

Estimation of chronic hepatitis C and future burden using various treatment scenarios

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Abstract

Estimation of chronic hepatitis C accounting for treatment and future treatment scenarios

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Background Hepatitis C is considered a major public health threat.^{1,2} In 2016, the World Health Organization Global Health Sector Strategy (WHO-GHSS) adopted goals to eliminate hepatitis as a global health concern by 2030. One proxy measurement of goal achievement is a 80% reduction in viremic prevalence of chronic hepatitis C between 2015 and 2030.³ Given improvements in treatment regimens, countries have unique opportunities to functionally cure those chronically infected with HCV and prevent progression to liver cancer and cirrhosis.⁴ This study identified hepatitis C treatment data sources, created a standardized data processing and application model, and evaluated the impact of treatment both within the Global Burden of Disease Study (GBD) and on future burden of chronic hepatitis C in 31 locations.

Methods This study used treatment data and estimates of chronic hepatitis C from the Global Burden of Disease Study 2020. Treatment data are processed through multi-step processing: multi-year splitting, both-sex splitting into sex-specific data points, age-splitting into 5 year GBD age groups, and application of treatment efficacy. Next, the cumulative effect of treatment is calculated as the summation of treatment in the current year as well as previous years and age groups. To generate final GBD estimates of chronic hepatitis C, the number treated by age, sex, year, and location are subtracted from the counterfactual, or unadjusted, treatment estimates of chronic hepatitis C. Four future treatment scenarios are evaluated to explore future burden of chronic hepatitis C: no treatment, sustained proportion, maximum absolute treatment, and using Egypt's 2019 mass-treatment campaign as an exemplar for proportional reduction.

Results This study found that in 2020 the number of chronic hepatitis C prevalent cases across the 31 locations estimated was 60.5 million (95% uncertainty interval [UI] 46.3 – 78.9). Under the unadjusted model/counterfactual scenario of no treatment, in 2020, the number of chronically infected individuals was 66.9 million (52.4 – 85.4). There was a 10.6% difference (95% 8.3 –

13.2) between the counterfactual and adjusted GBD estimates. In the no treatment scenario, in 2030, 74.0 million (58.0 - 94.4) persons would be infected with chronic hepatitis C. Under the three scenarios of sustained, maximum treated, and exemplar, prevalence would decrease between 2015 and 2030. The largest decline under the various scenarios would be seen in the exemplar scenario in which there is a 58.1% reduction between 2015 and 2030 (-66.3 to -48.4).

Interpretation Input data and modeling strategies related to hepatitis C treatment play an important role in accurate estimation of the burden of chronic hepatitis C. Future studies should identify additional data sources to improve data coverage. Regression methods should be used to estimate treatment coverage even in the absence of treatment data. Additionally, findings on future treatment scenarios indicate that continuation of current treatment will result in decreases in the burden of chronic hepatitis C by 2030. However, to achieve the WHO-GHSS goal of 80% reduction, global and local treatment initiatives must increase over the next decade.

1. Background and Significance

Hepatitis C is a major global health threat.¹ Hepatitis C is a virus that causes inflammation of the liver and can result in acute and chronic infection. People infected with chronic hepatitis C virus are at increased risk of developing cirrhosis or liver cancer. Without treatment an estimated 20-30% will develop long term sequelae like decompensated cirrhosis and liver cancer.²

In 2016, the World Hepatitis Assembly adopted the World Health Organization - Global Health Sector Strategy (WHO-GHSS) to eliminate viral hepatitis as a global health concern.³ Impact targets include 65% reduction in mortality and 80% reduction in new infections by 2030 compared to 2015.³ Service coverage targets include treating 80% of individuals infected with hepatitis C who are eligible for treatment.³ An 80% reduction in HCV viremic prevalence can be used as a proxy target where direct measurement of incidence and mortality is not feasible.³ The impact and service coverage targets aim to drive the response forward and monitor progress.

In 2015, the WHO estimated that only 7% of persons diagnosed with chronic HCV infection started treatment.⁴ Since 2015, there has been greater than a 20-fold increase in the number of individuals who have been treated.⁵ Additionally, there have been improvements in treatment technologies. The first treatment was interferon (IFN)-alfa and upon pegylation and the addition of ribavirin the response rate improved. Enhanced knowledge of HCV genetics led to the development of direct-acting antivirals (DAAs) and interferon-free therapies.⁵ Through advancements in treatment, the efficacy has improved to 95% with DAAs.⁶ The recent advancement in DAAs makes elimination more feasible if those infected can be identified and treated.

Elimination of hepatitis C requires a strong understanding of the epidemic to guide strategic directions and actions. Timely and reliable estimates are critical to understand what the local, national, regional and global burden of hepatitis C are. Data, predictive covariates, and statistical modeling can be used to estimate the prevalence of chronic infection. Hepatitis C treatment information must be adequately identified and appropriately integrated into estimation modeling for a more accurate picture of the burden of disease. Without comprehensive and thorough estimates that factor in treatment, estimates of prevalence can overestimate burden and mislead policy and programmatic responses.

In 2019, the GBD Study included hepatitis C treatment data directly in the estimation process of chronic hepatitis C for the first time.⁶ GBD Collaborators shared data in three locations: Egypt, Japan, and Australia. Given the structure of the data (i.e. differences in treatment type, years of coverage, and demographics covered), each data set was processed individually without consistent standards. While the addition of treatment data is critical to advancing our understanding of the impact of treatment on estimates of hepatitis C burden, these data were

limited and non-standardized data processing and application approaches for each location introduced potential for processing errors.

This study identified new data sources on treatment, expanding our treatment coverage. We developed systematic data processing methods for treatment data by age, sex, location, year, and treatment type. We also developed systematic methods to adjust chronic hepatitis C estimates to account for treatment as part of the GBD2020 Study. Finally, we forecasted the burden of chronic hepatitis C under various treatment scenarios to demonstrate the impact of treatment towards achievement of the WHO-GHSS elimination goals. By evaluating the impact of treatment on future burden, global and national health agendas and interventions can be re-evaluated so treatment programs, policies, and accessibility are improved to achieve hepatitis elimination goals.

2. Methods

2.1 Overview

In past GBD studies, chronic hepatitis C has been estimated using DisMod-MR 2.1 and ratios of anti-HCV to HCV-RNA.^{1,7,8} One limitation of DisMod is that it does not faithfully follow data when there are rapid temporal changes and cohort effects, like with chronic hepatitis C because of treatment initiatives.⁹ Thus, we elected to make a post-hoc adjustment using treatment data to adjust preliminary “counterfactual” GBD estimates. The counterfactual, or unadjusted, estimates represent estimates of chronic hepatitis C in the absence of treatment.

2.2 Data

The input treatment data were from reports on hepatitis C treatment in 31 locations. Because of the programmatic nature of hepatitis C treatment data, we anticipated that most treatment data would be available through ministries of health and hepatitis control programs, as compared to the scientific literature. We therefore collaborated with the Coalition for Global Hepatitis Elimination to seek data directly from programs and through WHO reports. Figure 1 shows a data coverage map of location-years. Most of the data were reported for both sexes combined. Only three locations (Egypt, Australia, and Iceland) reported treatment data separately for males and females. Additionally, the majority of the data is broad-age data (ie all age groups are reported together or unspecified ages). Egypt is the only location in which the data is age-specific. Furthermore, four locations (Georgia, Japan, Australia, and Egypt) report data aggregated across multiple years. Many locations do not have treatment data available or were not identified for inclusion in this study.

Table 1: Hepatitis C treatment data sources by geography

Number of countries	Number of regions	Number of super regions
31	13	7

2.3 Data processing

In order to adjust GBD estimates, we processed data by age, sex, location, and year groups that are compatible with GBD groupings. We followed guidance from GBD Collaborators when only both-sex or broad-age-range data were available. In the absence of sufficient data to directly estimate age- and sex-specific treatment coverage rates, we assumed that treatment distribution followed the same age and sex-patterns as in the unadjusted estimates of chronic hepatitis C prevalence. Data were processed using the following steps: year-splitting, sex-splitting, age-splitting, and efficacy. First, data that span multiple years were split into single years, assuming the number treated in each year was equal. Second, “both” sex data were split into “male” and

“female” sex-specific data points using the sex ratios of chronic hepatitis C prevalence from the GBD. Third, broad-age-range data were split into GBD 5-year age groups using age ratios calculated from chronic hepatitis C prevalence estimates. Finally, the number of treated individuals was multiplied by the respective treatment efficacy to calculate those effectively treated. Interferon-based regimens were treated as 70% effective in achieving sustained viral response or curing infection, while direct-acting antivirals were treated as 95% effective.^{4,6}

The equations below show how data was processed in each step.

l = location, y = year, s = sex, m = midage, a = GBD age group

Year-splitting equation

$$treatment_{year-specific} = \frac{treatment_{total}}{year_{end} - year_{start} + 1}$$

Sex-splitting equations

$$male\ proportion_{l,y,m} = \frac{male\ unadjusted\ GBD\ cases_{l,y,m}}{male\ unadjusted\ GBD\ cases_{l,y,m} + female\ unadjusted\ GBD\ cases_{l,y,m}}$$

$$female\ proportion_{l,y,m} = \frac{female\ unadjusted\ GBD\ cases_{l,y,m}}{male\ unadjusted\ GBD\ cases_{l,y,m} + female\ unadjusted\ GBD\ cases_{l,y,m}}$$

$$male\ treated_{l,y,m,s} = both\ sexes\ treated_{l,y,m} * male\ proportion_{l,y,m}$$

$$female\ treated_{l,y,m,s} = both\ sexes\ treated_{l,y,m} * female\ proportion_{l,y,m}$$

Age-splitting equations

$$age-specific\ proportion_{l,y,s} = \frac{age-specific\ unadjusted\ GBD\ cases_{l,y,s}}{total\ unadjusted\ GBD\ cases_{l,y,s}}$$

$$age-specific\ treatment_{l,y,s,a} = age-specific\ proportion_{l,y,s} * treated_{l,y,s}$$

Treatment efficacy equation

$$effectively\ treated_{l,y,s,a} = treated_{l,y,s,a} * \left(\frac{treatment\ efficacy}{100} \right)$$

2.4 Adjustment analysis

After processing the treatment data, we re-estimated prevalence of chronic hepatitis C from the GBD to account for the effect of treatment. We calculated the cumulative impact of treatment by summing treated cases from the current year as well as previous years and age groups to factor in treatment effects in the past and aging populations. The number of effectively treated individuals has three components. First, we performed a half-year reduction on the treatment effect in the current year of treatment for the year and age group treated. The half-year effect is a cost-effectiveness strategy to only account for half of the effect of an intervention in the current year. This factors in that people are treated throughout the year, not all at once at the start of the year. Second, we identified previous years of treatment within the same age groups. Finally, we identified previous years of treatment within younger age groups to account for aging cohorts since individuals treated earlier in time can age into an older age group. Because the specific age in GBD is not known, we assumed that, on average, each treated case will spend 3 years in an age group (the middle value of the 5-year GBD age groups). Table 2 shows an example of how treated cases are tracked through both age and time to adjust the prevalence of chronic hepatitis C.

Table 2: Example of adjustment analysis by year and age

Year	Age group	Treated	Y -1: Previous year	Y - 2	A -1: Previous age group	A- 2	Treatment effect	Unadjusted prevalence	Adjusted prevalence
2015	20-24	10	NA	NA	NA	NA	5	1,000	995
2016	20-24	15	10	NA	NA	NA	17.5	1,010	992.5
2017	20-24	20	15	10	NA	NA	35	1,025	990
2018	25-29	25	20	15	10	NA	57.5	1,045	987.5
2019	25-29	30	25	20	15	10	85	1,070	985

The below equation shows the adjustment calculation, where l = location, y = year, s = sex, a = GBD age group; floor rounds to the nearest integer down

$$\begin{aligned}
 & \text{adjusted cases}_{l,y,s,a} \\
 &= \text{unadjusted cases}_{l,y,s,a} - (0.5 * \text{treated}_{l,y,s,a}) - \sum_{i=1}^{n=2} \text{treated}_{l,y-i,s,a} \\
 & \quad - \sum_{i=3}^n \text{treated}_{l,y-i,s,a-(\text{floor}(\frac{i}{3}))}
 \end{aligned}$$

Additionally, many locations do not report data through 2020, which is the last estimation year in the GBD. This study assumed that the proportion of cases treated was sustained from the final year of known data to 2020.

$$proportion\ treatment = \frac{treated\ cases_{y,l,s,a}}{total\ prevalent\ cases_{y,l,s,a}}$$

2.5 Future treatment scenarios

We also evaluated the impact of various treatment scenarios on future prevalence of chronic hepatitis C. Four scenarios were evaluated: no treatment, sustained, maximum, and exemplar. First, a future scenario of “no treatment” was assessed. Forecasted population estimated from the Future Health Scenarios Team at the Institute for Health Metrics and Evaluation were multiplied by treatment-unadjusted estimates of chronic hepatitis C in 2020. This produced forecasted estimates until 2030 of what would chronic hepatitis C be in the absence of treatment, assuming constant prevalence at 2020 counterfactual levels.

$$\begin{aligned} forecasted\ cases_{l,y,s,a} \\ &= unadjusted\ GBD\ prevalence\ (\%)_{l,s,a,y=2020} \\ &* population\ counts_{l,s,a,y=2021:2030} \end{aligned}$$

The sustained, maximum, and exemplar scenarios were evaluated using a similar adjustment strategy described in the previous section in which the cumulative number of treated individuals were tracked through age and time. These values were subtracted from the no treatment future scenario. The sustained proportion scenario used the same strategy that was performed in the previous section. The proportion treatment calculated as the number of treated cases over the total prevalent cases in a given year was continued each year until 2030. The maximum scenario identified the historical maximum absolute number of treated cases in a given year and continued that maximum until 2030. Finally, the exemplar scenario used the treatment proportion in Egypt that was achieved as part of their mass treatment campaign in 2019 in other locations. Egypt had a successful testing and treatment campaign, the highest treatment coverage observed in our dataset, which demonstrates what is possible when there is high political and public commitment.^{5,10}

Table 2: Summary of the future treatment scenarios

Scenario	Method
No treatment	Absence of past and future treatment
Sustained	The proportion of cases treated in 2020 will continue in all subsequent years

Maximum	The absolute annual treatment from the highest historical treatment in a given location will continue in all subsequent years
Exemplar	The proportion of cases treated based on Egypt's 2019 mass treatment campaign will continue in all subsequent years

3. Results

Across the 31 locations assessed in this study, in 2020, an estimated 60.5 million (95% uncertainty interval [UI] 46.3 – 78.9) persons were infected with chronic hepatitis C (Figure 2). In 2015, the aggregate number of chronic hepatitis C cases was 60.1 million (47.6 – 75.7). Between 2015 and 2020, there was a 0.69% increase (-2.7 to 4.2) in the number of prevalent cases. In the absence of treatment, the number of individuals with chronic hepatitis C infection in 2020 would be 66.9 million (52.4 – 85.4). In 2015, prevalent cases would have been 61.0 million (48.4 – 76.6). The percent difference between the treatment-adjusted prevalent case estimates and counterfactual/unadjusted estimates in 2015 and 2020 were -1.5% (-1.8 to -1.2) and -9.5% (-11.7 to -7.7), respectively.

Under the no treatment scenario, in 2030, 74.0 million (58.0 – 94.4) persons would be infected with chronic hepatitis C. The number of prevalent cases would increase by 21.1% (19.7 – 29.3) from 2015. In the sustained treatment scenario, there would be 58.0 million (42.8 – 78.1) chronic hepatitis C infections in 2030. This represents a 3.5% decrease (-10.0 to -3.9) from 2015. Under the maximum treatment scenario, in 2030, the aggregate prevalent cases would be 55.3 million (40.9 – 73.7). This represents an 8.1% decrease (-14.0 to -3.3) from 2015. In the exemplar scenario, in 2030, an estimated 25.2 million (16.0 to 40.6) persons would be infected with chronic hepatitis C infection, which represents a 58.1% reduction (-66.3 to -48.4) from 2015 (Figure 3).

The exemplar scenario results in the largest relative reductions in prevalent cases of chronic hepatitis C between 2015 and 2030 in 27 locations. In six locations, the percent declines in the same time interval were largest under the maximum treatment scenario (Egypt, Georgia, Iceland, Japan, Mongolia, and Romania). In the absence of treatment, 23 locations would have increases in prevalent cases and only 8 would experience declines.

Under the no treatment scenario, Japan would have the highest percent change between 2015 and 2030 (60.4% [UI 62.7 – 78.3]) and England would have the lowest (-18.5% [UI -23.2 to -8.8]). In the sustained scenario, the highest and lowest percent change in prevalence cases between 2015 and 2030 would be in Japan (40.8% [UI 37.2 to 63.2]) and Egypt (-75.2% [UI -91.0 to 65.0]), respectively. Under the maximum scenario, the percent change in cases would increase the most between 2015 and 2030 in Malaysia (18.3 [UI 17.8 to 22.5]) and would decrease the most in Iceland (-98.7 [UI -99.4 to -81.4]). Under the exemplar scenario, the percent change in cases would decrease the least in Japan (-24.8 [UI -32.4 to -20]) and the most in Georgia (-79.8 [UI -87.2 to -69.6]).

Under the treatment scenarios explored in this analysis, the WHO-GHSS viremic prevalence target of 80% reduction in cases between 2015 and 2030 could be achieved for a few locations, but only under the maximum treatment scenario. The locations are Egypt, Georgia, Iceland, and Romania.

4. Discussion

This study offers a novel strategy for estimating the burden of chronic hepatitis C accounting for treatment effects as part of the Global Burden of Disease Study. By comparing unadjusted and treatment-adjusted estimates, we can understand the public health impact of treatment on the prevalence of chronic hepatitis C. Incorporating treatment effects allows us to more accurately estimate the burden of hepatitis C around the world in the GBD study. This will become increasingly important over time as treatment becomes more widespread.⁵ The impact on estimates varies by location because of heterogeneity in magnitude of treatment initiatives. However, treatment data and methods are particularly critical for locations, like Egypt, that have made major progress in reducing the burden of hepatitis C.^{10,11} Since 2018, Egypt has made advancements in widespread testing and linking identified positive cases with treatment. In 2019, this effort was scaled up and 1.5 million individuals received treatment. We estimated a 70% difference between the treatment-free counterfactual and the treatment-adjusted models in Egypt in 2020. By comparing counterfactual estimates and those incorporating treatment, we can see the dramatic public health effect of treatment.

Another important finding is that treatment scale up is required to meet the WHO Global Hepatitis Sector Strategy goal of the 80% reduction in viremic prevalence between 2015 and 2030. Across the 31 locations evaluated in this study, the exemplar scenario imitating Egypt's 2019 mass treatment campaign resulted in the largest declines. The sustained and maximum treatment scenarios will lead to reductions in the number of individuals infected with chronic HCV infection, but will still be well short of the 80% reduction goal. In the absence of treatment, the number of prevalent cases would increase by 21.2% because of increases in population growth. Under the three treatment scenarios, treatment initiatives would overcome population growth.

While prevention and treatment efforts make elimination feasible, advances along the continuum of hepatitis services are required to meet elimination goals.¹² Access to testing, diagnosis, and treatment have improved but progress is variable and globally services still remain low. In 2017, only 20% of individuals living in low and middle income countries who were infected with chronic hepatitis C were diagnosed.² Countries can improve diagnosis through the use of novel finger-stick tests. The technology offers several advantages compared to venipuncture, like diagnosis within a single visit and decreased invasiveness.¹³

Costs of testing and treatment also present challenges to achievement of elimination goals. A Clinton Health Access Initiative market report on HCV identified various challenges to affordability of HCV services.¹⁴ Factors include limitations in domestic and donor financing. Opportunities using existing public health financing programs, like the Global Fund, can be used to support synergistic initiatives. Furthermore, many low and middle-income countries have signed voluntary licensing agreements with pharmaceutical companies Gilead, Bristol-Myers Squibb, and AbbVie, improving access to generic direct-acting antivirals and reducing prices from local competition.⁵ Countries can use group initiatives to increase negotiations with companies and pursue local production efforts to improve medication affordability.

Despite the improvements in data collection and methodology, there are several limitations in this study. First, there is data sparsity in treatment coverage. Our model only accounts for treatment in 31 locations where we have data. However, the number of locations with treatment is much higher. One hundred twenty-five countries have implemented national viral hepatitis strategy plans.⁵ Additionally, many countries have signed voluntary licensing agreements with pharmaceutical companies to create generic drugs. For example, in 2020, 104 countries had agreements with Gilead, 138 with Bristol-Myers Squibb, and 96 with AbbVie.⁵ The data sources for this study account for 5.2 million treated cases, however, the WHO estimates 9.4 million individuals have received HCV treatment by the end of 2019.¹⁵

Second, the model implements several assumptions on year, age, and sex splitting. For data that reports multi-year splitting, the number of treated cases are split equally to generate single years of treatment data. However, many countries have likely scaled up treatment over time.² Furthermore, age splitting and sex splitting assumes that treatment follows the same distribution as chronic hepatitis C in the location of interest. However, differences in access to care and health seeking behaviors across sexes and ages may affect treatment.¹⁶

5. Future Directions

Several future directions should be pursued to expand on the current study. First, improvements in data collection and collaboration can be explored through collaborators in the GBD Collaborator Network and partners at the Coalition for Global Hepatitis Elimination. By leveraging partnerships, future studies can close the data coverage gap to identify where, when, and who has received treatment that is not currently captured in the study dataset. Second, treatment should be modeled in locations where we know treatment access and programs exists, but data has not been identified or extracted. Information about global treatment coverage can be used as a parent treatment envelope (ie. 9.4 million individuals from the WHO) and our current data sources can be subtracted to determine an envelope of missing treated cases. Then, predictive covariates such as healthcare access quality and index, socio-demographic index, and timing of voluntary licensing agreements and national strategic plans can be used to predict treatment.

6. Conclusions

This study underscores the importance of comprehensive and timely data and methods to estimate the burden of chronic hepatitis C. By comparing estimates that incorporate and do not factor in treatment data, we can understand the public health impact of treatment on the burden of chronic hepatitis C. The findings also indicate that achievement of hepatitis elimination goals will require scaled up treatment beyond historical and existing treatment interventions. Globally and nationally testing, diagnostic, and treatment efforts must be supported and increased to achieve the elimination goals.

7. Acknowledgments

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8. Figures

Figure 1: Location-year counts of hepatitis C treatment by location

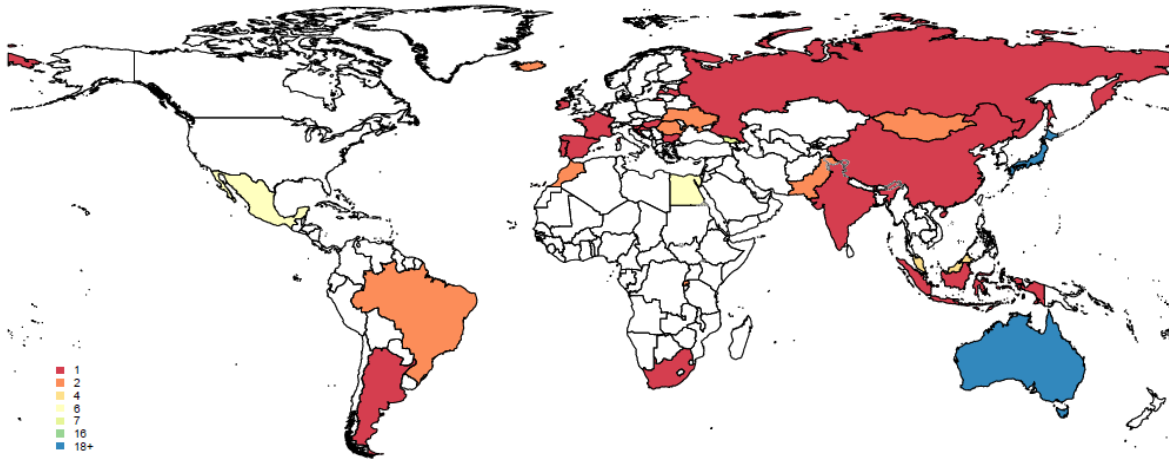


Figure 2: Unadjusted/counterfactual and treatment-adjusted GBD estimates of prevalent cases by year for aggregated 31 locations included in the study

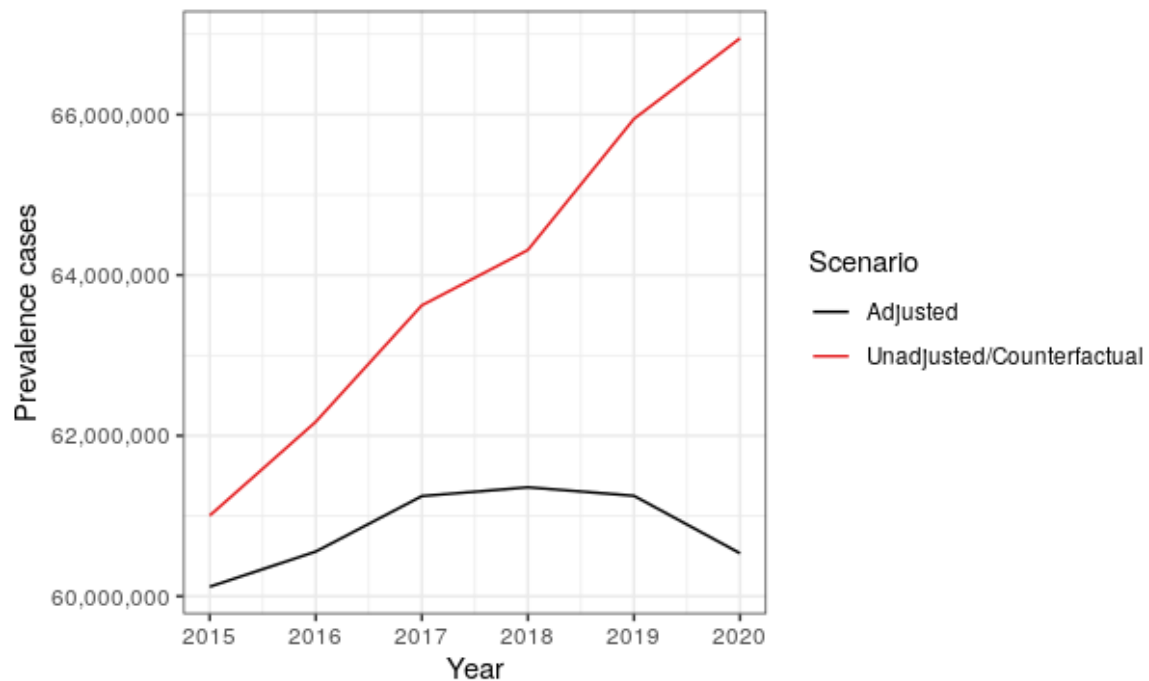


Figure 3: The number of individuals with chronic hepatitis C between 2015 and 2030 in 31 locations of interest under no treatment, sustained, maximum, and exemplar treatment scenarios

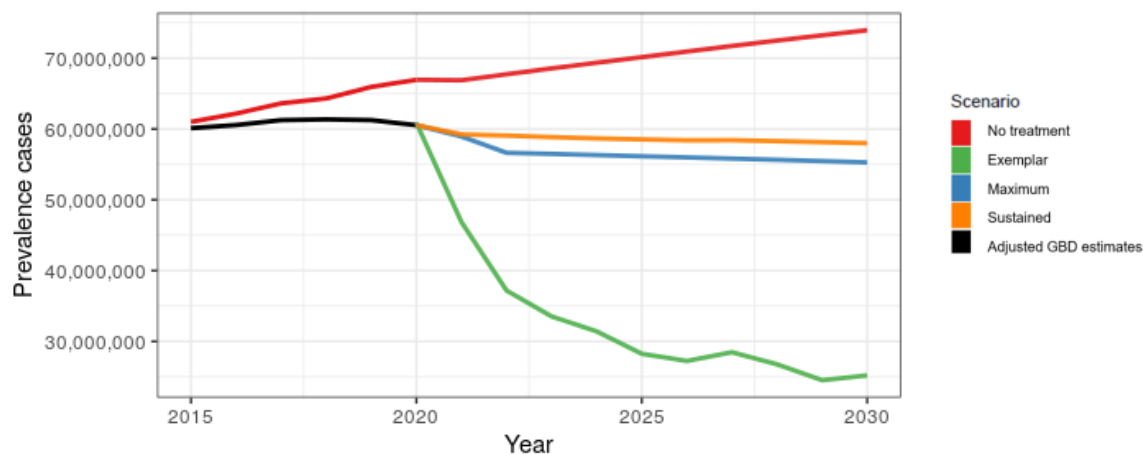
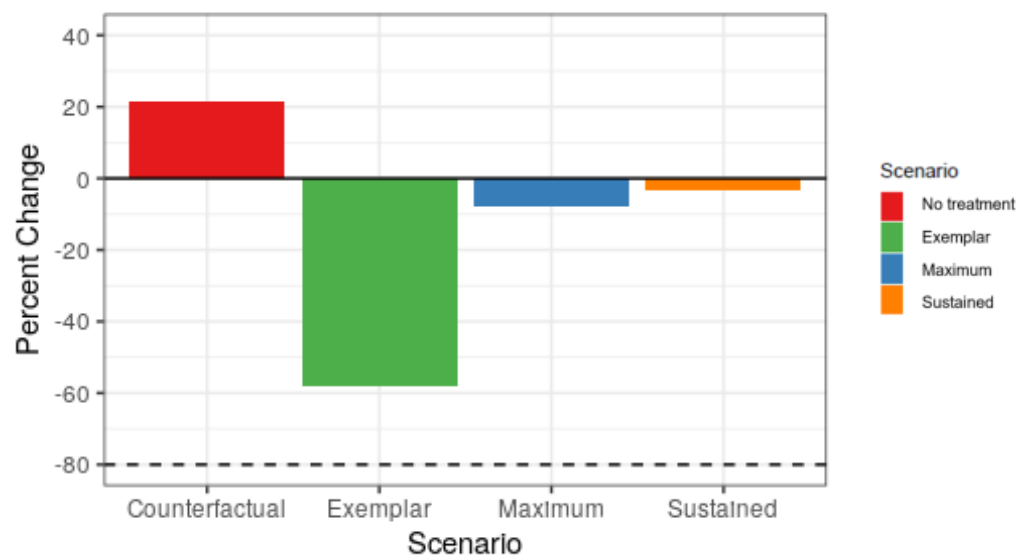


Figure 4: Percent change in the number of individuals with chronic hepatitis C between 2015 and 2030 in 31 locations of interest under no treatment, sustained, maximum, and exemplar treatment scenarios



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