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Projected Long-Term Impact of the Coronavirus Disease 2019 (COVID-19) Pandemic on Hepatitis C Outcomes in the United States: A Modeling Study

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Background. The coronavirus disease 2019 (COVID-19) pandemic disrupted access to and uptake of hepatitis C virus (HCV) care services in the United States. It is unknown how substantially the pandemic will impact long-term HCV-related outcomes.

Methods. We used a microsimulation to estimate the 10-year impact of COVID-19 disruptions in healthcare delivery on HCV outcomes including identified infections, linkage to care, treatment initiation and completion, cirrhosis, and liver-related death. We modeled hypothetical scenarios consisting of an 18-month pandemic-related disruption in HCV care starting in March 2020 followed by varying returns to pre-pandemic rates of screening, linkage, and treatment through March 2030 and compared them to a counterfactual scenario in which there was no COVID-19 pandemic or disruptions in care. We also performed alternate scenario analyses in which the pandemic disruption lasted for 12 and 24 months.

Results. Compared to the "no pandemic" scenario, in the scenario in which there is no return to pre-pandemic levels of HCV care delivery, we estimate 1060 fewer identified cases, 21 additional cases of cirrhosis, and 16 additional liver-related deaths per 100 000 people. Only 3% of identified cases initiate treatment and <1% achieve sustained virologic response (SVR). Compared to "no pandemic," the best-case scenario in which an 18-month care disruption is followed by a return to pre-pandemic levels, we estimated a smaller proportion of infections identified and achieving SVR.

Conclusions. A recommitment to the HCV epidemic in the United States that involves additional resources coupled with aggressive efforts to screen, link, and treat people with HCV is needed to overcome the COVID-19-related disruptions.

Keywords. COVID-19; coronavirus; hepatitis C; elimination; modeling.

The coronavirus disease 2019 (COVID-19) pandemic led to broad disruptions in the United States and globally, including access to and uptake of non-COVID healthcare services [1, 2]. The pandemic has had a disproportionately greater impact on vulnerable persons, including persons who experience homelessness, persons with substance use disorders, and Black, Indigenous, and people of color [3]. Not coincidentally, these same populations are disproportionately affected by the hepatitis C virus (HCV) epidemic in the United States [4]. Over the last 20 years, the epidemiology of HCV in the United States has shifted to younger, predominantly marginalized individuals, particularly those who inject drugs [5].

Prior to the COVID-19 pandemic, the United States targeted HCV elimination by 2030. The elimination targets were those outlined by the World Health Organization (WHO), which included (relative to 2015 benchmark levels): (1) diagnosing 90% of the HCV-infected population, (2) treating 80% of the eligible population, (3) reducing new HCV infections by 80%, and (4) reducing HCV-related deaths by 65% [6]. To achieve elimination, a particular focus was placed on persons who inject drugs (PWID)—the population with the highest incidence of HCV infections in the United States. Even with pre-pandemic investments, recent modeling demonstrated that only 3 US states were on track to achieve all 4 elimination targets by 2030 and that the United States would likely not achieve elimination until 2037 [7].

Even though these elimination goals may not be realistic, achieving these elimination goals was set back by the COVID-19 pandemic. Most service delivery was disrupted due to stay-in-place orders, along with diversion of public health and medical resources, leading to short-term interruptions in HCV care. In one safety-net hospital in Massachusetts with a well-established HCV treatment program, HCV testing

decreased by nearly 50% and new HCV-positive patient identification decreased by 42% in the three and a half months following stay-in-place orders compared to 3 and a half months before [8, 9].

The long-term impact of COVID-19-related HCV care disruptions on the HCV epidemic is not yet known. Public health officials need to understand the consequences of the COVID-19 pandemic on HCV epidemiology and the impact of potential future interventions at different points along the HCV care cascade. We projected the 10-year impact of 12-, 18-, and 24-month COVID-19 disruptions in healthcare delivery on HCV outcomes under a range of different scenarios of post-pandemic screening and treatment rates. We evaluate how targeted improvements could change HCV disease trajectories, including identified infections, linkage to care, treatment initiation and completion, cirrhosis, and liver-related death.

METHODS

Analytic Overview

We used the Hepatitis C Cost-Effectiveness (HEP-CE) model, a Monte Carlo microsimulation model of HCV [10], to estimate the impact of the COVID-19 pandemic on HCV outcomes by 2030. We created hypothetical scenarios consisting of different levels of disruptions in HCV care due to the pandemic and we compared them to a counterfactual scenario in which there was no COVID-19 pandemic, thus no disruptions in HCV care. We simulated different levels of disruption by changing the rates of milestones along the HCV cascade of care: HCV testing, linkage to care, treatment initiation, and treatment completion. We defined the abrupt pandemic disruption using decreased rates of HCV testing, diagnosis, linkage, treatment initiation, and treatment completion over an 18-month period. These decreases were informed by real-world values from a large, urban safety-net hospital in Boston [8, 9], which serves a population including those most at risk for and with HCV infection. We modeled 18-month COVID-related HCV care cascade disruptions starting in March 2020 preceding the following long-term scenarios stretching until March 2030: (1) continued pandemic rates, (2) 25% increase in rates to pre-pandemic levels, (3) 50% increase in rates to pre-pandemic levels, (4) 75% increase in rates to pre-pandemic levels, and (5) return to pre-pandemic rates. In each scenario, we assumed that those rates remain constant for the remainder of the simulated time period. We also performed alternate scenario analyses in which the pandemic disruption lasted for 12-months and 24-months, thus leaving varying amounts of time to achieve 2030 targets. We performed sensitivity analyses in which we increased individual and combined steps in the cascade to twice that of the pre-pandemic numbers (following an 18-month disruption) to determine what an influx of resources might accomplish in terms of getting "back on track."

We used data from national databases, clinical trials, and observational cohorts to inform parameter values (Table 1 and Supplementary Tables 2–5). The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guided writing of this manuscript (Supplementary Table 1).

HEP-CE Model Structure and Inputs
Model Structure
The model is a closed cohort microsimulation (Figure 1 and Supplementary Figure 1), meaning that there are no new entrants to the simulation; however, individuals who are successfully treated can become re-infected. We simulate the 10-year (March 2020–March 2030) course of a hypothetical cohort that

Table 1. Key Model Inputs for Analysis of Long-Term Impact of COVID on HCV in the United States, "No Pandemic" Scenario (Base Case)

Parameter	Estimate	Source
Mean age of cohort (years)	38.8	[39]
Male (%)	49.2	[39]
Risk behavior prevalence		
Current PWID	See Supplementary	
Former PWID	Table	
None		
HCV prevalence		
Overall	See Supplementary	
Current PWID	Table	
Former PWID		
None		
Mean age of infection (years)	23	[19, 20]
SMR, active PWID		[40]
Male	6	Calibrated[b]
Female	4	Calibrated[b]
SMR, former PWID	1	Calibrated[b]
Monthly initiation rate, PWID	0.000358	[18]
Monthly cessation rate, PWID	0.0139	[18]
Monthly relapse rate, PWID	0.0329	[18]
Acute infection clearance probability (%)	26	[41]
Post-SVR mortality multiplier	0.06	[15]
Reinfection, PWID (cases/100 person-years)	12	[42, 43]
Background screening (tests per 100 person-years)		
Active PWID[a]	38.8	[24]
No PWID[a]	2.69	[44]
Former PWID[a]	4.83	[44]
Background linkage to care (%)[a]	69	[45]
Relink (%)[a]	46.9	[46]
Voluntary relink (monthly probability)	0.001113	Expert opinion
Treatment initiation[a]		
Treatment naive (%)	27	[45]
Treatment experienced (%)	27	
Treatment completion (%)	79	[45]

Abbreviations: COVID, coronavirus disease; HCV, hepatitis C virus; PWID, person who injects drugs; SMR, standardized mortality ratio; SVR, sustained virologic response.

[a]Base case (no pandemic scenario) values. Adjustments to these numbers to simulate the pandemic and post-pandemic rates are outlined in Table 2.

[b]We began with SMRs from the published literature but adjusted to the final SMRs by calibrating to life expectancy and HCV prevalence.

has the demographics and HCV epidemiology of the US adult population in 2020. The mean age of the initial cohort was 40.5 years, and 49% were male. Approximately 90.9% had never injected drugs whereas 8.7% had ever injected drugs and 0.4% were actively using injected drugs (derivation described in detail in Supplementary Appendix). At the beginning of the simulation, the overall initial HCV seroprevalence was 1.0% [11]. The model includes several modules described below.

HCV Infection, Risk Factors and Natural History

HCV prevalence is stratified by age, sex, and risk behaviors. In this analysis, only a small proportion of the initial cohort had HCV (consistent with the epidemiology of the US adult population). We simulate initiation, duration, and cessation of injection drug use behavior. Incidence of HCV and mortality from non-HCV causes varied by current drug use status (Supplementary Appendix). The incidence of new HCV infections (both initial infection and reinfection) among simulated people is conditional on current injection drug use. In the model, this corresponds to higher HCV incidence among young people due to higher prevalence of injection drug use in that group, and the tendency for individuals to leave injection drug use as they age.

Liver-attributable mortality occurs only among individuals who have reached METAVIR stage F4 (cirrhosis).

HCV Testing

Simulated individuals have a monthly probability of HCV testing that varies by age, sex, and drug use status. In the model, routine one-time testing as is recommended [12] does not ensure that all people receive an HCV test, nor does it prevent some individuals from being tested multiple times in the study period.

HCV Treatment

When an individual is identified as HCV infected, they have a monthly probability of linking to HCV care. Individuals who do not link to care upon diagnosis have a different probability of relinking in the future (Supplementary Appendix). There is no predefined limit to the number of times an individual can link or relink. After successful linkage, individuals have a probability of accepting treatment and another for completing treatment.

HCV treatment that achieves SVR halts fibrosis progression [13, 14] and following SVR, liver-related mortality among cirrhotic individuals is reduced [15].

Model Data
HCV Infection, Risk Factors, and Natural History

We estimated age- and sex-stratified HCV prevalence among active PWID using published literature, whereas prevalence for other risk behavior groups were derived from OCHIN (formerly the Oregon Community Health Information Network), a national network of 500 community health center sites that

includes approximately 6 million patients (see Supplementary Appendix). We adjusted stratified prevalence to ensure an overall HCV prevalence of 1.0% in the starting cohort based on known estimates by Rosenberg et al [11]. We used standardized mortality ratios (SMRs) for current and former PWID and calibrated these inputs to the life expectancy of a 40-year-old in the United States (78.6 years)[16] and a 19-year-old person who injects drugs in the United States (61 years) [17].

We modeled movement between injection drug use states over the course of the simulation using AIDS Linked to the Intravenous Experience (ALIVE) cohort data [18].

The median time to cirrhosis from HCV infection (mean age of infection 23 years) was 25 years [19–22], and the rate of liver-related deaths with cirrhosis was 3 per 100 person-years [23].

HCV Testing

We estimated HCV testing rates among PWID using data from cohorts of that population [24]. We estimated testing rates in the non-drug injecting cohort using published data (see Supplementary Appendix) [25].

HCV Treatment

We modeled an oral, pan-genotypic HCV regimen for all fibrosis stages without treatment restrictions. Treatment duration and outcomes were derived from cohort studies and clinical trials [26–30].

COVID-19 Impact

We analyzed data from Boston Medical Center (BMC) to estimate the relative change in HCV testing, diagnosis, linkage, treatment initiation, and treatment completion since the beginning of the pandemic in Boston (1 March 2020) (Table 2). BMC is New England's largest safety net hospital with a patient population that largely reflects the US population at risk for or infected with HCV [8]. BMC developed an institution-wide HCV screening program which was implemented in November 2016 and has been used in conjunction with the medical center's hospital-wide outreach, linkage, and treatment efforts [8]. To calculate the pre-pandemic rates, we averaged BMC cascade data from January 2019 through February 2020. For pandemic rates, we averaged BMC data from March 2020 through February 2021. We divided pandemic rates by pre-pandemic rates to develop a "pandemic multiplier" that was applied to model parameters to estimate pandemic rates on a national level.

In our base case scenario analysis, we applied these rate reductions over an 18-month period (from March 2020 to August 2021). After that initial 18-month period, we increased the testing, diagnosis, linkage, and treatment parameters from pandemic levels toward pre-pandemic levels (increasing the cascade rates by 0%, 25%, 50%, 75%, and 100%) and ran the model for each of these scenarios until March 2030. In alternate scenario

Table 2. HCV Cascade of Care, the Impact of COVID, and Estimated Returns Following the Pandemic (Input Parameters)

	Antibody Screening Current PWID[a]	Antibody Screening Never PWID[a]	Antibody Screening, Former PWID[a]	Linkage (%)	Relinkage (%)	Treatment Initiation (%)	Treatment Completion (%)
Base case (pre-pandemic values)	38.80	2.69	4.83	69	46	27	79
0% return[c]	29.88	2.07	3.72	31	21	9	20
25% return	32.11	2.23	4.00	41	27	13	35
50% return	34.34	2.38	4.27	50	33	19	49
75% return	36.57	2.54	4.55	60	40	22	64
200% of pre-pandemic for screening	77.60	5.38	9.66	69	46	27	79
200% of pre-pandemic for linkage/ relinkage	38.80	2.69	4.83	100[b]	92	27	79
200% of pre-pandemic for treatment initiation/completion	38.80	2.69	4.83	69	46	52	100[b]
200% of pre-pandemic for all steps	77.60	5.38	9.66	100[b]	92	52	100[b]

Abbreviations: COVID, coronavirus disease; HCV, hepatitis C virus; PWID, person who injects drugs.

[a]Screening reported as HCV tests per 100 person-years.

[b]Doubling would have led to a number greater than 100%.

[c]0% return means that pandemic levels persist for the full 10-year period. These numbers were calculated by averaging BMC data from March 2020 through February 2021. We divided pandemic rates by pre-pandemic rates to develop a "pandemic multiplier" that was applied to model parameters to estimate pandemic rates on a national level.

analyses, we assumed that the pandemic disruptions lasted for 12 months and 24 months. After each of these periods, we again increased cascade rates from 0% to 100% and ran the model for each of these scenarios until March 2030.

We performed deterministic sensitivity analyses for each step of the HCV care cascade. For these analyses, all of these parameters returned to pre-pandemic rates after 18-months. We then varied one parameter at a time, increasing to up to 200% of pre-pandemic rates, to determine the "effort needed" at that particular cascade step to achieve 2030 "no pandemic" outcomes levels. We performed a sensitivity analysis in which we increased screening rates to 400% of pre-pandemic rates and treatment percentages to 100%. We also performed deterministic sensitivity analyses in which we increased the SMRs for people with current or former drug use and multi-way sensitivity analysis increasing both the SMR and the relapse rate.

IRB Approval

The project was reviewed by the Boston University Medical Campus Institutional Review Board and was determined to be non-human subjects research.

RESULTS

In the hypothetical, counterfactual "no pandemic" case, we estimated that by March 2030 there would be 5000 incident HCV infections per 100 000 people (including reinfection) over the 10-year period (Figure 2). We estimated that approximately 58% of all HCV infections would be identified, 18% of which would have initiated treatment, and 14% of identified infections would have achieved SVR (Figure 2). We also estimated that there would be 230 cases of cirrhosis and 71 liver-related deaths per 100 000 people. In the worst-case scenario where "pandemic levels" persist until 2030 (without any return to

pre-pandemic testing or treatment values), we estimated 4810 incident HCV infections per 100 000 people over the 10-year period. Compared to the "no pandemic" scenario, we estimated 1060 fewer identified cases per 100 000 people, only 3% of which would initiate treatment and <1% of which would achieve SVR. There would be 21 additional cases of cirrhosis and 16 additional liver-related deaths per 100 000 people.

In the best-case hypothetical scenario in which COVID-related impacts on HCV care only lasted 18-months and were followed by pre-pandemic rates until 2030, we estimated 4380 incident infections per 100 000; with 58% of all infections identified, 17% initiated treatment, and 13% of identified infections achieving SVR. Compared to the "no pandemic" scenario, we estimated 1 additional case of cirrhosis and 1 additional liver-related death per 100 000 people. As expected, when testing, linkage, and treatment rates did not return to pre-pandemic levels, all outcomes were worse than if they had. At the end of the 18-month period representing the pandemic disruption (August 2021), HCV prevalence was 11% higher than it would have been at the same time point in the counterfactual "no pandemic" scenario.

In the first alternate scenario in which the pandemic disruption lasted 12-months, outcomes were less pronounced than the 18-month disruption (Supplementary Figures 2–3). In the second alternate scenario in which the pandemic disruption lasted 2 years all clinical outcomes were worse (Supplementary Figures 4–5).

In a deterministic sensitivity analysis in which treatment initiation and completion were both doubled following an 18-month disruption, we estimated 16 fewer cases of cirrhosis and 16 fewer liver-related deaths per 100 000 people than the counterfactual (no pandemic) scenario (Figure 3). Doubling screening alone led to 4 fewer cases of cirrhosis and 8 fewer
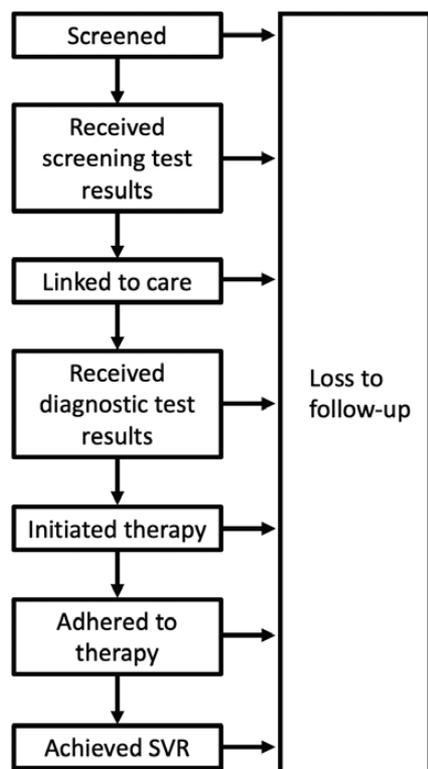
Figure 1. Cascade of care flow diagram. Flow diagram represents the steps of the HCV cascade of care, as well as key model parameters related to loss to follow-up. Arrows noted in the key represent points along the cascade at which candidate interventions improved follow-up. Individuals lost to follow-up prior to receiving their screening test results maintained a rate of re-screening such that their HCV status could be identified in the future. In addition, those who were lost to follow-up after obtaining screening test results had a monthly probability of relinking to HCV care. Abbreviations: HCV, hepatitis C virus; SVR, sustained virologic response.

liver-related deaths per 100 000. Finally, doubling linkage alone led to 10 fewer cases of cirrhosis and 10 fewer liver-related deaths per 100 000 compared to the counterfactual. When all components of the care cascade were increased to two times those of the base case values following an 18-month disruption in care, there were 48 fewer cases of cirrhosis and 35 fewer liver-related deaths (per 100 000 people) compared to the counterfactual scenario in which no pandemic occurred. Results from additional sensitivity analyses including those where the SMRs and relapse rates were increased are included in the Supplemental Appendix.

DISCUSSION

We used a simulation model of HCV screening and treatment to investigate the potential impact of the COVID-19 pandemic on the HCV epidemic in the United States. Even before the pandemic, it appeared unlikely that the United States would reach elimination targets by 2030. However, the disruption in clinical services and access to care caused by the pandemic have placed the United States even further behind. We found that, assuming

a realistic 18-month disruption in testing, linkage, and treatment before a return to 0% to 100% pre-pandemic rates, the United States is expected to have fewer identified cases and SVRs, and increases in cases of cirrhosis and liver-related death, compared to a counterfactual scenario in which the COVID-19 did not occur. Importantly, our findings demonstrate that if there is a rapid return to pre-pandemic levels of HCV screening and treatment, then there may be minimal pandemic consequences related to HCV outcomes (Figure 2).

Our analysis helps quantify the long-term impacts of the COVID-19 pandemic beyond the direct consequences of the disease itself. Other studies have attempted to project the potential long-term impact of healthcare service disruptions due to the pandemic on tuberculosis in high-burden countries [31], HIV incidence and mortality in the United States and around the world [32, 33], and malaria worldwide [34]. Other studies from earlier in the pandemic attempted to estimate the impact of COVID-19 on HCV liver-related deaths and liver cancer worldwide [35, 36].

Our study demonstrates that the "no pandemic" scenario resulted in more HCV infections than any of the pandemic scenarios. This seemingly paradoxical finding can be explained by more individuals being identified, linked to care, and treated—thus leaving them susceptible to reinfection—in that hypothetical scenario than the pandemic scenarios. Even though people may have been reinfected more often in the "no pandemic" scenario, they were also more likely to be identified earlier and treated before fibrosis progression as attested by the overall lower numbers of cirrhosis cases and liver-related deaths compared to any other "pandemic" scenarios. Furthermore, the "no pandemic" scenario resulted in lower HCV prevalence at the end of the first 18-months than at the end of the 18-month pandemic period.

Importantly, our sensitivity analysis demonstrated that the greatest mortality benefit would be achieved by ensuring that individuals who are already identified receive and complete treatment. By providing additional resources to ramp up treatment, the United States will see the greatest clinical impact in terms of cirrhosis and liver-related death (ie, get the United States closest to pre-pandemic numbers). This treatment-focused approach also promises to be a wise use of often limited resources, as prior studies have consistently demonstrated that investment in the later stages of care cascades will maximize cost-effectiveness [37, 38].

There were limitations to our study. First, as with all models, the outputs are highly dependent on the validity of the inputs. We used data from one safety net hospital to inform the impact of COVID-19 on continuum parameters and data from the ALIVE cohort to estimate injection drug use transitions. The program at BMC has been successful at improving diagnosis of HCV and linkage to care within the institution. As such, we assume that changes in the BMC HCV cascade resulting from the
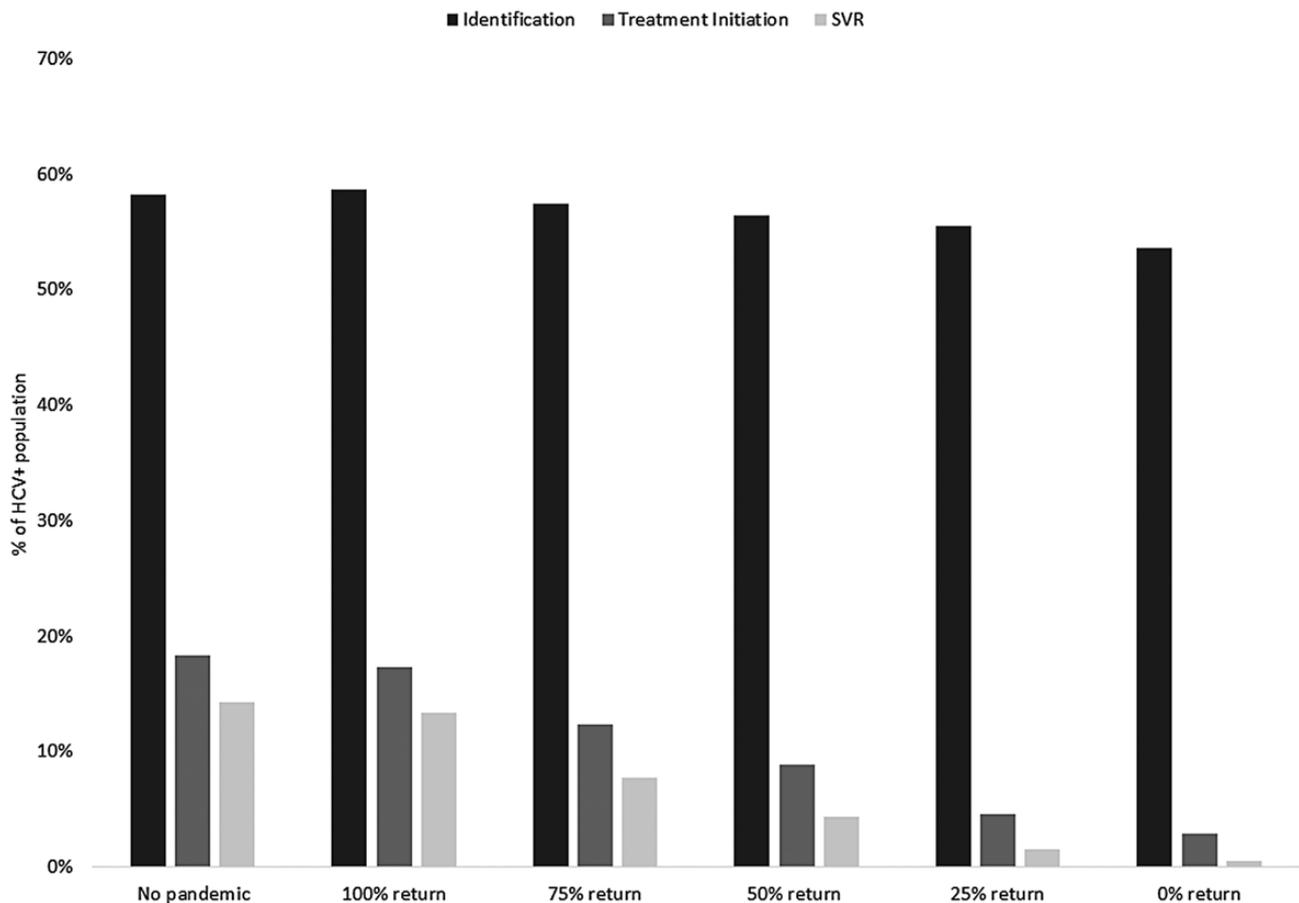
Figure 2. HCV cascade in March 2030 for identification, treatment initiation, and sustained virologic response, by scenario. This figure depicts the percent of individuals with HCV who were identified (*black bar*); the percent of those identified who are initiated on treatment (*dark gray bar*); and the percent of those who achieve SVR (*light gray bar*), by modeled scenario. Abbreviations: HCV, hepatitis C virus; SVR, sustained virologic response.

pandemic may represent a "best case scenario" for the United States. We expect that in some geographic areas lacking a robust infrastructure or having limited access to care, the impact might be more profound. Areas that were not hit as hard as Boston was during the first surge of COVID-19 (March–May 2020) may not have had as significant reduction in screening/treatment as was seen in Boston. Furthermore, if screening and treatment rates were worse than BMC, then pandemic-related reductions might be less severe. We explored this in sensitivity analyses. This limitation highlights the need for more robust surveillance of HCV and injection drug use, especially in the context of COVID-19. Specifically, real-time data on injection drug use behaviors in large cohorts from different geographic locations are necessary. Second, it is unclear for how long the care disruptions across the United States are likely to persist and the extent to which they will rebound. We accounted for this in our sensitivity analyses, which varied both the duration of impact and the extent of the return to pre-pandemic levels. Importantly, these analyses should serve as a roadmap for individual jurisdictions and national entities (eg, Centers for Disease Control and Prevention [CDC]). Third, because this is not a transmission model, it does

not allow for a decrease in transmitted infections following successful treatment nor does it allow for a potential increase in transmitted infections related to more patients with untreated infection and sustained viremia during the pandemic. As a result, we may overestimate infections in the "no pandemic" scenario and underestimate infections among people who do not inject drugs. Finally, our analysis did not evaluate the differential outcomes by race. Given the disproportionate impact of HCV, substance use, and COVID-19 on Black and brown communities due to structural racism and barriers to access, we anticipate that these individuals could be impacted more than others.

The COVID-19 pandemic caused an unprecedented disruption in the US healthcare system and healthcare service delivery. Vulnerable populations in the United States—including those with and at risk for HCV—are likely to experience worse outcomes as a result. Resources are finite and there are many competing health priorities as the United States eventually emerges from the COVID-19 pandemic. Recommitting resources and efforts to screen, link, and treat people with HCV—a major public health threat—should be considered.
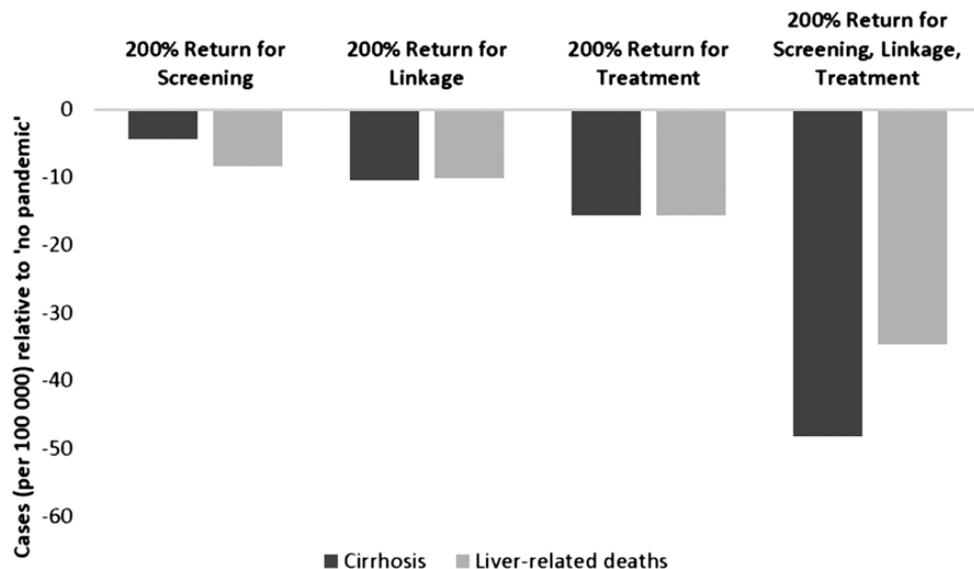
Figure 3. Cases of cirrhosis and liver-related deaths relative to hypothetical "no pandemic" scenario, March 2030 (per 100 000 people). This figure depicts the estimated number of cases of cirrhosis (*dark gray*) and liver-related deaths (*light gray*) compared to the "no pandemic" scenario. Each group of bars represents a scenario in which 1 or more steps in the care cascade are doubled over the pre-pandemic levels for the time following an 18-month disruption in HCV services. Abbreviation: HCV, hepatitis C virus.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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