homelessness history, history of snorting drugs, and history of injecting drugs (all  $p<0.05$ , see Table 1).

Of the 154 who reported screening for HCV, 18 (11.7%) participants reported receiving a positive test result. Among all 18, support services offered to participants after testing positive for HCV included: follow-up confirmatory blood test ( $n=13$ , 72.2%), referral for specialty hepatitis

care (n=12, 66.7%), education about living with hepatitis (n=9, 50%), education about how not to transmit hepatitis C to someone else (n=10, 55.6%), and referral to a support group (n=3, 16.7%). Only 3 (16.7%) reported having been told by their doctor that they had been cured of HCV. All participants who reported positive HCV screening test agreed to know how to protect others from acquiring HCV, while 16 (88.9%) agreed to know how to stay healthy while living with HCV.

In the multivariate analysis, two models were built to determine the independent correlates of prior HCV screening: model 1 was the model with the lowest QIC, while the most parsimonious model (model 2) was derived from model 1 after backward selection procedure to include only variables that attained statistical significance at a 0.05 significance level. In model 1, age group 18-23 years (adjusted prevalence ratio (APR)=0.72; 95% confidence interval (CI)=0.59-0.87) and history of discrimination from the medical community (APR=0.94; 95% CI=0.81-1.09) were associated with reduced likelihood of HCV screening. History of snorting drugs, history of injecting drugs, homelessness history, and history of difficulty accessing addiction treatment were also correlated with an increased likelihood of prior HCV screening, although associations were marginally significant (see table 2). In the final model (model 2), age group 18-23 years (APR=0.69; 95% CI=0.57-0.85), history of injecting drugs (APR=1.19; 95% CI=1.05-1.33), and history of ever being hospitalized for psychiatric illness (APR=1.23; 95% CI=1.09-1.39) were all significantly associated with HCV screening.

#### 4. DISCUSSION

This study examined the prevalence of self-reported HCV screening, testing, and care experiences among young adults who use prescription opioids non-medically in Rhode Island. The prevalence of prior HCV screening was moderately high within this cohort (reported by 3 in 4 participants); however, among those who reported receiving a positive result, post-screening diagnostic testing and referral to care were infrequent. Less than 18% of those with positive screening test further reported having been told by a physician that they had been cured of HCV. In addition, even though over 90% of participants who had ever injected drugs had been tested for HCV, approximately 1 in 3 participants with a positive HCV screening test were not referred to care. This is similar to reports in the literature showing that most individuals with HCV do not receive the care they need (41-43).

Collectively, these findings reveal gaps in current follow-up strategies for HCV management in young adults who screen positive, and indicate sub-optimal referral to HCV care for young people who use prescription opioids non-medically. In the face of changing HCV infection epidemiology, coupled with the pressing need to impact the future disease burden associated with chronic HCV infection, it is essential to refer and link young drug users who are HCV positive to care. Linkage to care and improved follow-up among young persons will reduce HCV transmission to other young individuals (44-46). Establishing case management programs focusing on HCV-positive young adults and involving trained case managers may improve referral and linkage to care, while also ensuring adequate supervision of patient follow-up. Similar approaches have utilized trained medical assistants and patient navigators to achieve optimal linkage to care (29, 47, 48). A case management approach may be most prudent since it would utilize an existing framework to screen and refer patients, after which case managers will maintain

follow-up. After successfully referring and linking patients to care, improvements in treatment uptake may be achieved by establishing youth-friendly programs in community and clinic-based settings (11, 49).

It is worthwhile to note that certain participant factors were associated with reduced HCV screening prevalence in this cohort. For example, screening was less common among participants who were between ages 18 – 23 years. This finding is concerning because previous studies have shown recent increases in HCV infection incidence within this age group (11, 17). Strategies may be needed to encourage young individuals to receive HCV screening and testing early in the course of illicit drug use.

Factors including a history of injecting drugs, homelessness, and history of hospitalization for psychiatric illness including depression were associated with higher prevalence of HCV screening within this cohort. During recruitment, some study participants were recruited from Rhode Island's needle exchange program (i.e., the Education, Needle exchange, Counseling, Outreach, and Referral [ENCORE] program), which offers free HCV testing to clients (50). The existence of HCV screening at the ENCORE program may account for the high prevalence of screening among persons with a history of injection drug use in this sample. Further, the state of Rhode Island has initiated community-based HCV testing programs for underserved populations, including the homeless and those living in correctional institutions (51). These programs provide high-risk clients with HCV testing services. In addition, various organizations (e.g., Rhode Island Defeats Hep C) are partnering with state authorities in expanding HCV testing capacity across the state (51). Therefore, the high prevalence of screening among those with a history of homelessness may likely be the result of these enhanced screening efforts. Alternatively, homelessness and mental illness are established risk factors for HCV infection among individuals at high risk (52-

54); as such it is possible that healthcare staff are more proactive in screening study participants with any of these characteristics in different settings.

With the changing demographic of HCV infection (55), findings from this study suggest the need for improvements in post-screening follow-up efforts, so that the impending public health crisis from untreated HCV infection among young drug users can be minimized. In this study, only two-thirds of participants with positive HCV screening test history reported having been referred for specialized hepatitis care, thus indicating that 100% referral and linkage to care was not achieved. An important task will be to strengthen existing programs which provide services of referring and linking HCV positive individuals to hepatitis care. Such renewed efforts will ensure adequate care and possibly complete cure. With the advent of highly effective anti-HCV medications, the need for prolonged follow-up after treatment initiation is eliminated and sustained viral response (SVR) rates are very high (56-58). The enactment of public health policies geared towards early detection, treatment, and follow-up can ultimately help eliminate the disease. One recent study demonstrated that eliminating HCV is possible in Rhode Island with a substantial increase in the number of patients screened and treated (59). Measures aimed at mitigating barriers to accessing HCV treatment (such as increasing system and provider-level access, as well as making clinical programs more youth-friendly) should be implemented. In addition, with over 85% of study participants reporting access to health insurance, it will be most beneficial to strengthen the program currently providing such high insurance coverage for young adults.

This study has some important limitations. First, given that this is a cross-sectional study, the strength of causal inference is limited. Further, the modest sample size in the study increases the likelihood of low statistical power to detect truly significant associations. Second, field-based recruitment occurred at multiple sites, including at needle exchange programs with HCV testing

capability. This could be the reason for the high HCV screening response in the cohort, and thus selection bias is possible in the recruitment of participants. As such, the results may not be generalizable to settings with more limited HCV testing services for people who inject drugs.

Third, it is assumed that participants reporting “yes” to screening implied having been screened using HCV antibody testing, while those who reported having confirmatory diagnostic testing implied having had follow-up test using HCV RNA to identify viremia and infection. This is a reasonable assumption since screening via HCV antibody is the first test in the cascade of HCV management. Information on post-screening support services, including confirmatory testing offered to respondents was specifically sought in the survey.

Fourth, some risk behaviors for HCV infection were not sampled in the study (e.g., history of body piercing and tattooing). However, the study questionnaire did cover risk factors that were pertinent to opioid use, and these are factors that pose a high risk for HCV infection (e.g., snorting opioids and injection drug use). Fifth, self-reported responses were subject to potential biases associated with the sensitive nature of illegal drug use (e.g., social desirability bias). To this end, the veracity of self-reported data in this study cannot be ascertained. Self-reported data have however been successfully utilized in previous studies on illegal drug use, and validation studies have reported on their accuracy (60). Furthermore, by showing the Substance Abuse and Mental Health Services Administration’s (SAMHSA’s) “pill card a”, information obtained from the respondents was subject to less recall bias since there was visual stimulation of recall. In addition, computers situated in secluded locations (to provide privacy) were used to capture responses that were deemed to be sensitive. Respondents were assured of the absolute confidentiality of all interactions with the research team.

## 5. CONCLUSION

In sum, the prevalence of screening for HCV was high among young adults who use prescription opioids in Rhode Island, even though post-screening diagnostic testing, support, and referral to care were inadequate. With the changing demographic of HCV infection, establishing comprehensive integrated care programs which incorporate peer support, counselors, case managers, and educators is recommended to improve follow-up care (48). These are important steps in tackling the re-emerging HCV epidemic, partly fueled by the nationwide prescription opioid crisis. Such efforts will contribute to ameliorating the future burden of the HCV epidemic among young people who use drugs.

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Table 1: Sociodemographic factors, risk behaviors, and barriers to HCV screening among the Rhode Island Young Adult Prescription Drug Study [January 2015-February 2016] stratified by HCV screening history.

| Characteristics                                              | Total (%)<br>(N=196) | HCV screening history |                       | p value |
|--------------------------------------------------------------|----------------------|-----------------------|-----------------------|---------|
|                                                              |                      | Screened<br>n (%)     | Not screened<br>n (%) |         |
| Age (years)                                                  |                      |                       |                       | <0.001  |
| 18-23                                                        | 72 (36.7)            | 43 (59.7)             | 29 (40.3)             |         |
| 24-29                                                        | 124 (63.3)           | 111 (89.5)            | 13 (10.5)             |         |
| Sex at birth                                                 |                      |                       |                       | 0.399   |
| Male                                                         | 130 (67.7)           | 100 (76.9)            | 30 (23.1)             |         |
| Female                                                       | 62 (32.3)            | 51 (82.3)             | 11 (17.7)             |         |
| Ever snorted drugs                                           |                      |                       |                       | <0.001  |
| Yes                                                          | 116 (59.8)           | 101 (87.1)            | 15 (12.9)             |         |
| No                                                           | 78 (40.2)            | 51 (65.4)             | 27 (34.6)             |         |
| Ever injected drugs                                          |                      |                       |                       | <0.001  |
| Yes                                                          | 59 (30.3)            | 56 (94.9)             | 3 (5.1)               |         |
| No                                                           | 136 (69.7)           | 97 (71.3)             | 39 (28.7)             |         |
| Ever been homeless                                           |                      |                       |                       | <0.001  |
| Yes                                                          | 109 (55.6)           | 96 (88.1)             | 13 (11.9)             |         |
| No                                                           | 87 (44.4)            | 58 (66.7)             | 29 (33.3)             |         |
| Ever been hospitalized for psychiatric illness or depression |                      |                       |                       | 0.003   |
| Yes                                                          | 65 (33.2)            | 59 (90.8)             | 6 (9.2)               |         |
| No                                                           | 131 (66.8)           | 95 (72.5)             | 36 (27.5)             |         |
| Health insurance access                                      |                      |                       |                       | 0.391   |
| Yes                                                          | 171 (87.2)           | 136 (79.5)            | 35 (20.5)             |         |
| No                                                           | 25 (12.8)            | 18 (72.0)             | 7 (28.0)              |         |
| Discrimination from medical community                        |                      |                       |                       | 0.078   |
| Yes                                                          | 59 (30.1)            | 51 (86.4)             | 8 (13.6)              |         |
| No                                                           | 137 (69.9)           | 103 (75.2)            | 34 (24.8)             |         |
| Unable to access addiction treatment program                 |                      |                       |                       | 0.019   |
| Yes                                                          | 39 (19.9)            | 36 (92.3)             | 3 (7.7)               |         |
| No                                                           | 157 (80.1)           | 118 (75.2)            | 39 (24.8)             |         |

Due to “don’t know / no response”, sample size may be less than 196.

Table 2: Modified Poisson regression models of HCV screening history and covariates, in the Rhode Island Young Adult Prescription Drug Study cohort [January 2015-February 2016].

| Characteristic                                               | Model 1          | Model 2          |
|--------------------------------------------------------------|------------------|------------------|
|                                                              | APR (95% C.I)    | APR (95% C.I)    |
| Age (years)                                                  |                  |                  |
| 18-23                                                        | 0.72 (0.59-0.87) | 0.69 (0.57-0.85) |
| 24-29                                                        | Ref              | Ref              |
| Ever snorted drugs                                           |                  |                  |
| Yes                                                          | 1.13 (0.94-1.36) | -                |
| No                                                           | Ref              | -                |
| Ever injected drugs                                          |                  |                  |
| Yes                                                          | 1.11 (0.97-1.28) | 1.19 (1.05-1.33) |
| No                                                           | Ref              | Ref              |
| Ever been homeless                                           |                  |                  |
| Yes                                                          | 1.14 (0.98-1.34) | -                |
| No                                                           | Ref              | -                |
| Ever been hospitalized for psychiatric illness or depression |                  |                  |
| Yes                                                          | 1.19 (1.05-1.34) | 1.23 (1.09-1.39) |
| No                                                           | Ref              | Ref              |
| Discrimination from medical community                        |                  |                  |
| Yes                                                          | 0.94 (0.81-1.09) | -                |
| No                                                           | Ref              | -                |
| Unable to access addiction treatment program                 |                  |                  |
| Yes                                                          | 1.02 (0.89-1.16) | -                |
| No                                                           | Ref              | -                |

APR= adjusted prevalence ratio, C.I= confidence interval, Ref= reference category

Model 1 adjusted for age, drug snorting history, injection drug use history, homelessness history, history of hospitalization for psychiatric illness or depression, discrimination from medical community, and addiction treatment access.

Model 2 adjusted for age, injection drug use history, and history of hospitalization for psychiatric illness or depression.

# **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 5F3); (2) immediate scale-up of treatment (to 430 annually) and less restrictive Medicaid reimbursement criteria (fibrosis stage 5F2); (3) immediate treatment scale-up and no fibrosis stage-specific Medicaid reimbursement criteria (5F0); (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 5F2 and 5F0 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 (~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 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 treat-

ment 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 ~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 5F2 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 5F3 (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 less restrictive Medicaid treatment authorization and reimbursement criteria (fibrosis stage 5F2); the other treatment scale-up scenario describes an immediate treatment scale-up to 430 patients annually and no fibrosis stage-specific Medicaid reimbursement criteria (5F0). 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, 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.

## R E S U L T S

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 590% 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 5F2 and 5F0 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 5F2 (21.7% vs. 10.0% reduction for the 5F0 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. 590% 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 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 5F2 produced greater reductions in all-cause and liver-related deaths compared to the 5F0 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 5F2 and 5F0), 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 5F2. More advanced HCV disease stages have a higher 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 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 reinfection [44]. Future work will seek to incorporate differential rates of spontaneous clearance based on reinfection 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 programs 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.

#### S U P P L E M E N T A R Y M A T E R I A L

For supplementary material accompanying this paper visit:

<http://dx.doi.org/10.1017/S0950268816001722>

#### A C K N O W L E D G E M E N T S

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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 modelling 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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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                       | 5F3           | —             | —             | [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.

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

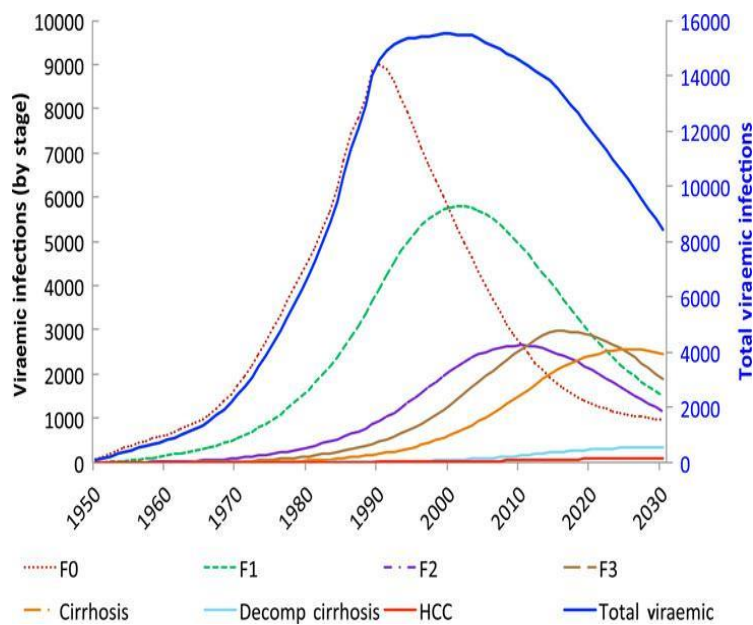


Fig. 2. Annual number of patients treated in the base-case and treatment scale-up scenarios, Rhode Island, 2004–2030. The annual number of treated patients between 2004 and 2013 was estimated from national data [36], and interpolated to the Rhode Island population.

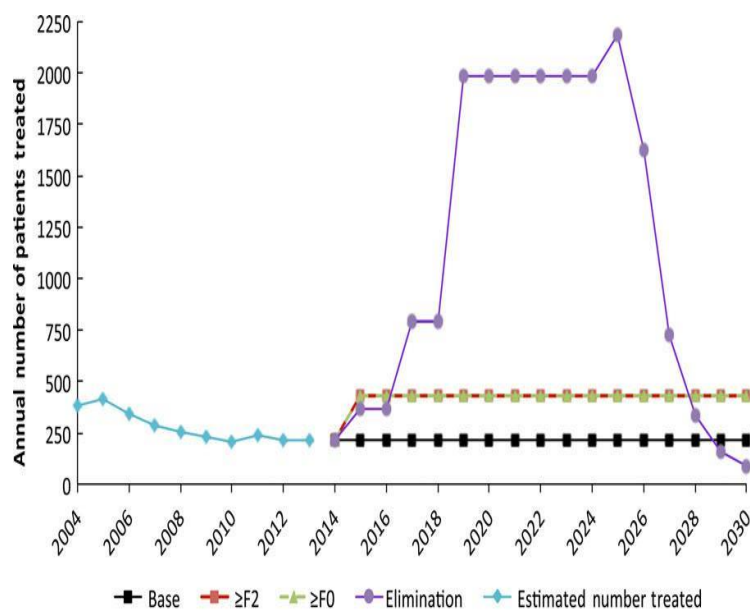


Fig. 3. Estimated number of total viraemic infections in Rhode Island, 1950–2030: base-case and treatment scale-up scenarios. Results of the Monte Carlo sensitivity analysis (95% uncertainty interval, base case) are shown by dashed blue lines. The 95% uncertainty interval at 2030 is 6260–10 490 total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

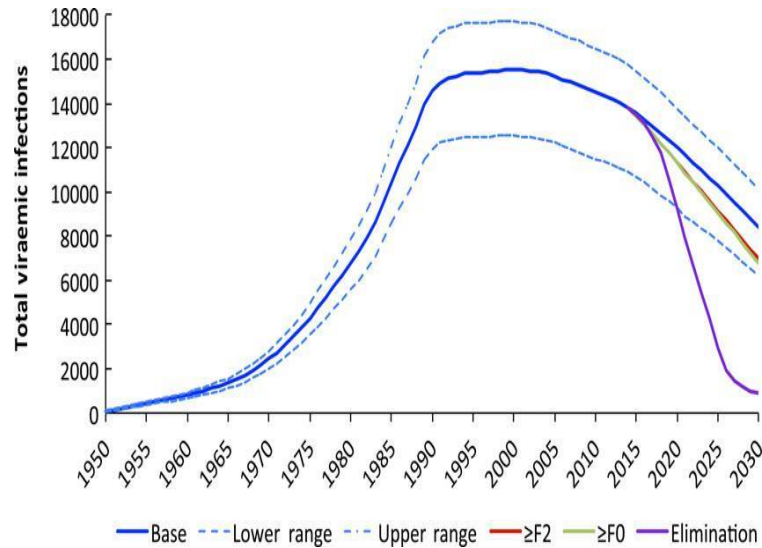


Fig. 4. Estimated number of cirrhotic cases in Rhode Island, 1950–2030: base-case and treatment scale-up scenarios. Results of the Monte Carlo sensitivity analysis (95% uncertainty interval, base case) are shown by dashed blue lines. The 95% uncertainty interval at 2030 is 1085–3092 cirrhotic cases.

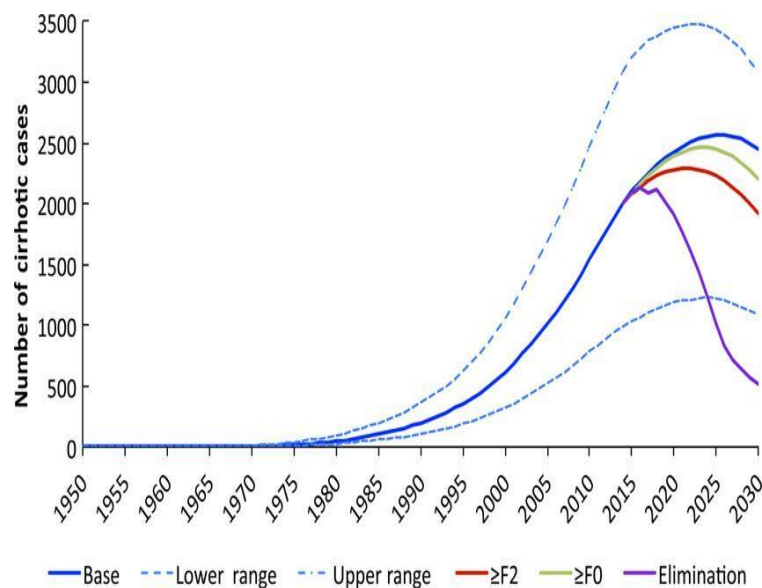


Fig. 5. Estimated number of deaths from any cause in the viraemic HCV population, Rhode Island, 1950–2030: base-case and treatment scale-up scenarios. Results of the Monte Carlo sensitivity analysis (95% uncertainty interval, base case) are shown by dashed blue lines. The 95% uncertainty interval at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

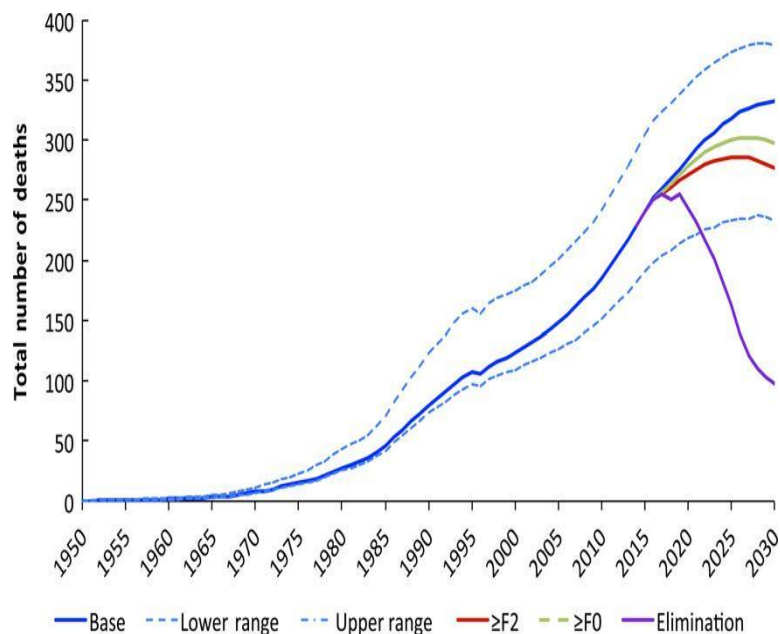
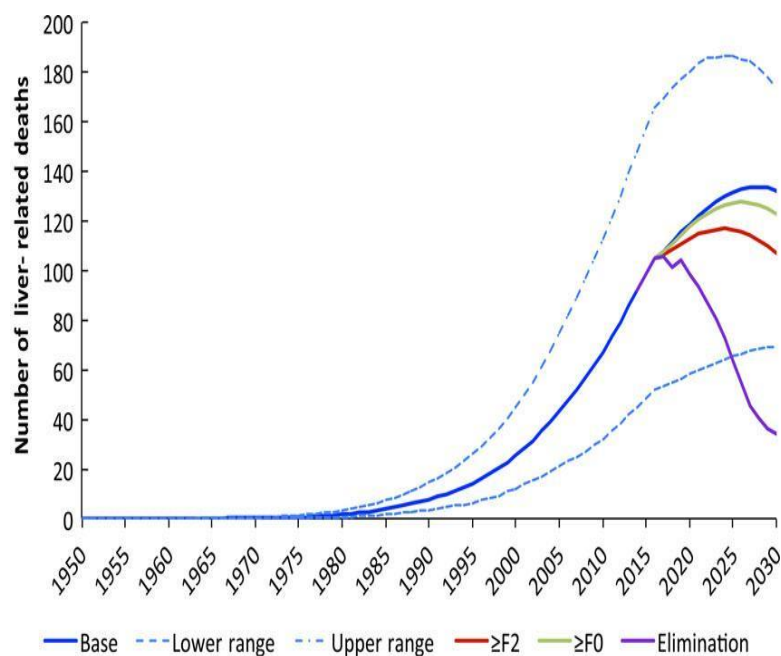


Fig. 6. Estimated number of liver-related deaths in the viraemic HCV population, Rhode Island, 1950–2030: base-case and treatment scale-up scenarios. Results of the Monte Carlo sensitivity analysis (95% uncertainty interval, base case) are shown by dashed blue lines. The 95% uncertainty interval at 2030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



APPENDIX

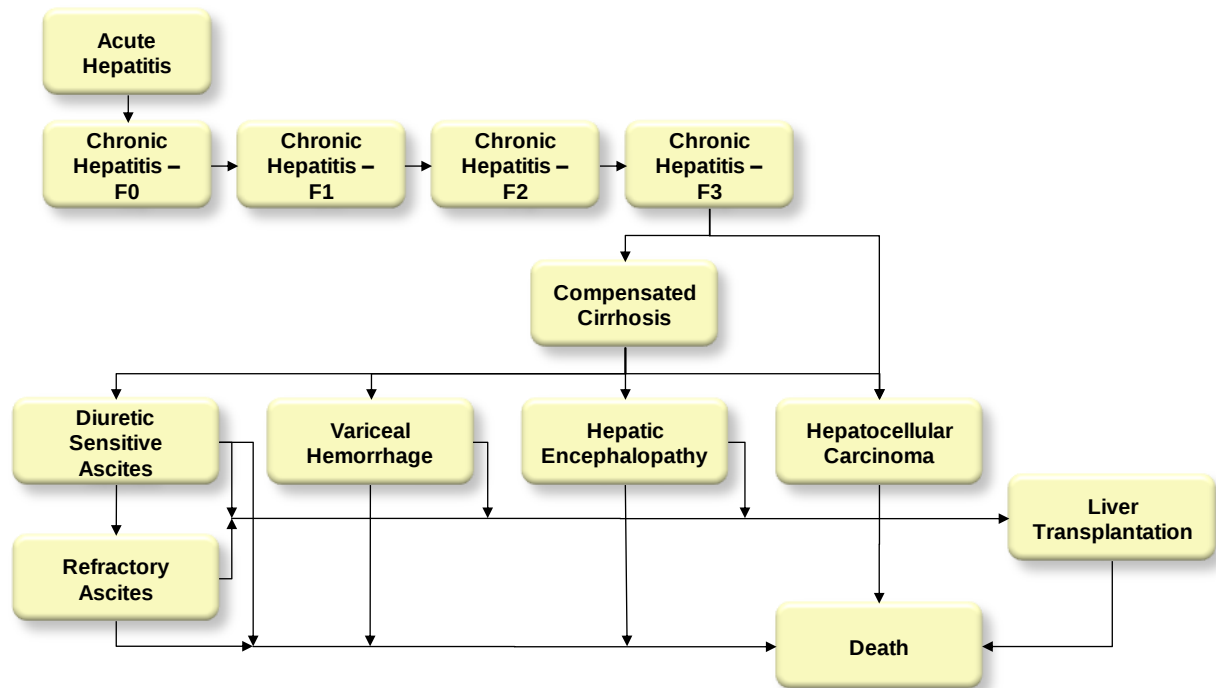
*Epidemiology and Infection*

**CHRONIC HEPATITIS C VIRUS (HCV) BURDEN IN RHODE  
ISLAND: MODELLING TREATMENT SCALE-UP AND  
ELIMINATION**

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O. Galárraga, L. E. Taylor, B. D. L. Marshall

**SUPPLEMENTARY MATERIAL**

**Supplementary Figure S1: HCV Disease Progression Schematic**



Adapted from Razavi et al., 2013 [1].

**Supplementary Table S1:** Age- and gender-specific fibrosis disease stage progression probabilities

| Age Cohorts                    | 0-4 | 5-9 | 10-14 | 15-19 | 20-24 | 25-29 | 30-34 | 35-39 | 40-44 | 45-49 | 50-54 | 55-59 | 60-64 | 65-69 | 70-74 | 75-79 | 80-84 | 85+  |
|--------------------------------|-----|-----|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|------|
| Progression rates – males, %   |     |     |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |      |
| F0 to F1                       | 5.3 | 5.3 | 6.4   | 6.4   | 5.2   | 5.2   | 3.8   | 3.8   | 13.9  | 13.9  | 17.1  | 17.1  | 19.4  | 19.4  | 21.8  | 21.8  | 17.9  | 17.9 |
| F1 to F2                       | 3.8 | 3.8 | 4.7   | 4.7   | 3.8   | 3.8   | 2.7   | 2.7   | 10.1  | 10.1  | 12.4  | 12.4  | 14.1  | 14.1  | 15.8  | 15.8  | 13.0  | 13.0 |
| F2 to F3                       | 5.4 | 5.4 | 6.6   | 6.6   | 5.3   | 5.3   | 3.9   | 3.9   | 14.3  | 14.3  | 17.5  | 17.5  | 19.9  | 19.9  | 22.4  | 22.4  | 18.3  | 18.3 |
| F3 to Cirrhosis                | 0.0 | 0.0 | 0.8   | 0.8   | 2.5   | 2.5   | 5.7   | 5.7   | 8.8   | 8.8   | 4.8   | 4.8   | 9.9   | 9.9   | 19.1  | 19.1  | 19.1  | 19.1 |
| F3 to HCC                      | 0.0 | 0.0 | 0.0   | 0.0   | 0.0   | 0.0   | 0.0   | 0.0   | 0.1   | 0.1   | 0.1   | 0.1   | 0.2   | 0.2   | 0.3   | 0.3   | 0.3   | 0.3  |
| Cirrhosis to HCC               | 0.3 | 0.3 | 0.3   | 0.3   | 0.3   | 0.3   | 0.5   | 0.5   | 0.9   | 0.9   | 1.4   | 1.4   | 2.4   | 2.4   | 3.9   | 3.9   | 3.9   | 3.9  |
| Progression rates – females, % |     |     |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |      |
| F0 to F1                       | 4.4 | 4.4 | 5.4   | 5.4   | 4.3   | 4.3   | 3.1   | 3.1   | 11.6  | 11.6  | 14.3  | 14.3  | 16.2  | 16.2  | 18.2  | 18.2  | 14.9  | 14.9 |
| F1 to F2                       | 3.2 | 3.2 | 3.9   | 3.9   | 3.1   | 3.1   | 2.3   | 2.3   | 8.4   | 8.4   | 10.4  | 10.4  | 11.7  | 11.7  | 13.2  | 13.2  | 10.8  | 10.8 |
| F2 to F3                       | 4.5 | 4.5 | 5.5   | 5.5   | 4.4   | 4.4   | 3.2   | 3.2   | 11.9  | 11.9  | 14.6  | 14.6  | 16.6  | 16.6  | 18.6  | 18.6  | 15.3  | 15.3 |
| F3 to Cirrhosis                | 0.0 | 0.0 | 0.6   | 0.6   | 2.1   | 2.1   | 4.7   | 4.7   | 7.4   | 7.4   | 4.0   | 4.0   | 8.3   | 8.3   | 15.9  | 15.9  | 15.9  | 15.9 |
| F3 to HCC                      | 0.0 | 0.0 | 0.0   | 0.0   | 0.0   | 0.0   | 0.0   | 0.0   | 0.0   | 0.0   | 0.1   | 0.1   | 0.1   | 0.1   | 0.2   | 0.2   | 0.2   | 0.2  |
| Cirrhosis to HCC               | 0.3 | 0.3 | 0.3   | 0.3   | 0.3   | 0.3   | 0.4   | 0.4   | 0.7   | 0.7   | 1.2   | 1.2   | 2.0   | 2.0   | 3.3   | 3.3   | 3.3   | 3.3  |

HCC = hepatocellular carcinoma

Re-produced from Razavi et al., 2014 [2].

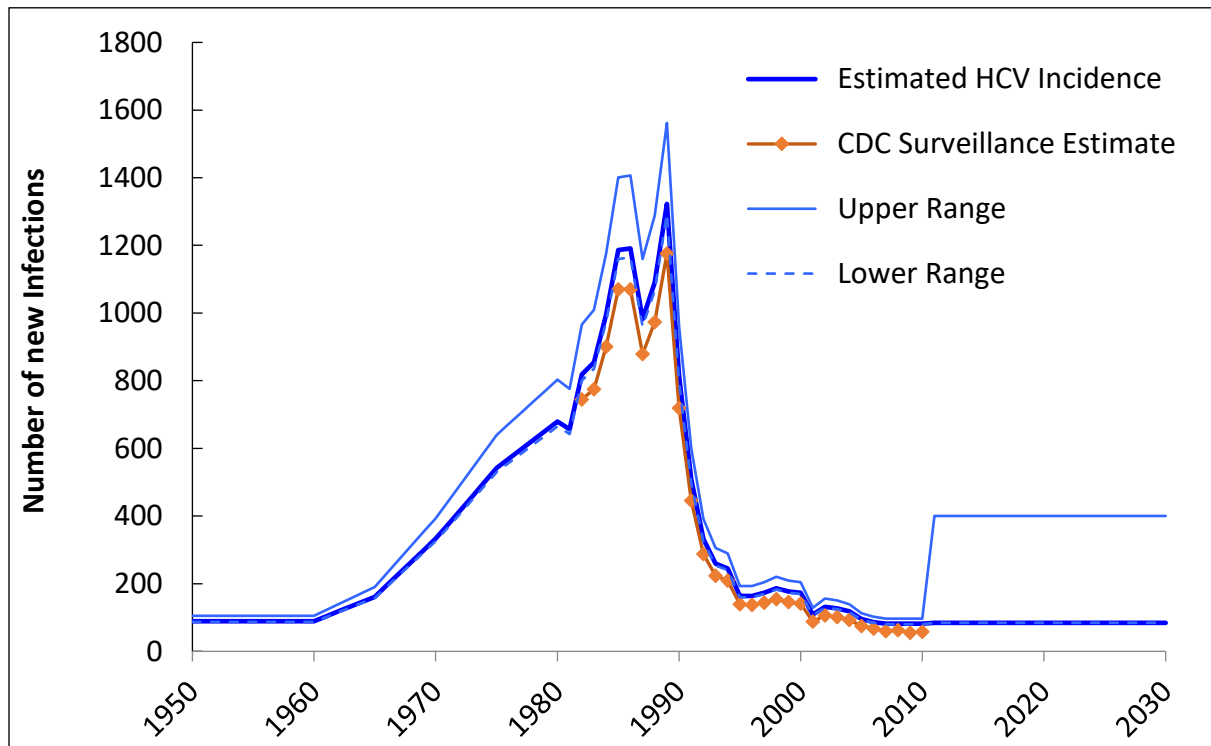
Rates were estimated from previous studies [3-5], and were based on data from the US Surveillance, Epidemiology, and End Results (SEER) database. We assumed that 90% of all liver cancers were HCC [6], and 40% of HCC cases were due to HCV [7, 8].

**Supplementary Table S2: HCV disease progression probabilities**

| Progression...                     | Base         | Range                            | Source            |
|------------------------------------|--------------|----------------------------------|-------------------|
| from Acute (Incidence)             |              |                                  |                   |
| % Progress to Chronic HCV          | 82.00%       | (0.85 - 0.55)                    | [9-11]            |
| from Cirrhosis                     |              |                                  |                   |
| ....Diuretic Sensitive Ascites     | 2.50%        | (0.018 - 0.032)                  | [4, 5]            |
| ....Variceal Hemorrhage            | 1.10%        | (0.006 - 0.016)                  | [4, 5]            |
| ...Hepatic Encephalopathy          | 0.40%        | (0.001 - 0.007)                  | [4, 5]            |
| ...HCC                             | See Table S1 |                                  |                   |
| from Diuretic Sensitive Ascites    |              |                                  |                   |
| ....Diuretic Refractory Ascites    | 6.70%        | (0.04 - 0.094 )                  | [4, 5]            |
| ....Liver Transplant               | See below    |                                  |                   |
| ....Liver Related Death            | 11.00%       | (0.077 - 0.143)                  | [4, 5]            |
| from Variceal Hemorrhage           |              |                                  |                   |
| ....Liver Transplant (1st Year)    | See below    |                                  |                   |
| ....Liver Related Death (1st Year) | 40.00%       | (0.334 - 0.466)                  | [4, 5]            |
| ....Liver Related Death (Sub Yrs)  | 13.00%       | (0.085 - 0.175)                  | [4, 5]            |
| from Hepatic Encephalopathy        |              |                                  |                   |
| ....Liver Transplant (1st Year)    | See below    |                                  |                   |
| ....Liver Related Death (1st Year) | 68.00%       | (0.659 - 0.701)                  | [4, 5]            |
| ....Liver Related Death (Sub Yrs)  | 40.00%       | (0.378 - 0.422)                  | [4, 5]            |
| from Diuretic Refractory Ascites   |              |                                  |                   |
| ....Liver Transplant               | See below    |                                  |                   |
| ....Liver Related Death            | 33.00%       | (0.28 - 0.38)                    | [4, 5]            |
| from HCC                           |              |                                  |                   |
| ....Liver Related Death (1st Year) | 70.70%       | (0.43 - 0.77)                    | [4, 5, 12]        |
| ....Liver Related Death (Sub Yrs)  | 16.20%       | (0.11 - 0.23)                    | [4, 5, 12]        |
| Liver Transplant (1950-1970)       | 0%           | Transplant rates were negligible |                   |
| Liver Transplant (1971-1987)       | 5.3%         | (0.031 - 0.0542)                 | [4], Trended Data |
| Liver Transplant (1988-2010)       | Actual Data  | 33% attributed to HCV            | [13]              |
| Liver Transplant (2011-2030)       | 1.7%         | (0.0169 - 0.045)                 | Trended Data      |

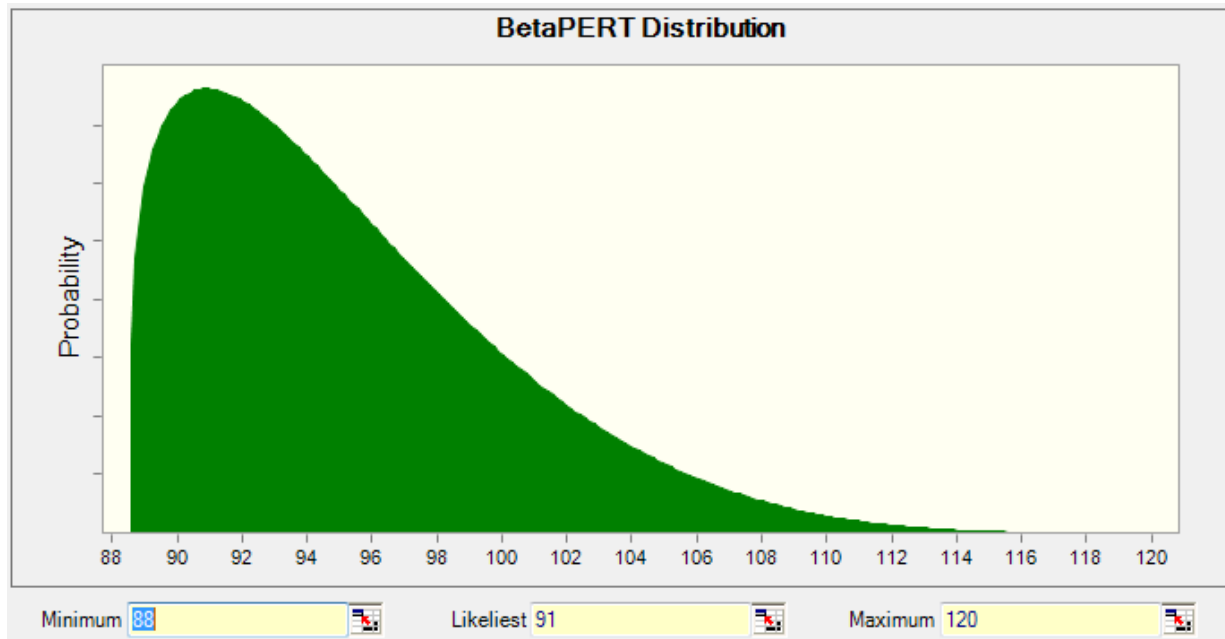
HCC = hepatocellular carcinoma

**Supplementary Figure S2: Estimated HCV incidence, Rhode Island (1950-2030)**

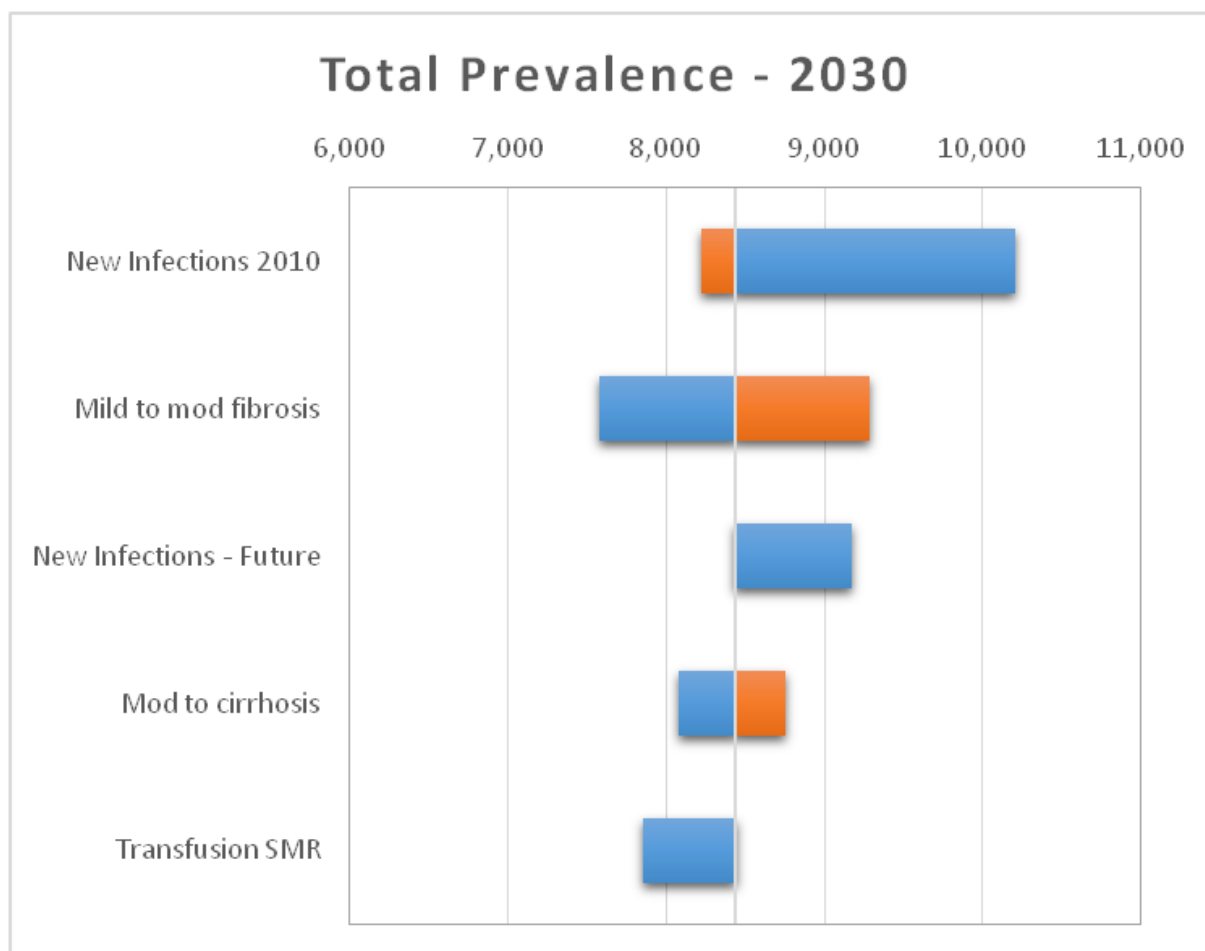


Note: CDC surveillance estimates (orange) reflect the total number of estimated cases using methods to account for under-ascertainment of reported cases [14]. The estimated number of acute HCV infections in Rhode Island was derived by multiplying the national values reported by the CDC by the proportion of the US population residing in Rhode Island in each year (based on US census data).

**Supplementary Figure S3:** Example beta-PERT distribution used in the Monte Carlo sensitivity analyses, with minimum, likeliest value 91, and maximum value 120.



**Supplementary Figure S4:** Tornado diagram summarizing the results of one-way sensitivity analyses, selected variables.



Note: each bar represents the minimum and maximum denoted by the lower and upper range shown in Table 1 or Table S2.

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- (1) **Razavi H, et al.** Chronic hepatitis C virus (HCV) disease burden and cost in the United States. *Hepatology* 2013; **57**: 2164-2170.
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- (14) Centers for Disease and Control Prevention (CDC). Viral hepatitis surveillance: United States, 2011. In: Division of Viral Hepatitis, ed. Atlanta, GA: National Center for HIV/AIDS, Viral Hepatitis, STD, & TB Prevention, 2011.