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Modeling HCV elimination recovery following the COVID-19 pandemic in the United States: Pathways to regain progress

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ABSTRACT

Background: As of 2019, the United States (US) was not on track to achieve targets for elimination, due to increasing incidence and treatment barriers. In 2020, the COVID-19 pandemic disrupted HCV services globally and in the US. As healthcare services normalize, there is an urgent need to reassess progress and evaluate scenarios that restore a pathway toward HCV elimination.

Methods: We updated a validated Markov model to estimate HCV-related morbidity and mortality in the US. Five scenarios were developed to bookend possible HCV outcomes in the wake of the pandemic. These included 1) return to pre-COVID-19 treatment forecasts; 2) achieve elimination targets through treatment and harm reduction; 3) long-term treatment disruptions; 4/5) achieve elimination targets through increased treatment without increased harm reduction, starting in either 2022 or 2025.

Findings: From 2014–2019, more than 1.2 million patients were treated for HCV in the US. Elimination targets in 2030 could be achieved in the US by treating an additional 3.2–3.3 million patients from 2020 to 2030, or by preventing new infections through expanded harm reduction programs and treating up to 2.7 million patients. Intervention scenarios could prevent over 30,000 HCC cases and over 29,000 liver-related deaths.

Interpretation: The US has made strides toward HCV elimination, but gains could be lost in the wake of the pandemic. However, it is still possible to avert nearly 30,000 deaths through increased harm reduction and increased treatment rates. This requires a coordinated effort from the entire HCV community.

Introduction

In 2020, there were an estimated 56.8 (95 % UI: 55.2–67.8) million hepatitis C virus (HCV) infections globally, a decrease of around 6.8 million infections from 2015 [63.6 (95 % UI: 61.8 – 75.8) million) [1]. Despite this decline, relative inaction from a majority of countries means that very few countries are on track to achieve the World Health Organization targets for elimination of HCV as a public health threat [2]. According to the Centers for Disease Control and Prevention (CDC) 2019 National Progress Report, the United States (US) was on track to achieve three of the five hepatitis C virus (HCV) outcome measures by 2025 [3]. Goals that have been met include a ≥ 20 % reduction in rates of hepatitis C-related deaths in 2025 (overall), and a ≥ 30 % reduction among American Indian and Alaska Native, and non-Hispanic Black persons. Goals that have not been met include reducing new HCV infections by ≥ 20 % by 2025 and reducing rates of new HCV infections among persons who inject drugs by ≥ 25 %. The COVID-19 pandemic introduced disruptions to healthcare services. Actions taken over the next few years will determine the trajectory of the HCV epidemic in the United States.

Abbreviations: HCV, hepatitis C virus; PWID, people who inject drugs; COVID-19, coronavirus disease 2019; DAA, direct acting antiviral treatment; HCC, hepatocellular carcinoma; LRD, liver-related death; SVR, sustained virologic response

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Research in context

Evidence before this study: Chronic HCV infection is a major contributor to liver morbidity and mortality in the United States. Previous results of modeling show that increased efforts to diagnose and treat chronic HCV infection will avert a large number of cases of HCV-related advanced liver disease (cirrhosis and liver cancer), as well as prevent liver-related deaths among the infected population. New cases of HCV infection in the United States are largely due to epidemic levels of injection drug abuse; efforts to treat in combination with harm reduction measures will therefore also result in decreased disease transmission. However, the provision of healthcare services in the US has been disrupted due to the COVID-19 pandemic, and there is an urgent need to consider the trajectory of disease burden in the coming years.

Added value of this study

We report long-term projections of HCV-related disease burden to 2030 for the United States under 5 different scenarios. Our approach integrates the latest estimates of HCV diagnosis and treatment, and extrapolates potential trajectories after the COVID-19 pandemic. Baseline (status quo) projections based on the recent pre-pandemic trends can serve as a benchmark against which the effect of the COVID-19 pandemic or other interventions can be measured. Scenarios were designed to simulate the impact of continued declines in treatment after the pandemic, as well as scenarios where goals for HCV elimination are reached by increasing treatment alone, or in tandem with reductions in new infections through harm reduction.

Implications of all the available evidence

There were an estimated 2.5 million chronically infected individuals in the United States in 2020, with over 900,000 new infections occurring from 2007 to 2019. Under the base scenario, over 100,000 Americans were projected to die of HCV-related liver disease. Based on modeling forecasts, approximately 30,000 liver deaths can be prevented in the United States by 2030 through increased diagnosis and treatment in tandem with infection prevention efforts. HCV elimination can be achieved in the next 9 years with an increased emphasis on prevention (harm reduction), one-time screening for all adults (plus regular screening for high-risk groups), and timely access to direct acting antiviral treatment without restriction. In order to achieve targets without harm reduction, an additional 500,000–600,000 additional individuals would have to be treated. In the wake of the COVID pandemic, further efforts are needed to screen, diagnose, and treat persons with chronic HCV infection in the United States in order to avert a large disease and economic burden of liver disease.

The HCV epidemic can be characterized in two distinct waves. The first was concentrated among individuals born during 1945–1965 [4], and included historical transmission through blood donation, nosocomial routes, and drug use, while the more recent wave has been spurred by the opioid crisis. The availability of highly effective direct acting antiviral (DAA) treatments as well as preventive measures including blood safety protocols in healthcare settings and harm reduction services for persons who inject drugs (PWID) suggest that HCV can be eliminated with the right combination of prevention and treatment.

As the US reaches > 50 % of the total population fully vaccinated for COVID-19 and healthcare services begin to normalize, there is an urgent need to reassess the country's progress toward HCV elimination and evaluate scenarios for recovery. The objective of this analysis was to establish a baseline for HCV prevalence and cascade of care in the US and evaluate the impact of scenarios on future disease burden.

Methods

This analysis uses a previously published and internationally validated Markov model [5] to forecast the prevalence and disease burden of chronic HCV infection in the US [6–8]. The data used for modeling were obtained through literature review, unpublished sources, and expert input (Table 1, Appendix Fig. 1). Estimated HCV prevalence, prevalence by age and sex, and the number of persons previously diagnosed and treated were applied in the model. After the last year of available data, the model forecasted the HCV-RNA+ population through 2050 by single year age- and sex- cohorts, disease stage (with age-, sex- and disease stage- specific progression rates), mortality (all-cause and liver-related), and interventions (Appendix Section 1). All-cause mortality rates were adjusted for excess mortality among the portion of infected individuals actively injecting (Appendix Section 1).

The model considers both horizontally and vertically acquired new infections. Vertically acquired infections were based on mother-to-child HCV transmission rate [9], modeled age group-specific chronic prevalence of HCV and reported fertility rates among women of childbearing age [10]. HCV-infected infants entered the disease burden model at age zero, and their subsequent disease progression was tracked.

Historical prevalence of HCV was obtained from an analysis of NHANES data collected during 2003–2010 combined with studies of high-risk groups estimating that there were 3.5 million [range 2.5 million-4.7 million] HCV-RNA+ adults living in the US in 2006 [11]. The prevalence of HCV by age and sex was based on an analysis of 2001–2008 NHANES data, weighted to the total number of HCV infections in the US in 2006 [12].

The proportion of patients who had been diagnosed previously was retrieved for the year 2010 [12,13], with annual estimates of newly diagnosed obtained from CDC surveillance reports and publications [14–16]. The annual number of patients initiated on

Table 1
Model inputs and sources.

Input	Year	Value (Range)	Source
Prevalence (HCV-RNA+)	2003–2010	3.5 (2.5–4.7) million 1.1 % (0.8–1.5 %)	[11]
Prevalence by age and sex	2006	Appendix Fig. 1	[12]
Viremic rate	2010	75 %	[11]
Genotype	2003–2014	79 % G1	[27]
Annually diagnosed	2010–2018	110,000	[14]
Previously diagnosed	2010	1.5 million (45 %)	[13]
Treated	2019	195,000	Medicine
	2020	140,000–150,000	Sales data
	2021	110,000 – 120,000	
HCV+ IDU	2011	7 %	[28]
Liver transplants	1988–2018	1700 in 2018	[29]

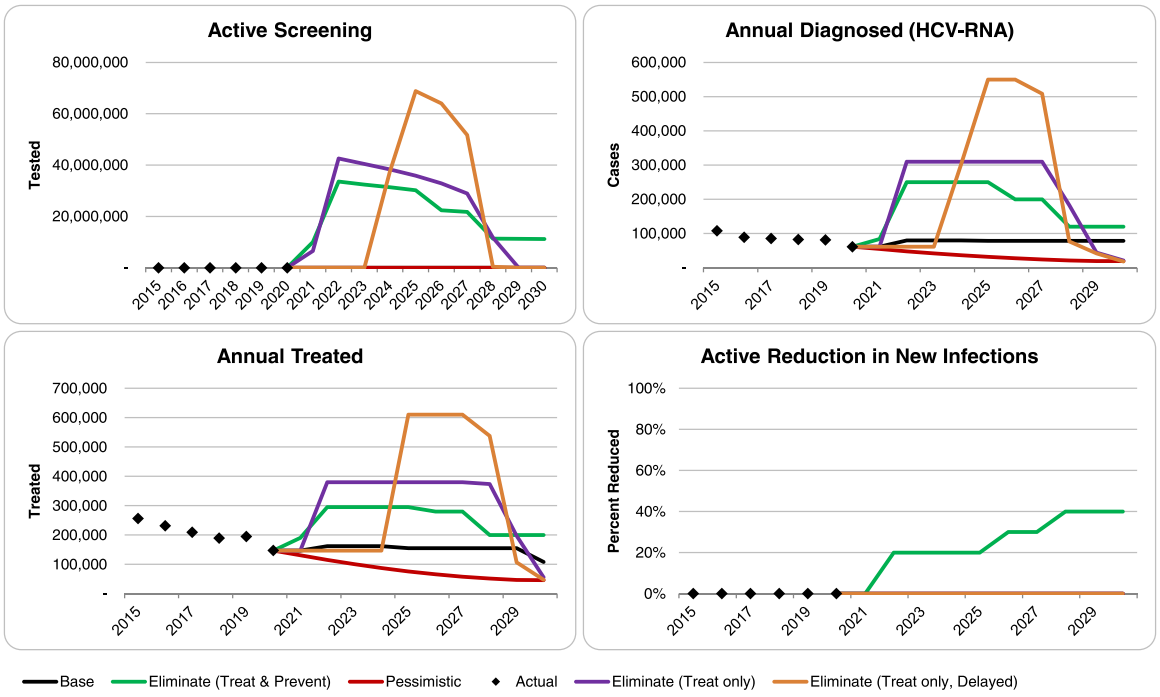

Fig. 1. Scenario inputs.

treatment was retrieved from medicines sales data through July 2021 [17].

As risk factors for HCV transmission have transitioned to a younger and harder to reach population, new (acute) infections are increasingly likely to be underreported in state and federal surveillance systems. As a result, two methods for estimating new infections were combined. First, the model was calibrated to the number of adjusted incident cases reported to CDC through 2006 [14, 16, 18]. Next, unpublished analyses conducted in collaboration with 23 individual states were used to calculate average state incidence. Within each state studied, the number of diagnosed infections (acute or chronic) among persons under 35 years of age was used as a proxy to estimate the minimum number of new infections occurring within the state (assuming that most infections among this population occurred within the last few years), and state level estimates were aggregated.

Modeled scenarios

Once the model was developed, a variety of "what-if" scenarios were run to evaluate the impact of future decisions. The scenarios included are as follows:

A historical baseline scenario (2019 Base) was developed using empirical diagnosis and treatment data through 2019, before considering the impact of the COVID-19 pandemic. After 2019, screening was assumed to remain constant, resulting in fewer newly diagnosed cases each year. Assuming no major improvements in case finding or linkage to treatment, the number of patients starting treatment each year would decrease.

A current baseline scenario (Base) was developed using empirical treatment data for the year 2020 and partial year data from 2021, and assuming two years of reductions in the number of patients initiated on treatment following the COVID-19 pandemic (Fig. 1). Beginning in 2022, interventions were assumed to resume as initially described in the 2019 Base scenario.

A pessimistic scenario (Pessimistic) was developed to identify the impact of long-term declines in HCV diagnosis and treatment following the COVID-19 pandemic (Fig. 1). In this scenario, diagnosis and treatment declined continuously until 2030.

An elimination scenario [Eliminate (Treat & Prevent)] was developed to identify the steps needed to achieve the WHO targets (90 % diagnosed; 80 % treated; 65 % reduction in mortality; 80 % reduction in incidence) as well as the US national elimination goals of a reduction in acute HCV (20 % by 2025; 90 % by 2030) and mortality (25 %; 65 %, respectively), as well as an HCV viral clearance rate of 58 % by 2025 and 80 % by 2030. First, the number of treatment initiations annually was increased to achieve mortality targets and treatment targets. Next, the number of patients diagnosed was increased so that enough patients would be available to treat, and achieve diagnosis targets. Finally, annual reductions in new infections was applied, to simulate the impact of prevention measures, until the incidence target was met. This scenario assumed that the national screening of pregnant women and all adults would be fully implemented by 2022, with the number of screening tests calculated based on the number of patients diagnosed in the scenario (Fig. 1).

Two additional elimination scenarios were developed to assess the measures needed to achieve 2030 elimination goals by only increasing treatment and diagnosis (as described for the scenario above), without reducing new infections beyond what would be predicted as a result of reduced prevalence. Under the Eliminate (Treat only) scenario, diagnosis and treatment were increased beginning in 2022 to reach 2030 targets, while under the Eliminate, (Treat only, delayed) scenario, increases began in 2025 to reach 2030 targets.

Uncertainty analysis

Crystal Ball release 11.1.2.3.500 was used to calculate uncertainty intervals (UIs) and conduct sensitivity analyses. β-PERT distributions were used for all uncertain inputs. A Monte Carlo simulation with 1000 trials was used to estimate 95 % UIs.

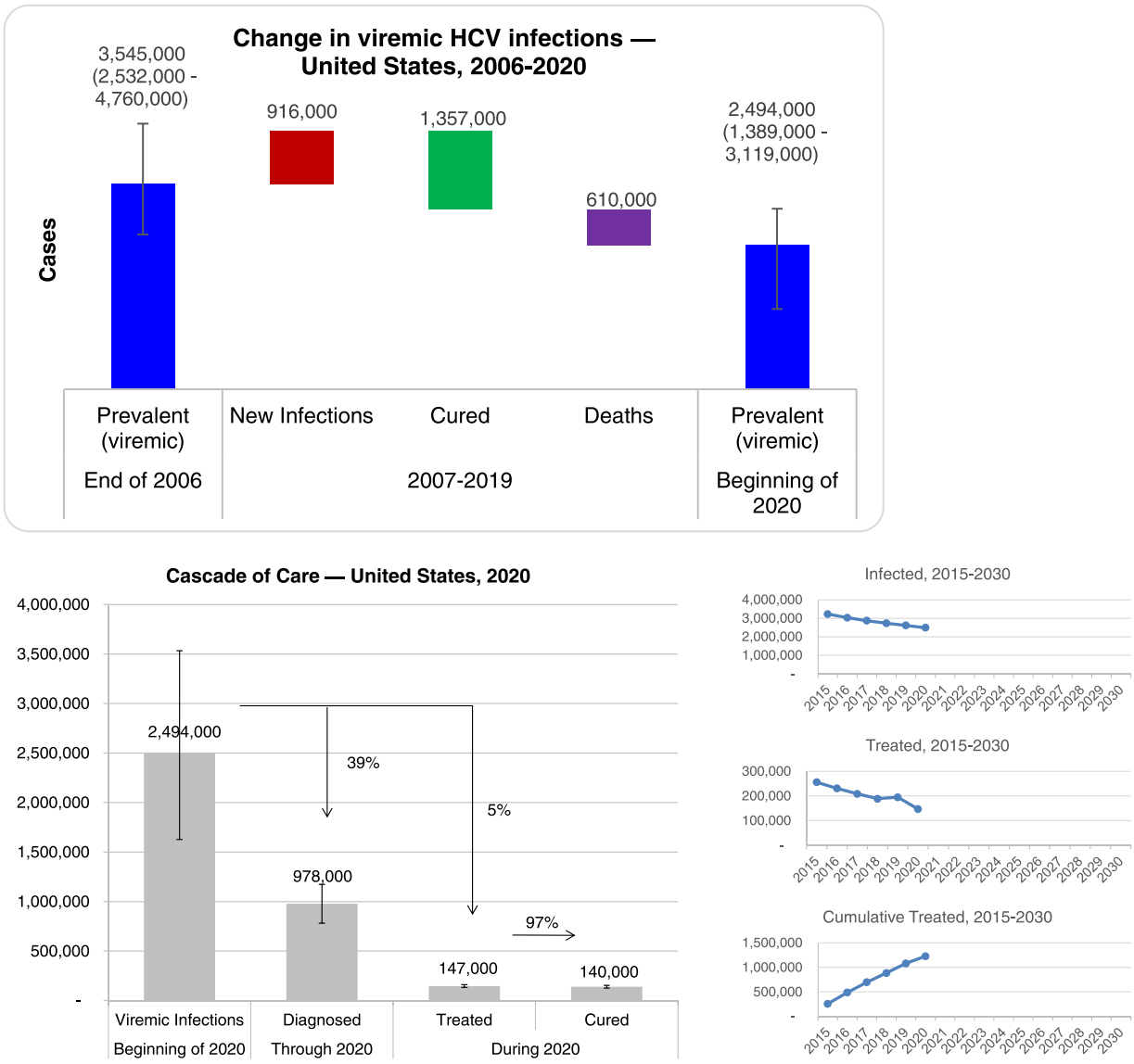

Fig. 2. Change in viremic HCV infections, 2006–2020 & Cascade of Cascade, 2020.

Funding source

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IRB approval

This study was a retrospective analysis of previously collected published or unpublished aggregate data. No identifiable information was accessed over the course of the study.

Results

At the beginning of 2020, there were an estimated 2.5 million (95 % UI: 1.4 million –3.1 million) viremic (HCV-RNA+) infections in the US, a reduction of just over 1 million infections from 2006 (Fig. 2). Between 2007 and 2019 there were an estimated 916,000 new chronic infections, 610,000 deaths (all cause or liver related) and 1.4 million cured infections (Fig. 2). In 2020, it was estimated that 39 % (n = 978,000) of viremic patients had been diagnosed, and that 147,000 (5 %) were treated during the year, with 140,000 (97 %) achieving sustained virologic response (SVR) (Fig. 2). Relative to 2019, the number of patients treated in 2020 declined by 30 %. Preliminary data from the first half of 2021 suggest that the number of patients initiating treatment was 34 % lower than the first half of 2019. Assuming no major changes in treatment over the second half of 2021, between 110,000 and 120,000 patients could be expected to initiate treatment over the course of the full calendar year.

There were an estimated 4.3 million births among 75.4 million women of childbearing age in the US in 2020. HCV prevalence by age group (among females in the model) was used to estimate that 23,400 births (0.5 % of total) occurred among chronically infected women, with an estimated 1400 new infections in 2020 among infants as the result of vertical transmission.

The key drivers of uncertainty for model prevalence in 2020 were the input range around starting prevalence in 2016, and uncertainties around acute HCV to spontaneous clearance rate, and mild to moderate fibrosis transition rates (Appendix Fig. 2).

Base

Under the base scenario, there were 836,000 new HCV diagnoses and 1.7 million patients treated for HCV between 2020 and 2030,

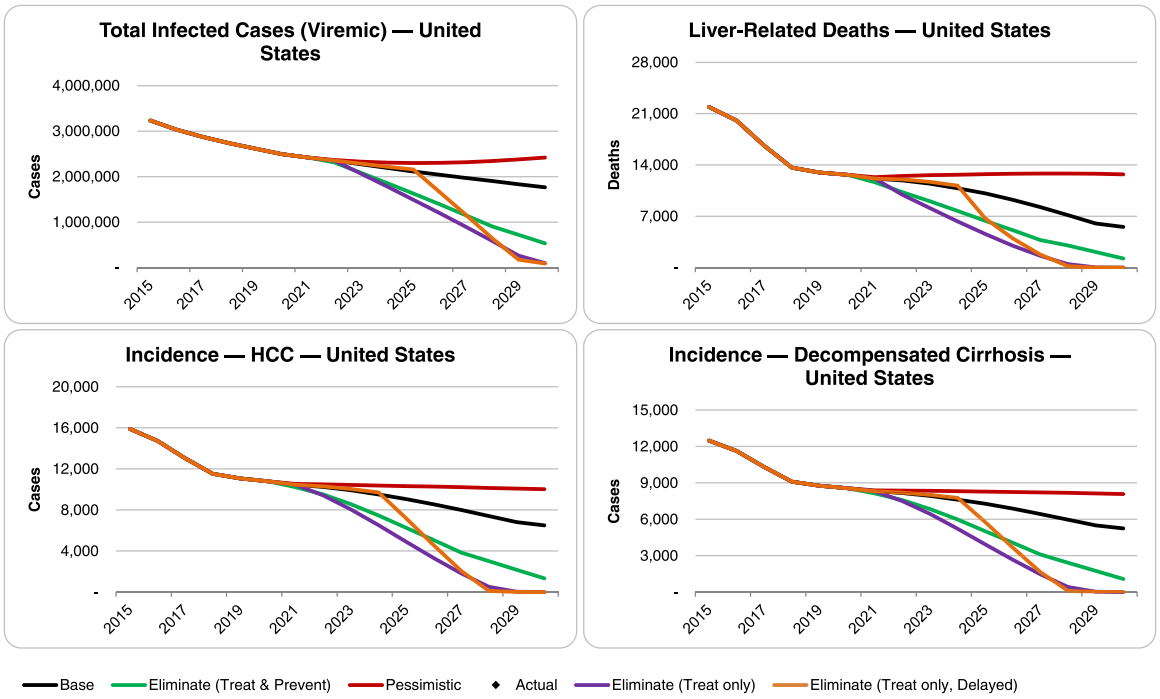

Fig. 3. Progress toward the WHO 2030 targets for liver-related deaths and incidence of HCV – United States, 2015–2030.

with an annual maximum of 80,100 new diagnoses and 162,000 initiated on treatment observed in 2022 (Fig. 1). There were 1.2 million incident chronic cases during 2020–2030. Incident cases remained nearly constant during 2020–2030 at 103,000 annually.

Of the 2.5 million viremic infections in the US in 2020, there were an estimated 352,000 (121,000–561,000) individuals with cirrhosis or advanced liver disease. By 2030, the number of infected cases was estimated at 1.8 million (740,000–2.5 million) (30 % decline from 2020) and there were 205,000 (59,700–332,000) individuals with cirrhosis or advanced disease (40 % decline). There were an estimated 10,800 (3700–16,800) cases of incident HCV-related HCC in 2020, 8600 (3000–13,600) new cases of decompensated cirrhosis, and 12,700 (3500–20,900) liver-related deaths (LRDs). By 2030, there were 6500 (1900–10,200) annual incident HCC cases (40 % decline), 5200 (95 % UI: 1400–8300) decompensated cirrhosis cases (40 % decline), and 5500 (95 % UI: 1600–9800) LRDs (55 % decline) (Fig. 3). During the study period (2020–2030), there were 105,000 LRDs, 77,800 cumulative incident decompensated cirrhosis cases, and 97,200 incident HCC cases.

Outcomes of the historical baseline scenario (2019 Base) compared with the base scenario are presented in the Supplementary materials (Appendix Fig. 3).

Eliminate (treat & prevent)

This scenario was developed to reach all elimination targets by 2030. Under this scenario, 218 million HCV screening tests were performed during 2020–2030, leading to 1.9 million new HCV diagnoses. Considering treatment of newly diagnosed as well as previously diagnosed infections, there were 2.7 million total HCV treatments during 2020–2030, with an average of 260,000 patients treated annually during 2022–2030. In addition to the impact of treatment as prevention, active reductions in new infections were needed, beginning in 2022 and reaching peak levels by 2028 (Fig. 1). This resulted in annual incident cases decreasing by 90 % from 103,000 in 2020–9500 in 2030, with 633,000 incident chronic cases during 2020–2030.

In 2030, the numbers of prevalent cases (n = 535,000) and patients living with cirrhosis or advanced liver disease (n = 66,200) were estimated to be 70 % lower than the base scenario, while incident HCC cases (n = 1300), incident decompensated cirrhosis cases (n = 1100), and annual LRDs (n = 1200) were estimated to be 80 % lower than the base scenario. Cumulative (2020–2030) cases of HCC (n = 68,200), decompensated cirrhosis (n = 54,500) and LRDs (n = 72,900) were reduced by 30 % relative to the base.

Pessimistic

Under a pessimistic scenario where HCV programming declines indefinitely, there was no active screening for HCV, leading to only 532,000 diagnoses during 2020–2030. In total, 937,000 HCV treatments were provided during 2020–2030. With reduced treatment and no active reductions in new infections, annual incident cases were increased by 25 % from 103,000 in 2020–129,000 in 2030, with 1.3 million cumulative incident chronic cases.

In 2030, the number of prevalent cases (n = 2.4 million) and patients with cirrhosis or advanced liver disease (n = 323,000) increased by 35 % and 60 %, respectively, compared with the base scenario. Incident HCC cases (n = 9900) and incident decompensated cirrhosis cases (n = 8000) increased 50–55 %, while annual LRDs (n = 13,000) were estimated to be twice as high as the base scenario. Cumulative measures were also increased relative to the base with HCC cases (n = 113,000) and decompensated cirrhosis cases (n = 90,200) increasing 16 % and LRDs (n = 140,000) increasing 35 %.

Eliminate (treat only)

In the scenario modeling elimination through treatment alone, there were 3.2 million total HCV treatments during 2020–2030, 233 million screening tests and 2.2 million newly diagnosed. Due to the impact of treatment as prevention, incident cases decreased by 90 % from 103,000 in 2020–9900 in 2030 (791,000 cumulative incident chronic cases during 2020–2030).

Under this scenario, there were an estimated 98,200 prevalent cases in 2030, 95 % fewer than the base scenario. All annual end

Table 2
Scenario outcomes, 2020–2030.

Scenario	Cumulative Actively Screened	Cumulative Diagnosed	Cumulative Treated	Change in Incident Cases, 2020–2030 (%)	Change in LRDs, 2020–2030 (%)	Averted HCC	Averted LRDs
Base	–	836,000	1,664,000	– 0.3 %	– 55 %	–	–
Eliminate (Treat & Prevent)	218,111,000	1,927,000	2,692,000	– 90 %	– 90 %	–32,400	– 29,000
Pessimistic	–	921,000	937,000	+25 %	+1 %	+34,200	+16,500
Eliminate (Treat only)	232,675,000	2,228,000	3,200,000	– 90 %	– > 99 %	–46,500	– 41,400
Eliminate (Treat only, Delayed)	234,265,000	2,292,000	3,257,000	– 90 %	– > 99 %	–33,000	– 32,100

stage outcomes were estimated to decline by > 99 % decline from the base scenario, while a 45 % reduction was estimated for all cumulative measures (2020–2030: 55,800 HCC cases, 44,500 decompensated cirrhosis cases, and 58,800 LRDs).

Eliminate (treat only, delayed)

Under this scenario, where implementing a treatment-only elimination program was delayed by two years (2025 instead of 2022), there were 3.3 million total HCV treatments during 2020–2030, and 234 million screening tests leading to 2.3 million new diagnoses. Due to the impact of treatment as prevention, incident cases decreased by 90 % from 103,000 in 2020–9900 in 2030 (884,000 cumulative incident chronic cases during 2020–2030).

Under this scenario, there were an estimated 89,100 prevalent cases in 2030, 95 % fewer than the base scenario. All annual end stage outcomes were estimated to decline by > 99 % decline from the base scenario, while a 35 % reduction was estimated for all cumulative measures (2020–2030: 65,200 HCC cases, 52,000 decompensated cirrhosis cases, and 72,400 LRDs).

Discussion

The results of this analysis demonstrate that the burden of chronic HCV infection will persist in the coming decades without renewed action. Due to extreme pressures on healthcare systems during the COVID-19 pandemic, progress toward HCV elimination has been slowed. From 2014–2019, ~1.2 million patients were treated for HCV in the US, however in 2020 and 2021, > 30 % fewer patients were initiated on treatment each year than in 2019. Continued declines in diagnosis and treatment (as seen in the pessimistic scenario) could result in 34,000 excess HCC cases and 16,500 excess LRDs over the next ten years, relative to the base scenario. Alternatively, intervention scenarios to achieve elimination targets could prevent more than 32,000 HCC cases and at least 29,000 LRDs.

To achieve all national targets by 2025 and 2030, 1.9 million people would need to be diagnosed, with 1.4 million people initiated on treatment before 2025 and 2.7 million treated by 2030 (average of 260,000 treated per year from 2020 to 2030). Reducing new infections by 90 % without prevention measures could be achieved with 380,000 patients treated annually beginning in 2022 (95 % greater than 195,000 treated in 2019), and 3.2 million cumulative treated. Waiting until 2025 would require a minimum of 610,000 treated per year (215 % greater than 2019), and 3.3 million cumulative treated. After 2026, eliminating new infections through treatment alone would not be possible.

Although it is not possible to predict which trajectory HCV elimination will follow in the US; elements of the response to HCV are in line with strategies used by other countries on track for elimination [2,19]. A recent study found that a one-time universal screening of US residents, followed by treatment for those with chronic HCV was cost effective in populations with an anti-HCV prevalence greater than 0.07 % [20]. If a universal screening strategy is well implemented with high uptake in the population, and all identified patients are linked to care in a timely fashion, then the expected trajectory may approximate that of the elimination scenario. However, a major limitation in the US response is the lack of comprehensive harm reduction programs (including needle and syringe programs and opioid substitution therapy) across all states and communities.

Preventing transmission of HCV should be a top priority for health systems and policy makers. The current analysis shows that 500–600 thousand additional treatments will be necessary to achieve the same outcomes, at likely greater cost, as compared with a scenario with reduced incidence. As most new infections in the US are attributed to injection drug abuse, harm reduction programs should be implemented that include opioid substitution therapy, needle exchange, and counseling; the impact of multiple harm reduction measures has an additive impact on preventing transmission [21]. In addition, harm reduction measures have the potential to reduce overall mortality, with an estimated > 500,000 deaths averted during 1999–2013 if midlife mortality rates in the US had continued their historical downward trajectory [22].

Based on estimates from the NHANES datasets, and high-risk populations [11,23], viremic cases among adults declined from 3.5 million during 2003–2010–2.4 million during 2013–2016. In the current analysis, we applied the estimates from 2003 to 2010 due to increasing levels of uncertainty in recent years, particularly the marked increase in injection drug abuse that has resulted in a greater portion of HCV cases in high-risk groups. While these high-risk populations were quantified in CDC analyses, they are subject to greater uncertainty than general population surveys. In 2020, drug overdose deaths in the US reached a record high of 93,331, an increase of more than 20,000 from 2019 [24]. This portends ongoing potential for high incidence among vulnerable populations.

The USPSTF currently recommends screening all adults aged 18–79 years for HCV infection [25]; in addition, screening for HCV as part of pregnancy has the potential to increase overall diagnoses and prevent vertical transmission of HCV. A viremic mother has a 5.8 % (95 % CI: 4.2–7.8%) chance of transmitting HCV to her child during pregnancy or delivery and 10.8 % (95 % CI, 7.6–15.2 %) if she is co-infected with HIV [9]. Based on 2012 guidelines [4], only pregnant women with HCV risk factors were recommended to receive HCV screening, however a 2018 update [26] recommends universal screening of all pregnant women except in very low prevalence (< 0.1 %) settings. There should be greater efforts to raise awareness of HCV screening recommendations among patients and providers and the usage of standardized tools such as electronic medical records to prompt clinicians to offer HCV screening. Table 2.

Conclusion

The current analysis demonstrates that substantial reductions in HCV disease burden have been possible with coordinated efforts to screen, diagnose and treat chronic HCV patients. However, the dual

impact of an escalating opioid crisis and a healthcare system stressed by the COVID-19 pandemic have the potential to result in increasing rates of new infections, and long-term increases in liver-related morbidity and mortality. In order to avert these increases, there is an urgent need for clinicians and policy makers to redouble their efforts to screen and treat infected patients, as well as offer effective harm reduction programs to decrease transmission and new infections.

IRB approval

This study was a retrospective analysis of previously collected published or unpublished aggregate data. No identifiable information was accessed over the course of the study.

CRediT authorship contribution statement

SB, **CE** and **HR** prepared the first draft and finalized the draft based on comments from other authors. All other authors provided data, analyzed data, reviewed results, provided guidance on methodology, and provided critical feedback on the report.

Competing interests

SB and CE are employees of the Center for Disease Analysis Foundation (CDAF). Over the past 3 years, CDAF has received research grants from Gilead and AbbVie. CDAF has also received grants from CDC Foundation, John C. Martin Foundation, ASTHO, Zeshan Foundation, and private donors. KB reports grants from Sagimet, Gilead, Salix, Novonordisk, Allergan and Intercept. RB reports grants and research support from Abbvie and Gilead. PMG reports consulting fees and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Gilead Sciences and AbbVie. NT reports grants or contracts from Gilead Sciences, Genentech, Roche; consulting fees from EXIGO Mgmt LLC, ENYO, PPD Pharma; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from University of Maryland. HR reports being a member of advisory boards for Gilead, AbbVie, Abbott, Merck. CDA has received research funding from Gilead, Assembly Biosciences, AbbVie, and Roche. CDA Foundation has received research grants from Gilead.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2022.11.021.

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