

**Colorado Prevalence and Incidence of Hepatitis C Virus Infection: A Modeling Study**  
Center for Disease Analysis. September, 2017

**Introduction**

Hepatitis C virus (HCV) infection is a contagious liver disease that mainly spreads through contact with blood and can range in severity from a mild illness that clears on its own to a serious, lifelong illness that can result in death. HCV infection is the most common bloodborne pathogen in the U.S. and a major cause of liver cancer.[1] Hepatitis C-associated mortality is increasing in the U.S. and has surpassed the 60 other nationally notifiable infection conditions combined.[2]

Prevalence in the United States is estimated to be 1.3 percent (range of 1.0 percent to 2.0 percent).[3, 4] In Colorado, prevalence based on these estimates ranged between 54,566 and 109,131 in 2015.[5] The Colorado Department of Public Health and Environment (CDPHE) has reported receiving approximately 4,000 new reports of chronic hepatitis C each year across urban and rural areas, with increasing numbers in recent years. In addition, approximately 25 to 40 cases of acute hepatitis C are reported annually. These numbers are much lower than actual infections due to under-ascertainment and under-reporting. CDC estimates there are 13.9 actual acute infections for each acute case reported.[6]

The CDPHE 2015 Viral Hepatitis Surveillance Report [5] indicates that people born between 1945 and 1965 historically and currently represent most chronic HCV infections, although adults ages 20 to 29 represented an increasing proportion of chronic hepatitis C infections in the past five years; most acute hepatitis C infections have occurred in this age group as well. The proportion of cases in people ages 30 to 39 years has also increased in the past five years. Injection drug use (IDU) is currently the primary cause of new HCV infections in Colorado, and the proportion of cases that report IDU increased to 65.0 percent in 2015, from 36.1 percent in 2011. Nationally, CDC also reports IDU as the most common risk behavior, reported by 64.2 percent of acute HCV cases in 2015.[6]

There is no vaccine to prevent HCV infection. Improvements in screening and treatment can help decrease the burden of HCV infection, but due to limited data in Colorado it is unclear how many individuals have been screened for HCV infection and whether recommended risk groups are being tested, how many individuals have received treatment for HCV infection, and, as reflected in the wide interval of prevalence estimates, a precise assessment of the burden of HCV infection in Colorado is not available. Public health surveillance for HCV is limited by several factors in Colorado, including failure to routinely identify: 1) classification of all cases; 2) people who spontaneously clear infection; 3) people receiving treatment; 4) people who are cured and are no longer infected; 5) deaths due to the virus or other causes; or 6) re-infection with HCV.[5]

National estimates of HCV infection are limited since they are based on surveys of the general population (such as NHANES) with adjustments of estimated rates from excluded sub-populations, and some national estimates are of current infections whereas others include past and present infections. Applying these rates to Colorado is further limited by the fact that national rates may not reflect HCV epidemiology in Colorado.

In synthesis, HCV infection is a major public health challenge in Colorado. Emerging trends indicate increasing HCV infection among younger age groups, IDU is a driving factor in new HCV infections, and effective treatment is available; but screening and treatment rates are unknown, and current public health surveillance systems are imprecise.

Improved understanding of HCV epidemiology in Colorado is important for generating an appropriate public health response. In particular, the context of the opioid addiction crisis in Colorado and implications for potential increases in IDU provides an additional sense of urgency. In order to address gaps in public health surveillance systems and generate additional information on the epidemiology of HCV in Colorado, a modeling study of HCV epidemiology in Colorado was conducted.

## **Methods**

This analysis represents an integrated and validated methodology that has been previously described. Prior literature review and an established Markov model developed by the Center for Data Analysis provided the foundation for a Colorado-specific adaptation that incorporated local data; the Markov model has been previously described in detail.[7] HCV infection prevalence and incidence projections are driven by a range of inputs, as detailed in the appendix. Among the key inputs for this Colorado-specific model were diagnosis and treatment of HCV infection. Data on diagnosis is limited in Colorado. Data on screening for HCV infection is not routinely collected, and there is no validated methodology to de-duplicate laboratory data that may provide information about HCV infection diagnoses. Model inputs were reviewed by an *ad hoc* expert committee. Undiagnosed fraction of people was estimated by comparing the total prevalence of HCV patients minus the total number of diagnosed and treated patients. Methodology details are provided in the attached appendix.

## **Results**

Primary outcomes from the model include HCV infection prevalence and incidence for the years 2015 through 2025. The landscape of HCV treatment significantly changed with the introduction of the first oral direct acting agent in December 2013. To incorporate the impact of advances in HCV treatment, the prevalence of HCV was displayed starting 2015 and projected for the next ten years.

The estimated prevalence was 50,153 (range 35,824 to 67,349) in 2015, with projected decline to 30,688 by 2025. Figure 1 shows HCV infection prevalence in Colorado by age group during this time period. HCV prevalence projects an overall decline over the next 10 years having peaked around the year 2000 (not shown). Table 1 also show a shift in the demographics of HCV infection, with an increasing proportion of infections in the 15-44 year old age group. This was similar pattern observed in males and females, while the overall distribution of HCV infection remained about 60% male.

Figure 1. Hepatitis C Virus Infection: Prevalence (viremic infection), Colorado 2015-2025

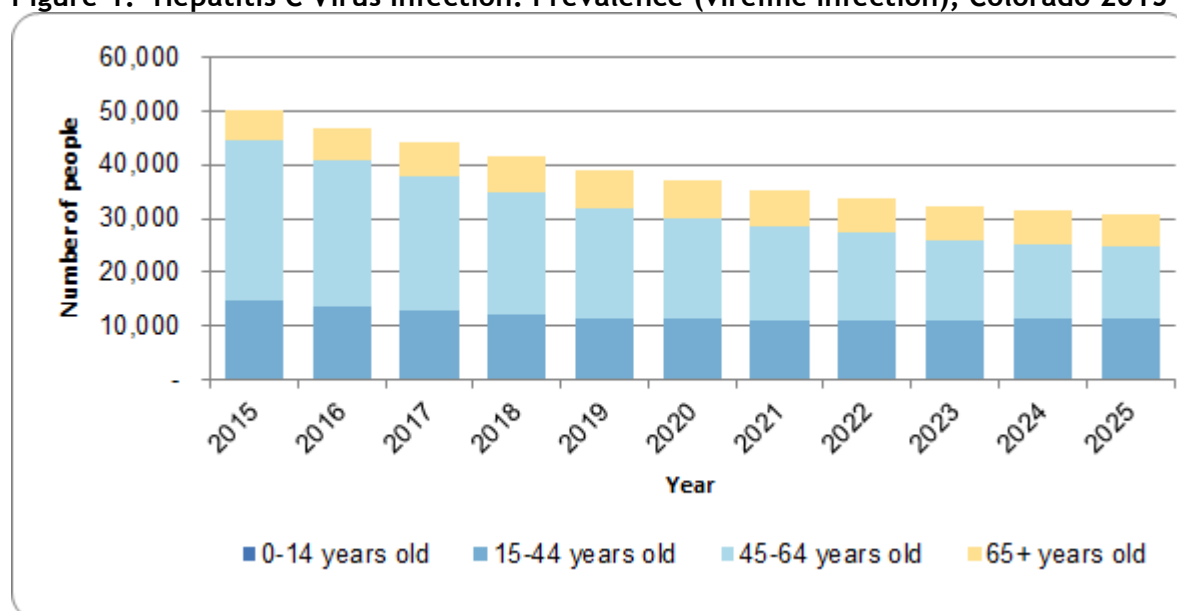


Table 1. Hepatitis C Virus Infection: Prevalence (viremic infection), Colorado 2015-2025

Year	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
<b>Age Cohort - Total</b>	<b>50,153</b>	<b>46,862</b>	<b>44,152</b>	<b>41,456</b>	<b>38,809</b>	<b>37,055</b>	<b>35,361</b>	<b>33,727</b>	<b>32,154</b>	<b>31,397</b>	<b>30,688</b>
0-14 years old	136	147	159	169	179	187	195	201	205	208	210
% of total	0.3%	0.3%	0.4%	0.4%	0.5%	0.5%	0.6%	0.6%	0.6%	0.7%	0.7%
15-44 years old	14,527	13,607	12,679	11,914	11,301	10,979	10,856	10,801	10,800	10,973	11,202
% of total	29.0%	29.0%	28.7%	28.7%	29.1%	29.6%	30.7%	32.0%	33.6%	34.9%	36.5%
45-64 years old	29,753	27,064	24,974	22,766	20,491	18,833	17,577	16,286	14,990	14,139	13,272
% of total	59.3%	57.8%	56.6%	54.9%	52.8%	50.8%	49.7%	48.3%	46.6%	45.0%	43.2%
65+ years old	5,737	6,044	6,339	6,607	6,838	7,056	6,733	6,439	6,159	6,077	6,004
% of total	11.4%	12.9%	14.4%	15.9%	17.6%	19.0%	19.0%	19.1%	19.2%	19.4%	19.6%
<b>Males - all ages</b>	<b>31,004</b>	<b>28,769</b>	<b>26,978</b>	<b>25,205</b>	<b>23,472</b>	<b>22,321</b>	<b>21,252</b>	<b>20,225</b>	<b>19,242</b>	<b>18,769</b>	<b>18,330</b>
% of total	61.8%	61.4%	61.1%	60.8%	60.5%	60.2%	60.1%	60.0%	59.8%	59.8%	59.7%

Model projections are specific for viremic infection (confirmed by positive RNA tests) and account for clearance of infection (either by spontaneous clearance or treatment), HCV related mortality, and incident cases. Incident HCV cases are shown in Figure 2. Table 1 shows an increase in the proportion of prevalent cases in the 15-44 and 65+ year old age groups between 2015-2025. However Figure 2 and Table 2 reveal that there are far fewer incident cases in the 65+ age group, while the younger age group (15-44 years) experiences ongoing increases in incident rates of HCV infection, ultimately accounting for more than 85% of new infections.

Figure 2. Hepatitis C Virus Infection: Incidence, Colorado 2015-2025

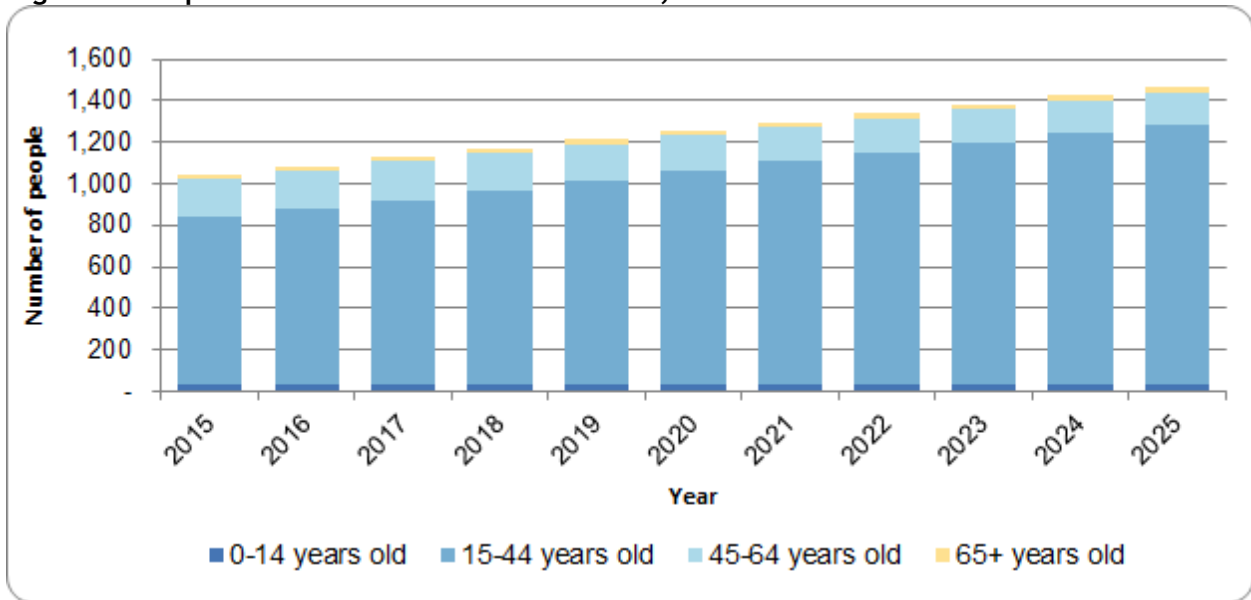
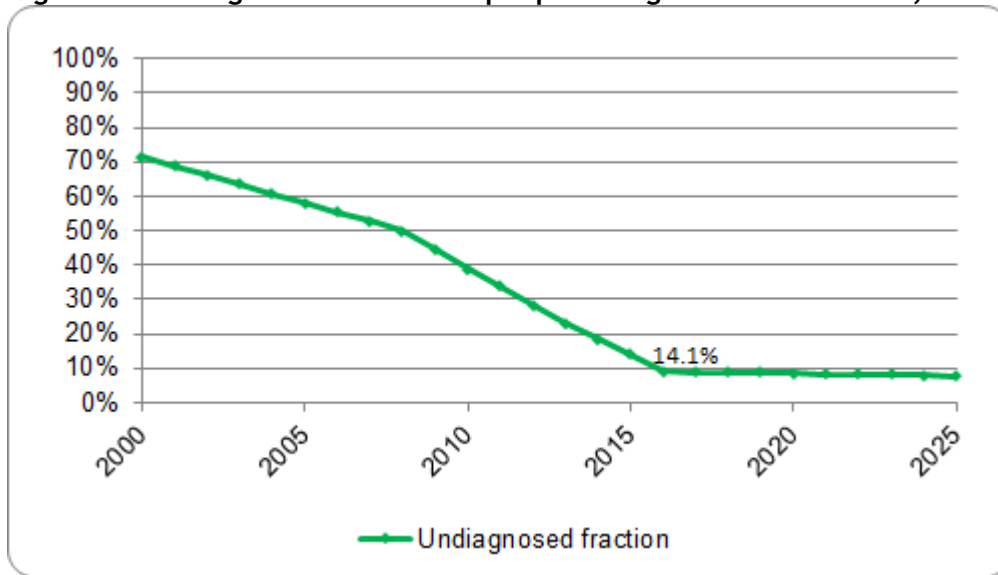


Table 2. Hepatitis C Virus Infection: Incidence, Colorado 2015-2025

Year	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
<b>Age Cohort - Total</b>	<b>1,044</b>	<b>1,086</b>	<b>1,128</b>	<b>1,170</b>	<b>1,213</b>	<b>1,255</b>	<b>1,297</b>	<b>1,339</b>	<b>1,382</b>	<b>1,424</b>	<b>1,466</b>
0-14 years old	32	34	34	33	33	33	33	33	32	32	32
% of total	3.1%	3.1%	3.0%	2.9%	2.7%	2.6%	2.5%	2.4%	2.3%	2.3%	2.2%
15-44 years old	810	842	888	934	981	1,029	1,074	1,118	1,164	1,210	1,256
% of total	77.6%	77.6%	78.7%	79.8%	80.9%	82.0%	82.8%	83.5%	84.2%	85.0%	85.7%
45-64 years old	182	189	185	181	175	169	167	164	160	156	151
% of total	17.4%	17.4%	16.4%	15.4%	14.5%	13.5%	12.8%	12.2%	11.6%	11.0%	10.3%
65+ years old	20	21	22	22	23	24	24	25	25	26	26
% of total	1.9%	1.9%	1.9%	1.9%	1.9%	1.9%	1.9%	1.9%	1.8%	1.8%	1.8%
<b>Males - all ages</b>	<b>652</b>	<b>678</b>	<b>705</b>	<b>731</b>	<b>758</b>	<b>785</b>	<b>811</b>	<b>838</b>	<b>865</b>	<b>891</b>	<b>918</b>
% of total	62.5%	62.5%	62.5%	62.5%	62.5%	62.5%	62.5%	62.6%	62.6%	62.6%	62.6%

The model indicates significant progress in reducing the undiagnosed fraction of people living with HCV infection, with approximately 85% having had their infection diagnosed as shown in Figure 3.

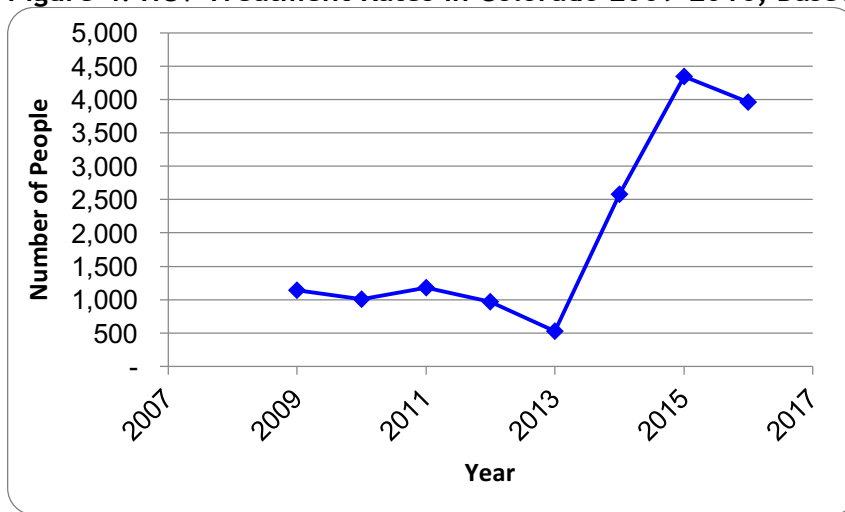
**Figure 3. Undiagnosed fraction of people living the HCV infection, Colorado 2000-2025**



### Treatment of HCV infection

Prevalence estimates in Table 1 were adjusted to incorporate those who were treated with any HCV treatment regimen. Regimens included pegylated interferon-based therapies administered alone or in combination with Telaprevir or Boceprevir (triple acting therapies) and any of the newer oral direct anti-viral acting agents. The All Payer Claims Database (APCD) in Colorado collects treatment and utilization data (claims) for over 80% of insured individuals residing in Colorado starting in the current year. However, these data are not currently accessible and in lieu of APCD information, treatment inputs for this model were based on national estimates to determine how many HCV infected Colorado residents received treatment between 2009-2016. Treatment rates of HCV from 2009-2016 shows that the annual number of treated patients increased by over 400% in a 5 year period, while treated patients in 2016 declined (Figure 4).

**Figure 4. HCV Treatment Rates in Colorado 2009-2016, Based on National Data**



## Discussion

The results of this model provide new information for understanding the epidemiology of HCV infection in Colorado. Among key outputs, the prevalence estimate of 50,153 stands out when compared to the previously published estimate of 70,000, and the estimated prevalence reported here is lower than the 54,566 lower bound of the previously published estimate.[5] The lower estimate generated in this model is likely driven by several key factors. For example, public health surveillance systems do not account for treatment cures. Incorporating treatment data into the model revealed both a fairly high level of treatment in Colorado and a significant impact of treatment on HCV infection epidemiology in the state. This is also related to screening and case finding rates, which likewise are not tracked by public health surveillance systems in Colorado.

Public health surveillance systems also do not routinely incorporate mortality data, and the HCV registry likely includes individuals who are deceased (whether from complications of HCV infection or other causes). This model incorporated estimated mortality rates, which have an important impact on outcomes considering that the bulk of HCV infection burden in Colorado is currently among older age cohorts. In addition, spontaneous clearance of HCV infection is not captured in public health surveillance systems. This model is distinguished by focus on estimating viremic HCV infection, rather than antibody screening, and this may also explain differences in prevalence estimates.

Overall, the modeled estimate of HCV infection prevalence in Colorado reflects a significant burden of disease. While the prevalence estimates generated here are lower than prior estimates, there are still more than four times more people living with HCV infection in Colorado, compared to HIV infection. Furthermore the demographics of HCV infection in Colorado appear to be shifting in important ways, with ongoing increases in specific age cohorts. Of particular concern, increasing incidence among 15-44 year olds is likely linked to the opioid addiction crisis.[6]

This would also indicate that this group, at high risk for HCV infection acquisition and onward transmission, is hard to reach and even harder to engage in testing and linkage to care and treatment. Implications include the need for targeted HCV epidemic control measures that focus on this population. Interventions include expansion of harm reduction interventions designed to reduce HCV infection burden in combination with the opioid crisis and additional epidemiology analyses that focus on this population, including estimates of undiagnosed infection and access to care among hard-to-reach populations of people who inject drugs (PWID). An additional element may include increasing sexual transmission among HIV-infected men who have sex with men,[8] and future HCV epidemiology analysis should address this risk group as well.

As anticipated, prior to the introduction of oral direct acting anti-viral agents at the end of 2013, treatment rates with older treatment regimens (that were far longer in treatment duration and associated with far more intolerable for patients) were much lower. The steep increase in treatment between 2013-2014 is an expected finding, although the slight downturn between 2015-2016 is potentially concerning, and may reflect either saturation of demand for treatment, or failure to diagnose and link cases to care. Colorado-specific data will be critical for better understanding this dynamic, with particular focus on treatment trends. If the extrapolation of national trends as shown in Figure 4 is accurate for Colorado,

it implies that a cumulative total of approximately 10,600 individuals treated with modern regimens of direct-acting antivirals between 2014-2016, or about 21% of the estimated prevalence of HCV infection in 2015.

Undiagnosed fraction and linkage to care should also be explored. The steep decline in undiagnosed fraction may be explained by focused outreach efforts and health care system response to the 1945-1965 birth cohort that represents the bulk of the HCV infections and may be more likely than younger counterparts to be engaged in medical care. The undiagnosed fraction may change dramatically as HCV infection epidemiology shifts towards a younger population of hard-to-reach individuals, including people who inject drugs (PWID). It is also important to note that the undiagnosed fraction is sensitive to prevalence estimates, and the current study has generated an estimate that is significantly lower than previously published estimates, which helps drive lower estimates of undiagnosed fraction as well.

Limitation of this report include the inherent uncertainties of mathematical modeling exercises. In particular, development of estimates remains limited due to scarcity and low quality of data inputs. Collaborators for this Colorado-specific model attempted to limit biases that could impact model outputs, but it is not possible to completely eliminate the risk of confirmation, observer, and recall bias. Validation of the model itself has been previously described.[7]

For Colorado in particular, this model has limited power to examine age-specific elements of screening and treatment access for HCV infection; urban vs. rural HCV infection epidemiology; how treatment expansion through Colorado Medicaid and other payers can be better targeted to a the younger age groups where the disease burden has shifted; HCV infection relapse or re-infection rates; and more granular development of our epidemiologic understanding regarding HCV infection among sub-populations, such as PWID. In this area the model is also limited by availability of information about PWID in Colorado. National estimates were used in this modeling exercise, but these estimates may be outdated (the most current data used to inform the national estimate was from 2009), represent past-year use only, and may not reflect drug injection patterns in Colorado. [9] Estimates in Colorado may be three times higher (0.9%, CDPHE unpublished data) but in order to generate a conservative model based on the most robust information available, the national published figure was used.

Future areas for exploration include addressing these limitations, examining statistical trends including significance of differences between age groups and over time, and generating counterfactual models that can inform the statewide response to HCV infection, including optimization of treatment criteria, targeted outreach for specific populations, and focused efforts for expansion of testing services and access to care.

Perhaps most importantly, divergent estimates of HCV infection prevalence in Colorado need to be reconciled. This modeling study provides an important new data point for comparison with estimates that can be generated through surveillance systems and examination of APCD information.

Although the overall magnitude of HCV infection is decreasing in Colorado, particular risk populations are experiencing ongoing increases. The epidemic of HCV infection is not going

away; rather, it is shifting in scope and shape, and the most immediate challenge will be appropriate assessment and response to the emerging epidemiology of HCV infection in Colorado.

**Contributors** (listed alphabetically)

Chris Estes, Kavita Nair, Homie Razavi, and Daniel Shodell prepared the first draft and finalized the draft based on comments from other authors. All other authors were collaborators who provided data, analyzed data, reviewed results, provided guidance on methodology, and provided feedback on the report.

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**Declaration of interests**

Kavita Nair is a member of the Center for Improving Value in Health Care Data Release Review Committee. All other contributors and collaborators declare no competing interests

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## APPENDIX

### Modeling the Prevalence of Hepatitis C Virus Infection in Colorado

#### Contents

Chronic hepatitis C virus infection (HCV) is a leading cause of cirrhosis, hepatocellular carcinoma (HCC) and liver transplantation in the US, including Colorado.[10-12] The advent of direct acting antiviral (DAA) therapies in recent years means that HCV can be treated with sustained viral response (SVR) rates in excess of 90%, and treatment regimens continue to become more efficacious and easier to tolerate for patients.[13] Achieving SVR has positive health, quality of life, and economic implications for cured patients.[14] This analysis will consider the impact of treatment uptake on disease burden at the State level under different scenarios. Understanding future disease burden and potential strategies to mitigate burden is critical for the elimination of HCV in Colorado, and the US.[15]

A previously established model has been published [7]; this appendix includes only aspects subject to modification for a Colorado-specific exercise.

#### Forecasting Viremic HCV Prevalence

**Indicator** - This analysis focused on estimating the viremic HCV infections, which reflects the presence of HCV RNA. The analysis used anti-HCV prevalence, serological evidence of past or present infection and the viremic rate in a Markov model to estimate 2016 end of year viremic prevalence.

**Time period** - State surveillance data from January 1, 1993 to December 31, 2015 [5] and National surveillance data from January 1, 2003 to December 31, 2014 [16, 17] were used in this analysis..

**Geographical scope** - There were sufficient data to build models to project the change in HCV prevalence over time in Colorado.

#### Modeling HCV Prevalence

The model was used to forecast the HCV prevalence at the end of 2016 for Colorado. The details of the model have been published previously.[7, 18]

**Required inputs** - The following inputs were required to build and calibrate the model.

Model input	Definition	Source
Population by 5-year age cohort	The number of people, reported annually from 1950 to 2050 (by gender and 5-year age cohort)	[19, 20]
Mortality rate by 5-year age cohort	The percent of deaths among the total population, annually from 1950 to 2050 (by gender and 5-year age cohort)	[21]
Anti-HCV + prevalence rate	Percent of total population who are anti-HCV(+)	[3-5]
Viremic rate	Percent of anti-HCV(+) individuals who are HCV-RNA(+)	[3-5]
Age and gender distribution	HCV prevalence rate by age (5 year cohorts) and gender	[3, 4]
Annually treated	Number of HCV infected individuals who have received treatment in a given year	National report, based on published studies and drug sales data adjusted for average patient consumption by genotype.[15]

<b>Total diagnosed</b>	Viremic HCV cases diagnosed and alive in 2008	Assumed that 50% of cases were diagnosed in 2008 based on national estimates reported by CDC.[3, 22]
<b>Newly diagnosed</b>	Annual number of newly diagnosed HCV cases (2008-2016)	[5]

**Prevalence by age** - Prevalence of HCV was not available for ages excluded from NHANES estimates. For younger age groups (<20 years old), an exponential decline in prevalence was used. Inputs included confirmed cases of HCV from the Colorado Department of Public Health and Environment’s electronic reporting system (CEDRS-Colorado Electronic Disease Reporting System).

**Treated patients** - The number of individuals treated annually for HCV was estimated through: 1) national databases; 2) audit drug sales data; 3) government reports; 4) reports from major treatment centers (and extrapolated to the whole State); 5) drug suppliers.

**Cured patients** - In the absence of better information, it was assumed the genotype distribution of the treated population was the same as the total infected population (they have the same probability of being diagnosed and treated). The sustained viral response (SVR) rates by genotype were used to estimate the number of patients cured per year. Interviews were used to determine the real world SVR for the different treatment regimens – interferon based therapy in combination with ribavirin (RBV) (dual therapy), with RBV and a protease inhibitor (PI) (triple therapy), RBV with direct acting antivirals (DAAs). Experts took into consideration the percentage of the population who were treatment experienced and treatment naïve on each treatment option and disease stages of the patients being treated (e.g., F1, F2, F3 and F4). The average SVR by genotype has been reported previously.[18, 23, 24]

**Diagnosed patients** - HCV has been a notifiable condition since 1993 and a stable annual number of newly diagnosed cases has been reported.[5] Total diagnosed cases was calculated by summing data from all years after taking into consideration the mortality among the diagnosed cases. It was assumed that the viremic rate among the diagnosed population was the same as the total infected population.

For modeling purposes, it was assumed that 50% of the viremic population was previously diagnosed in 2008, equivalent to 29,340 diagnosed viremic cases in Colorado.[3, 25] Diagnoses after 2008 were based upon annual CDPHE diagnosed cases with adjustment for 75% viremic rate.[5]

**Undiagnosed fraction** - determined by comparison of estimated prevalence of HCV infection and total number of diagnosed patients.

**All-cause mortality** - The all-cause mortality rates by age and gender were gathered from the from the United Nations mortality database.[20] The rates were adjusted for incremental increase in mortality due to injection drug use (IDU) and transfusion. A standard mortality ratio (SMR) of 10 (9.5-29.9) was used for the portion of the HCV infected population who were active IDU between ages 15-44.[26-31] An SMR of 2.1 (1.3-17.6) was applied to all ages for the portion of the population infected due to transfusion.[32] The number of active PWID and HCV prevalence among PWID was gathered through published studies and divided by the total HCV infected population to estimate percent of all HCV infections that is among active PWID. Based on US data showing that 0.3% of individuals aged ≥13 years were active PWID and that 43.126% were anti-HCV positive,[9] it was estimated that there are 251,900 viremic active PWID, assuming a 75% viremia rate.[4, 33] A standard mortality ratio (SMR) of 10.0 was estimated [26-31] and applied to background mortality rates for the 7.3% of viremic cases who are active PWID aged 15-44 years. In addition, an estimated 6.5% of the infected population reported a history of transfusion;[34] an SMR of 1.5 [32] was applied to background mortality rates for these cases.

**Validation of the model** - The model was validated by comparing its output against empirical data. In the US, at least two robust prevalence studies were available for comparison.[3, 35] In addition, the incidence of HCC cases was available through SEER.[36, 37] Studies that reported percent of all HCC cases due to HCV [10, 38] were used to adjust the reported HCC cases and compare them against the model output.

## Prevalence, Age Distribution, Viremic Rate, and Sources

Geography	Anti-HCV Prevalence - Base	Study Year	Anti-HCV Prevalence - Low	Anti-HCV Prevalence- High	Viremic Rate	Source (base)	Source (low)	Source (high)	Age source	Viremic Rate Source
Colorado	1.5%	2010	1.1%	2.0%	75 %	[3, 4]	[3, 4]	[3, 4]s	[3]	[3]

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