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Introduction

Over the past few decades, the number of hepatitis C (HCV) cases worldwide has steadily increased, and the World Health Organization (WHO) estimated in 2019 that 58 million people are infected with chronic HCV, and about 1.5 million new cases per year are recorded.[1] The WHO estimates that upwards of 90% of HCV patients can be cured through the use of antiviral medications,[2] but there is a lack of access to diagnostics and treatment. It is estimated that less than 5% of those afflicted by HCV are aware of their diagnostic status.[2] Under-diagnosis is a serious barrier to more widespread treatment of HCV, and implementation of new national policies and guidelines for testing can help to identify the disease at earlier stages, and when coupled with more accessible and cheaper medications can lead to a decrease in the global burden of HCV and progress towards the WHO's targets.

The WHO has adopted the *Global Health Sector Strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022-2030*, which seeks to eliminate HCV as a public health threat by the year 2030, which hopes to reduce the global number of new cases per year from 1.575 million to 1 million by 2025, and to 350,000 by 2030, a reduction in rate of about 80%.[2] The strategies also hope to eliminate HCV in 20 countries within that same time period, reduce prices of medications by 60%, get timely doses of vaccines to 90% of newborns to prevent vertical (mother-child) infections, and reduce global HCV deaths annually from 290,000 to 140,000.[2] Reaching these milestones will require increased surveillance, diagnostics, access to medications, negotiations for lower pricing of these medications, and vitally, low-cost treatments to increase affordability worldwide.

It is crucial to model the impact levels of current treatments that are in place in order to determine how much progress is already being made in achieving these goals, and where improvements are needed. Existing models are often inapplicable to the global scale, focusing on treatment impact on specific subsets of the population. Many models focus exclusively on people who inject drugs (PWID),[3-4] producing results about treatment impact that are important for one marginalized sector of the population but aren't useful for considering broader global impact. Other models are targeted at one specific geographic region,[4-5] which are not able to be generalized globally. Other models produce effective data about HCV treatments but fail to break down the category of Direct-acting antivirals (DAAs) into specific medications,[6] which doesn't yield any information about the impacts of any one treatment. Treatments often vary depending on which genotype of HCV they are aimed at, and other factors such as the severity of the

disease (whether it is acute or chronic) vary from case to case and necessitate different treatments. Pangenetic therapies, such as Sofosbuvir and Daclatasvir, are recommended by the WHO and are made affordable in some LMIC, but remain expensive in other parts of the world.[1] This model divides and calculates the efficacy of treatments by severity and by genotype, which yields more accurate and specialized data. Determining whether or not the HCV infection is chronic not only dictates the necessary treatment, but also helps prevent further negative results of infection, including cirrhosis and other liver damage.[1] With chronic infections making up a majority of the impact of this disease, it is important to differentiate between different levels of severity when modeling the impacts of treatments. Proper modeling of the impacts and efficacy of treatments can help researchers, NGOs, governments, manufacturers, other policy-makers, as well as academics and others within the public health space to distribute resources and track progress towards control and elimination goals, and be more informed and capable of combating HCV on the global scale.

The first treatment developed for hepatitis C was interferon alpha 2a (IFNα-2a) in 1991, followed in the coming years by several other interferon-based treatments. However, these regimens had low efficacy and high rates of often debilitating side effects.[7] By the late 1990s, the use of ribavirin (RBV) was discovered to bolster the effectiveness of IFN-based treatments, and by the year 2000, the efficacy of IFN-based regimens had increased to around 40%, with the help of ribavirin.[8]

Today, the majority of drugs used to treat hepatitis C fall under the heading of direct-acting antivirals (DAAs), which are a newer class of drugs with fewer side effects and much better effectiveness than IFN-based regimens.[9]

Methods

The 2019 Hepatitis C Virus (HCV) model is built using four basic components: country-level disability-adjusted life year (**DALY**) data for 2019 (for both acute and chronic cases, the latter of which is described in the DALY data as "with liver disease/LD," as the burden of disease of chronic hepatitis C is quantified by the liver damage caused by chronic infection), which comes from the IHME's GBD Results Tool;[10] **efficacy** data is sourced from the WHO's Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C infection[11] and for adults the data is broken down further `in the Annex, which is also organized into spreadsheet form` here. Region-level **treatment coverage** data from "Annex C of Global Hepatitis Report 2017" [12] -and country-level **genotype distribution** data, which is specific to the HCV model, and comes from "Global prevalence and genotype distribution of hepatitis C virus infection in 2015." [13] For countries without country-level distribution data, regional data derived from "Global distribution and prevalence of hepatitis C virus genotypes." [14] is used as a fallback.

In addition to these components, **patent holder** data is used for each of the regimens in the model in order to assign credit for the impact of these regimens to their original patent holders; this data is not sourced from a single document, but from a variety of individual sources pertaining to the specific companies and regimens, which are individually cited within Tables 2-3.

Regimens used in the current iteration of the model were taken from the WHO's Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C infection[11](the same source as the efficacy data). See below for a complete list of regimens included in the model.

Regimen	Abbreviation	Treatment Duration w/ Cirrhosis (# Weeks)	Treatment Duration w/out Cirrhosis (# Weeks)	Recommended for genotypes
glecaprevir + pibrentasvir	GLE + PIB	12 (all others); 16 (for G3 who have received IFN and/or RBV in past)	8 (all others); 16 (for G3 who have received IFN and/or RBV in past)	Pangenotypic
sofosbuvir + daclatasvir	SOF + DCV	24 (all others); 12 (may be considered in countries where genotype 3 distribution is known and prevalence is <5%)	12	Pangenotypic
sofosbuvir + velpatasvir	SOF + VEL	12	12	Pangenotypic
sofosbuvir + ledipasvir	SOF + LDV	12 (all others); 24 (treatment experienced and with compensated cirrhosis)	12 (all others); 24 (treatment experienced and with compensated cirrhosis)	1, 4, 5, 6 (adolescents)
sofosbuvir + ribavirin	SOF + RBV	12 (genotype 2); 24 (genotype 3)	12 (genotype 2); 24 (genotype 3)	2-3 (adolescents)
pegylated interferon/ + ribavirin	PEG + RBV	24 (children with decompensated cirrhosis)	Defer all treatment until age 12 (children)	2-3 (children)

Table 1: Regimens Included In Model.

The model begins with the DALY data, which falls into one of two categories: *acute*, indicating a recent onset of HCV, and *with liver disease* (LD), indicating a long-term, chronic infection. These categories are divided up by age into bins that align with the age-based guidelines given by the WHO's "Guidelines for the care and treatment…" (2018); 0-11 (children), 12-17 (adolescents), and 18+ (adults).[11] This is done by dividing up the age-based bins of IHME DALY data (0-9, 10-19, and 20+) for both acute and chronic hepatitis C, by assigning DALYs to the WHO age bins based on the proportion (out of 10 years per bin) of DALYs that overlap with each IHME age bin. For example, to estimate the number of DALYs lost to acute hepatitis C in Afghanistan for children aged 0-11, we calculate the following:

Acute DALYs ages 0-11 in Afghanistan:

> [Acute DALYs 0-9 in Afghanistan] + [2/10 * Acute DALYs 10-19 in Afghanistan] = 363.937812 + (2/10)*97.0357568 = 383.34496336

Of note, this assumes that DALYs are distributed evenly across age within these categories (e.g., that 2/10 of the DALYs lost to children aged 10-19 belong to 10-11 year olds), although in actuality this is likely not the case.

These are summed to give the total DALYs lost to HCV in each country, for each age group; however, the total DALYs are not used in the model on a country level, but rather are summed to calculate the total DALYs lost globally, with which the burden of disease (BoD) is calculated. The country-level acute and chronic DALYs for each age group are then multiplied by the corresponding genotype distribution data to give what percentage of the total DALYs can be attributed to each genotype within that country, for both acute and chronic HCV, in children, adolescents, and adults. As with other kinds of data, if country-level genotype distribution data does not exist for a given country, regional average data is used as a fallback (and global average is used if regional data does not exist).

It is important to note that some data we use is not country level. Because we have only regional treatment coverage data, this is used across the board for the model. Likewise, the current model also uses global efficacy data for each regimen included from the WHO (see Table 6 of the appendix). The model also distinguishes between efficacy differences across genotypes (1-6 and Mixed/Other), age groups (child, adolescent, adult), cirrhotic vs. non-cirrhotic adult patients, as well as between treatment-naive and treatment-experienced adults (in cases where WHO efficacy data is available for both groups). If it is not available or is only available for one group but not the other, we default to using the combined "all treatment experience" SVR. Additionally, where we lack within-group (cirrhotic vs. non-cirrhotic) genotype-specific efficacy data for a given pangenotypic regimen, we use the average efficacy for that regimen across all other genotypes as fallback data. .

Additionally, the model incorporates a few global estimates which allow us to better refine the calculations to align with the WHO treatment guidelines. Specifically, the model uses a global estimate of the percentage of Chronic HCV patients with cirrhosis, 22.5% , based on the estimate that a range of 15%-30% of patients with chronic HCV progress to cirrhosis.[15] We also estimate the prevalence of cirrhotic patients with decompensated cirrhosis, using the general formula of Prevalence = (Incidence Rate) * (Average Duration of Disease). Decompensation occurs in 3-6% of patients with cirrhosis per year, from which we take the average of 4.5% incidence.[16] Given that the median survival time after hepatic decompensation occurs is two years,[17] we can calculate the following: 4.5% incidence * 2 years = 9% prevalence. Furthermore, given that a range of 1-5% of patients are estimated to fail initial treatment with DAAs,[18] we use the average of 3% treatment failure to account for cases where the guidelines differ between treatment-naive and treatment-experienced patients (e.g., estimating 3% are treatment experienced after having failed initial DAA therapy). Lastly, the proportion of children with hepatitis C with cirrhosis is reported to be approximately 2%;[19] therefore, we multiply this by the estimate of cirrhosis that is decompensated given above (9%) to estimate the percentage of pediatric cases of hepatitis C that have decompensated cirrhosis (0.18%), used to calculate impact for pediatric populations in genotypes 2 and 3 in accordance with the treatment guidelines which recommended treatment for these genotypes only in the case of decompensated cirrhosis (that is, assuming that only 0.18% of the chronic DALYs for children would be eligible for treatment under these guidelines).

Given this data, impact can then be calculated via this formula:

$$\textbf{Impact} = \frac{D \cdot \theta \cdot e}{(1 - e \cdot \theta)}$$

Where D is DALYs, θ is treatment coverage (when calculating the impact of each regimen, this is divided by the number of regimens used for each group; three for adults for all genotypes, one per genotype for both adolescents and, where applicable, children), and e is efficacy. In the case of the HCV model, impact is calculated separately for each genotype; as well as for acute vs. chronic cases, due to differences in efficacy across genotypes and in non-cirrhotic versus cirrhotic patients with hepatitis C (only a proportion of chronic patients progress to cirrhosis, whereas all acute patients are assumed to be non-cirrhotic); and for treatment-naive vs. treatment-experienced patients, where data for both is available. As such, D in the HCV model differs depending on whether we are looking at acute or chronic cases, as well as based on the percent genotype distribution by which it is multiplied. Like DALYs, efficacy also differs by genotype and severity (cirrhotic vs. non-cirrhotic), and different regimens are used for different genotypes. The effect of cirrhosis on efficacy is accounted for by splitting chronic DALYsinto patients with and without cirrhosis. To account for the recommendations given for patients with compensated cirrhosis, we multiply chronic DALYs by the percentage of chronic hepatitis C patients with cirrhosis, multiplied by the percentage of cirrhosis that is compensated (calculated

by subtracting the percentage of decompensated cirrhotic hepatitis patients from 100%). Separately, we account for the recommendations for patients without cirrhosis in chronic hepatitis C by multiplying chronic DALYs by the percentage of chronic hepatitis C patients without cirrhosis (calculated by subtracting the percentage of patients with cirrhosis from 100%). This is then multiplied by the efficacy of a regimen for a given genotype in patients with compensated cirrhosis. For acute DALYs, we assume all patients are non-cirrhotic, so these are only multiplied by the efficacy of a regimen for a given genotype in patients without cirrhosis. In cases where efficacy is split between treatment-naive and treatment-experienced, we estimate the proportion of treatment experienced patients by multiplying DALYs by the percentage of patients who fail initial treatment (and thus require retreatment), 3%.[18] We assume the rest (97%) of the DALYs are for those who are treatment-naive, so we multiply DALYs by the remaining 97% to get treatment-naive DALYs.

The impact of every regimen on each genotype (1-6 and Mixed/Other), for both acute and chronic HCV (as DALYS are provided from IHME separated in this way[1]), is calculated separately and then summed to give the total impact on HCV.

Here is an example of how we calculate impact for a company, in this case, Gilead. Gilead is credited with patents for the regimens SOF + VEL, SOF + LDV, SOF + RBV, and SOF used in SOF + DCV (there is no single patent on this regimen, so credit is split evenly between Gilead as the patent holder for SOF and Bristol-Myers Squibb as the patent holder for DCV). . In order to calculate the impact of a company, we must first calculate the impact of each regimen the company has patented, in each country. These can be seen listed on the patent accreditation chart below.

Company	AbeVie Inc.[20]	Bristol-Myers Squibb[21]	Hoffmann-La Roche[22]
Company Impact Score	337,895.26	159,476.74	1.53
Patent Date	2015	2008	2006
Drug	glecaprevir + pibrentasvir	sofosbuvir + daclatasvir	pegylated interferon + ribavirin
Abbreviation	GLE + PIB	SOF + DCV	PEG + RBV
Regimen Impact Score	337,895.27	159,476.74	1.53

Table 2: Patent Accreditation Chart (Part 1).

Company	Gilead[23]	Gilead[24]	Gilead[25]	Gilead[26]
Company Impact Score	385,392.23			
Patent Date	2005	2014	2014	2013
Drug	sofosbuvir + daclatasvir	sofosbuvir + velpatasvir	sofosbuvir + ledipasvir	sofosbuvir + ribavirin
Abbreviation	SOF + DCV	SOF + VEL	SOF + LDV	SOF + RBV
Regimen Impact Score	159,476.74	223,061.26	1,513.23	1,341.00

Table 3: Patent Accreditation Chart (Part 2).

Here, we will demonstrate how impact is calculated on the most specific level, for SOF + DCV used to treat Chronic G3 HCV in treatment-naive adults without cirrhosis in India, but the same process is used for all other regimens, genotypes, severities, and countries. However, there is some variation in the level of specificity depending on how much information is available; for example, while we use separate efficacy data for treatment-naive versus treatment-experienced adults without cirrhosis wherever possible (e.g., see below), we lack this separated data in many cases (such as in G3 adults with compensated cirrhosis for GLE + PIB), and thus utilize "all treatment experience" (combination of treatment-naive and treatment-experienced) efficacy data in these cases.

Adult DALYs - Chronic	= 2,065,073.56
Treatment Coverage SEA	= 7.10%
G3 Efficacy SOF+DCV in treatment-naive adults without cirrhosis	= 94%
% HCV that is Genotype 3 in India	= 64.10%
% Patients who are treatment-naive	= 97%

Impact of SOF+DCV in India on Chronic Genotype 3 HCV in treatment-naive adults without cirrhosis:
= ([Chronic DALYs * % HCV that is Genotype 3 in India * % Patients who are treatment-naive] * [Treatment coverage in SEA/3] * G3 Efficacy of SOF+DCV in treatment-naive adults without cirrhosis)/(1 - [Treatment coverage in SEA/3] * G3 Efficacy of SOF+DCV in treatment-naive adults without cirrhosis)
= 22,641.37

The global impact of SOF + DCV on Chronic Genotype 3 HCV in treatment-naive adults without cirrhosis was found to be 62,753.03 , meaning that over a third (36.08%) of the global burden of disease alleviated by SOF + DCV for Chronic Genotype 3 HCV in treatment-naive adults without cirrhosis comes from India. Across genotypes, drugs, and acute versus chronic HCV, India accounts for a significant proportion of impact. This is notable because India has the highest Hepatitis C burden of any country in the world (2,169,732.89 DALYs).[10] However, this is not indicative of a pattern of highest impact corresponding to highest need on a global scale, which we will discuss in more detail in the Discussion section.

The process above is repeated for every country, every genotype (1-6 and Mixed/Other), and for both acute and chronic forms of HCV (in the case of chronic HCV, broken down further into with and without cirrhosis), and the results are then summed to get the global impact of the regimen SOF + DCV on HCV overall.

To get the total impact score for Gilead, we simply sum the impact of the regimens it has patented: SOF + VEL, SOF + LDV, SOF + RBV, and SOF + DCV. However, because there is no singular patent holder for SOF + DCV, we split credit between the patent holders for SOF (Gilead) and DCV (Bristol-Myers Squibb), such that Gilead and BMS each receive 1/2 of the credit for the regimen. We would calculate the overall impact of Gilead as follows:

Total impact score for Gilead*:

(Impact of SOF + DCV)/2 + (Impact of SOF + VEL) + (Impact of SOF + LDV) + (Impact of SOF + RBV)
= 159,476.74 + 223,061.26 + 1,513.23 + 1,341.00
= 385,392.23[1]

We calculate the impact of individual drugs, by dividing the impact of all the regimens including that drug by the number of drugs in the regimen, and then summing those impacts. This is because (for all drugs in all regimens in our model) we divide credit for impact evenly among all drugs included in that regimen, so for a regimen consisting of two drugs, each drug would be credited 50% of the regimen's total impact score. For example, the total impact of SOF would be calculated as follows.

[1]*Note: see Patent Accreditation Chart for Gilead above for detailed breakdown of regimen impact scores.*

Total impact score for SOF:

(Impact of SOF + DCV)/2 + (Impact of SOF + VEL)/2 + (Impact of SOF + LDV)/2 + (Impact of SOF + RBV)/2
= 159,476.74 + 111,530.63 + 756.615 + 670.54
=272,434.525

An important side note comes from the way that the model incorporates “mixed or other” genotypes (beyond 1-6) into our country-level calculations. While the genotype distribution data used in the model suggests that some proportion of the burden of HCV comes from genotypes other than strictly 1-6, these other genotypes are less well-defined and understood. For this group, we utilize the “Mixed” genotype efficacy data provided by the WHO, and only include the pangenotypic regimens used for adults, as the pediatric use of SOF + LDV and SOF + RBV are only indicated for genotypes 1, 4, 5, and 6 and 2-3 (respectively) in adolescents, and the use of PEG + RBV is only indicated for genotypes 2-3 with severe liver disease or coinfection in children under 12.

Results

The following results show pooled data across both acute and chronic cases for all genotypes.

The model shows that a total of 12,403,425.63 DALYs were lost to HCV in the year 2015, not counting morbidity and mortality due to hepatitis C-associated hepatocellular carcinoma (HCC, which is excluded from the model, as it requires an entirely different set of treatments which are not accounted for by this model).[27] Because the IHME lists DALYs lost due to acute hepatitis C, hepatitis C with liver disease, and hepatitis C-associated HCC as three separate entities, we were able to exclude the latter from our count of overall DALYs lost to hepatitis C in order to model only the morbidity and mortality which could be alleviated by DAAs and other HCV-targeting medications (the focus of this model), which are not used to treat HCC directly. The greatest burden of disease was seen in the SEA region, but there was also a significant burden of disease seen in other countries across multiple regions, including China in WPR, the United States in AMR, and Egypt in AFR.

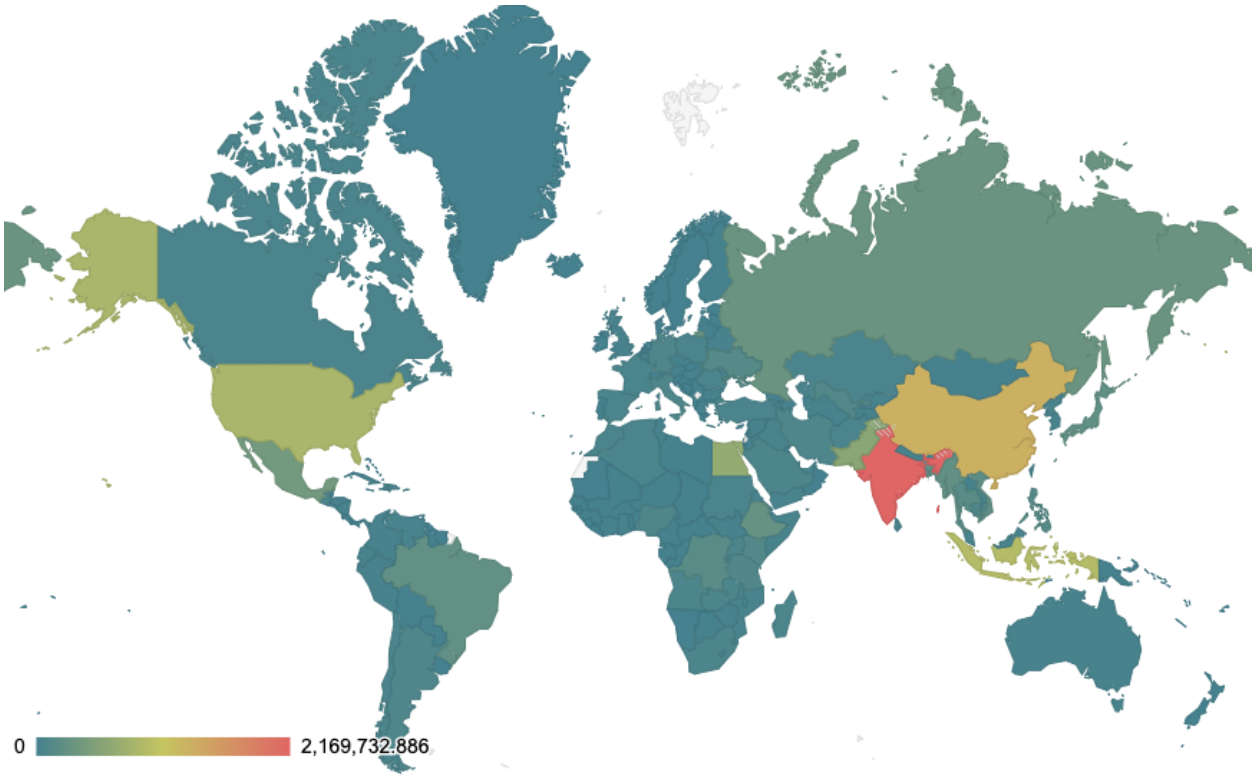

Figure 1: Total DALYs Lost to HCV in 2019.

The model also shows a total impact of all regimens, or "DALYs saved," of 882,765.77. While the greatest impact is seen in India, commensurate with its need, this trend does not hold for many other high-need countries. For example, China and Indonesia have a greater need for treatment than the United States in terms of burden of disease, but see a significantly smaller impact. These trends serve to highlight the inequitable distribution of HCV medications on a global scale.

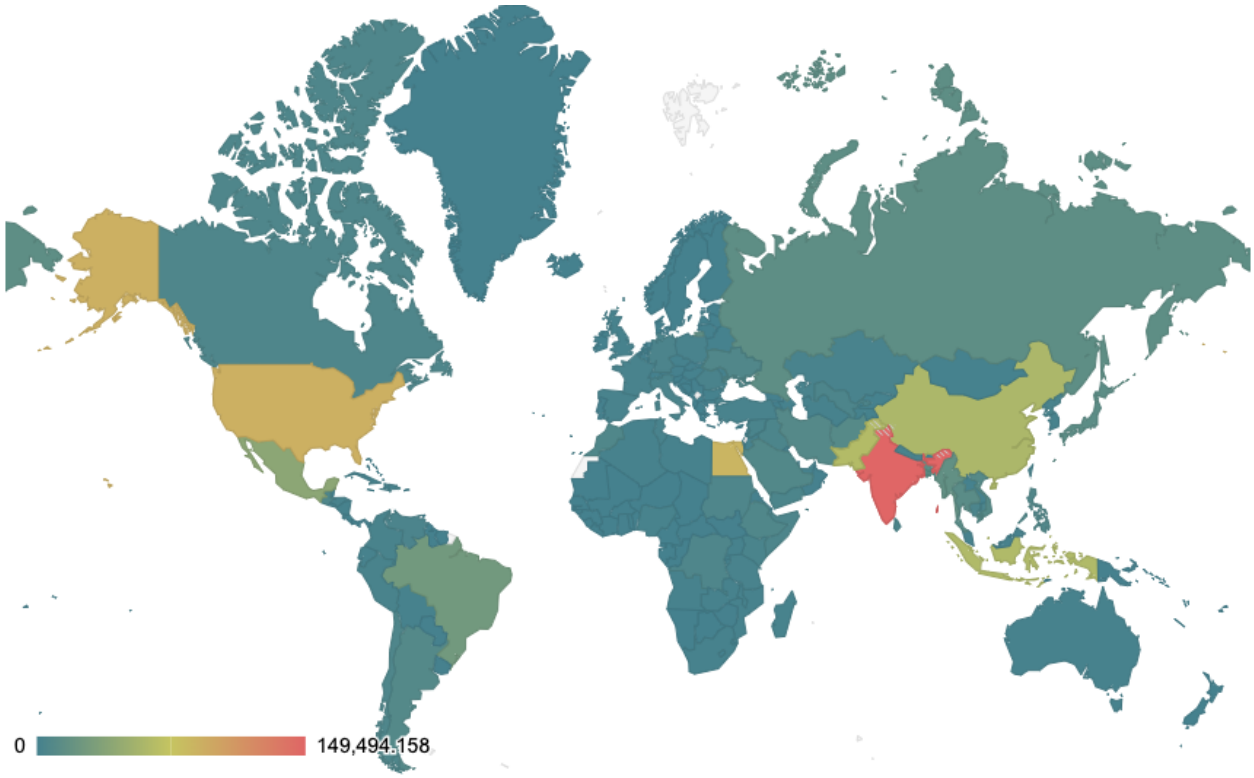

Figure 2: Total Impact on HCV in 2019.

By summing both the total DALYs lost to HCV with the total Impact on HCV, we can also estimate the total burden of disease (BoD) there would be in the absence of treatment, a total of 13,286,191.40 DALYs.

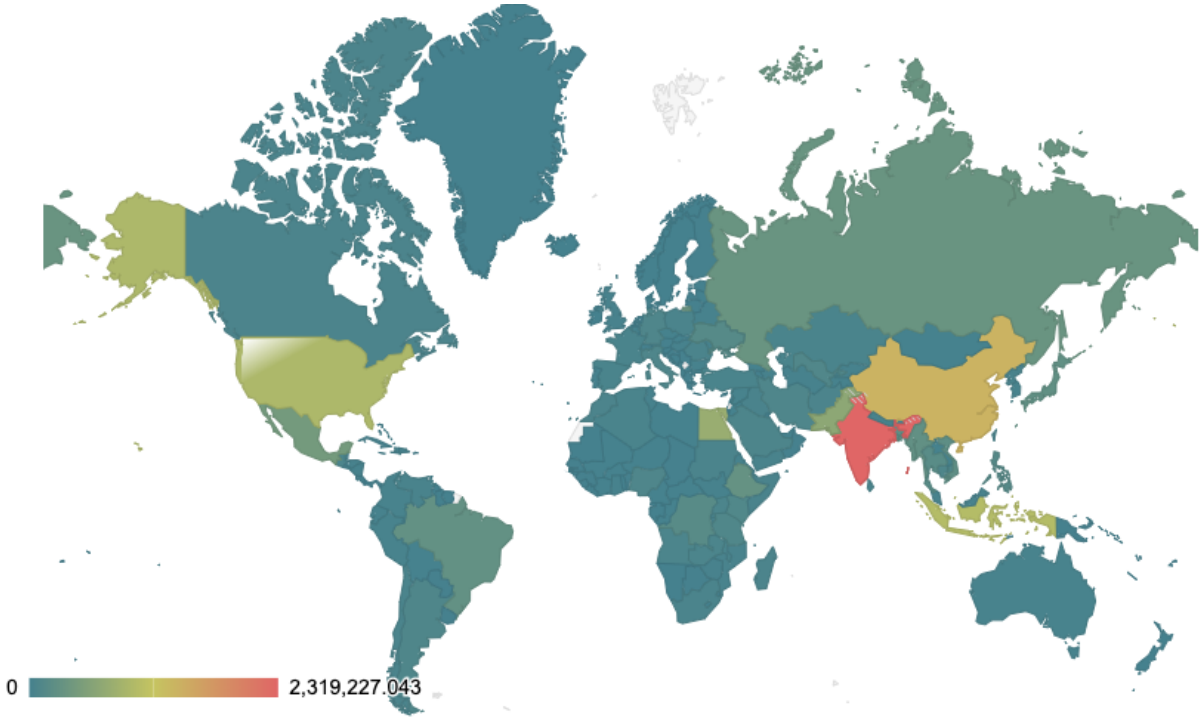

Figure 3: Total Burden of Disease Absent Treatment in 2019.

The impact of the individual drugs used to treat HCV was also calculated, with SOF having by far the greatest impact of any single drug at 272,434.49. However, 93.4% of the global burden of HCV is still unalleviated.

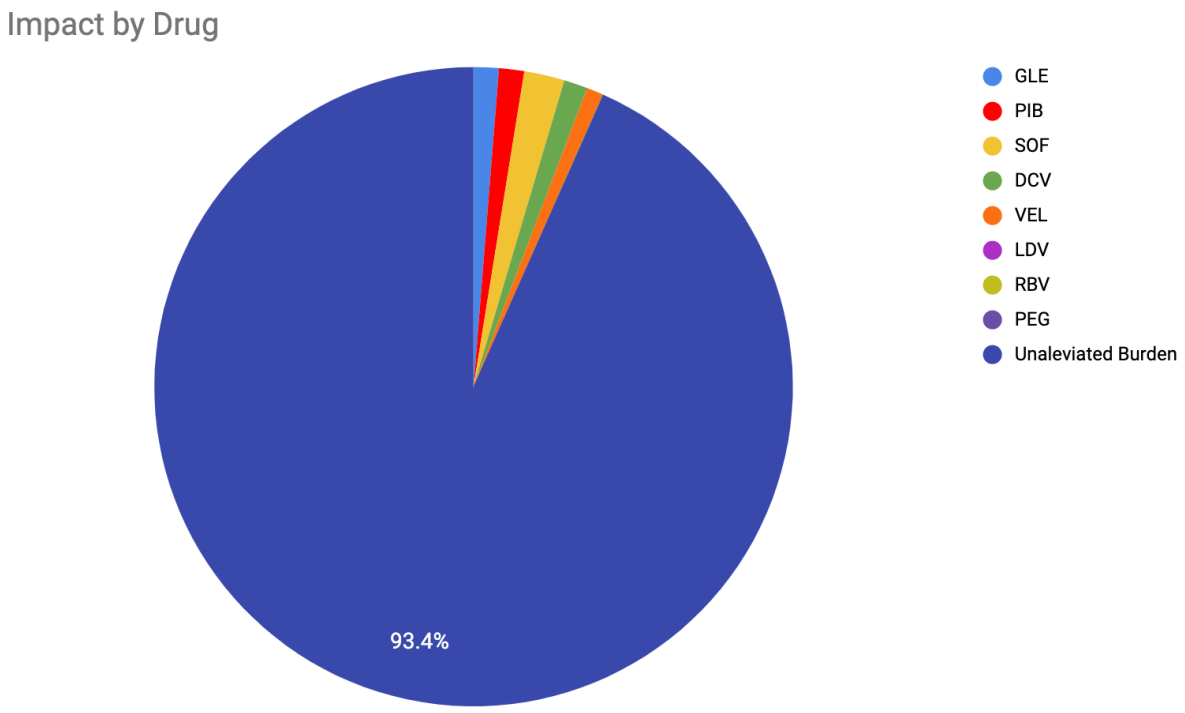

Figure 4: Total Impact by Drug in 2019.

Of the patent holders included in the model, Gilead was responsible for by far the largest share of impact, 385,392.23 DALYs averted. This should be interpreted with caution given the limited number or regimens included, but is also to be expected given the fact that Gilead has a patent on most SOF-containing regimens in the model, and SOF has the largest impact of any single drug.

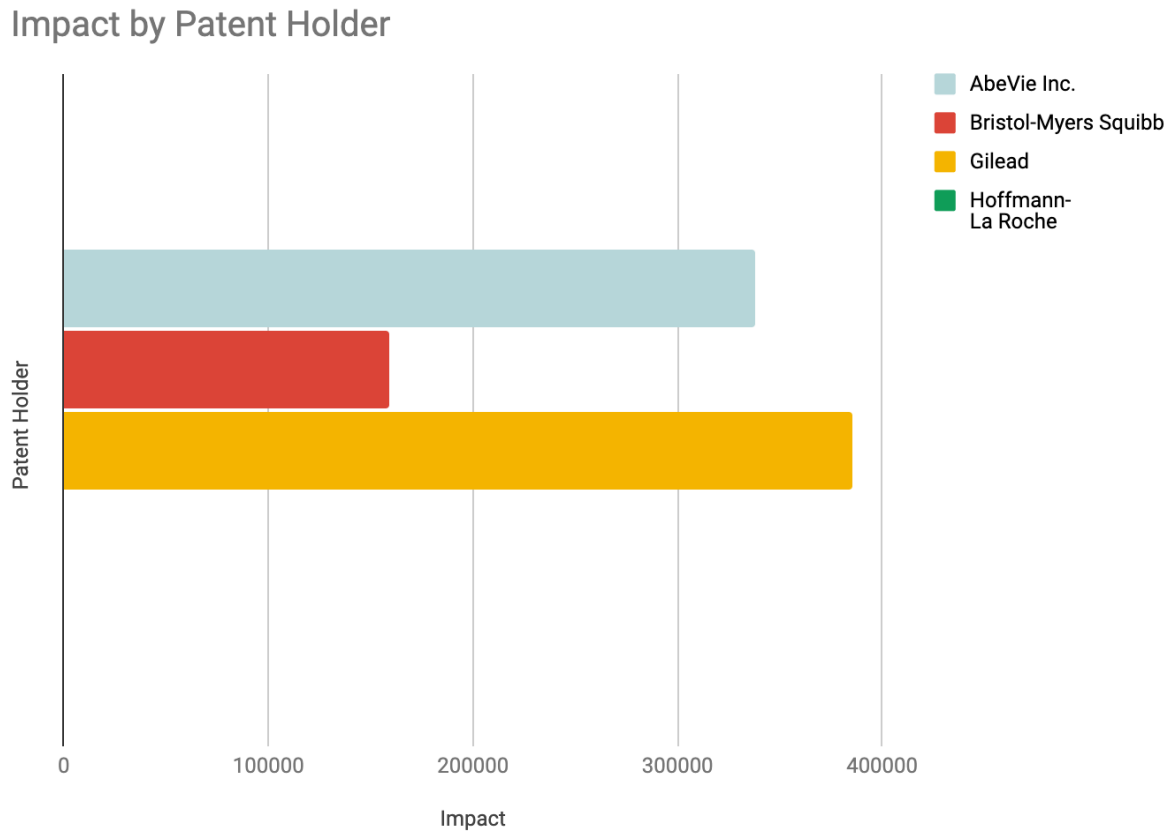

Figure 5: Total Impact by Patent Holder in 2019.

Discussion

By breaking down the morbidity and mortality associated with hepatitis C by genotype, and by separating the contributions of acute and chronic infection, our model has been able to estimate more specific contributors to the burden on disease of hepatitis C in each country with greater precision. This is particularly significant because treatment efficacy differs significantly by genotype, so incorporating country-level genotype distribution data has allowed us to understand how the impact of pangenotypic regimens in adults and more genotype-specific regimens in children and adolescents varies depending on which genotypes are most prevalent in a given country. Differentiating between the efficacy of regimens recommended for the treatment of each genotype in both acute and chronic cases, with and without cirrhosis and in treatment-naive versus treatment-experienced patients, in turn gives us greater precision in estimating the impact of each regimen on treating different genotypes and severities of infection. For example, according to WHO efficacy data for SOF + DCV, SVR for genotype 1 is 98% for hepatitis C without cirrhosis and 93% for hepatitis C with compensated cirrhosis, while for genotype 3 it shows only 92% SVR for hepatitis C without cirrhosis and 63%for hepatitis C with compensated cirrhosis.[15] Thus, the impact of a regimen in a country with predominantly genotype 1 can differ from its impact in a country with predominantly genotype 3, as well as based on the proportion of chronic versus acute cases (as efficacy data for cirrhotic patients, which tends to be lower, is only incorporated for a proportion of cases of chronic hepatitis C); or, in the case of children, treatment may not be recommended at all for certain genotypes and in less severe cases (treatment guidelines only specify treatment for genotypes 1-6 (excluding Mixed/Other) for adolescents, and genotypes 2-3 with decompensated cirrhosis or coinfection in children under 12). This level of nuance means that credit for burden of disease alleviated (impact score) can be assigned to each regimen with much higher specificity by incorporating a combination of age group and acute/chronic specification for DALY data, country-level genotype distribution data, and regional treatment distribution data.

This combination improves our ability to estimate drug impacts within each country, especially in terms of highlighting which countries show the highest burden of disease and which show the greatest impact of treatment. These trends are most evident when we compare the map-style graphs displaying Total DALYs Lost with Total Impact. India, which has the highest number of DALYs lost to hepatitis C (2,169,732.89) has seen an estimated impact of 149,494.16 DALYs saved, having alleviated 6.89% of the burden of hepatitis C.By comparison, the United States has had an estimated 91,386.4210 DALYs saved, resulting in 10.80% of the burden of hepatitis C alleviated, in spite of having less than half as many DALYs (846,087.38) lost to hepatitis C. Other countries with a high burden of hepatitis C like China and Indonesia demonstrate this discrepancy in access to medicines even more starkly, having lost significantly more DALYs to hepatitis C (1,321,255.92 in China; 936,457.10 in Indonesia) than the United States, but having only alleviated 4.51% (59,621.49 DALYs) of the burden of hepatitis C in China, and 6.64%

(62,174.01 DALYs) in Indonesia. Additionally, many African countries in particular have a much lower proportion of impact relative to their overall burden of disease, with many hovering at only about 2-3% of the burden alleviated. This is most striking in Ethiopia, which has the 10th highest number of DALYs lost to hepatitis C (276,951.97), but has seen only 2.30% of the burden of hepatitis C alleviated (6,371.71 DALYs). This pattern aligns with the AFR region having the lowest regional treatment coverage used in the model (2.20%), and also serves to highlight the lack of access to treatment in this region in particular. Allowing us to examine discrepancies in need versus benefit received is one of the most significant highlights the model has to offer.

Also of note is the impact of Sofosbuvir-containing regimens in particular; on a drug-specific level, Sofosbuvir is responsible for the largest burden of disease alleviated of any drug included in the model (2.05%); this follows from its broader usage within many recommended regimens, with four of the six regimens included in the model containing Sofosbuvir (the largest proportion of any drug). Likewise, we can attribute the impact of drugs patented by Gilead, which has alleviated 2.90% of the burden of disease for hepatitis C (the highest of any patent holder included in the model), to the fact that it holds the patents for three and a half (half of SOF + DCV) of the six regimens within the model, including the split patent it holds with BMS for SOF + DVC, while other included companies hold only one patent (or half of one, in the case of BMS). However, above all else it is important to highlight that 12,403,425.638 DALYs remain unalleviated by any treatment; this unalleviated burden accounts for 93.36% of the estimated total burden of disease absent treatment. Future efforts may focus on tracking efforts to close this gap in treatment impact in more recent years (as the current model uses data from 2019), as well as focusing on which countries are prioritized in terms of treatment distribution relative to their need based on burden of disease, and incorporating manufacturers of the included regimens in order to account for those directly responsible for the treatment distribution process.

Conclusion

As the prevalence of hepatitis C continues to increase globally, access to diagnostic testing and effective treatment lags behind. When identified and treated early enough, it is usually curable with DAAs; left untreated, chronic hepatitis C can lead to decompensated cirrhosis and hepatocellular carcinoma, both of which can be fatal. The specificity of our model with regard to age groups, infection duration (acute vs. chronic), stage of liver disease in chronic patients (cirrhotic vs. non-cirrhotic), treatment experience, genotype distribution, and SVR variability across both of these variables, allows us more comprehensive insight into how the burden of disease for hepatitis C is distributed across the world, and how the distribution and effectiveness of DAAs works to reduce morbidity and mortality due to hepatitis C. In turn, this serves to highlight discrepancies between where these medications are most needed and where they are most accessible, which raises the question of how treatment distribution is prioritized by the companies responsible for these life-saving treatments. We hope that the data provided by this model can provide further insight into the practical need for increased treatment distribution, particularly in countries with more limited access relative to their high burden of disease, and will help guide others in the fields of public health and epidemiology to take further steps to close this gap in unalleviated burden.

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Appendix

Drug	Identified patent	Company	Patent Year	Citation
Glecaprevir + Pibrentasvir	GLE + PIB	AbeVie Inc.	2015	Bernstein B, et al. Methods for Treating HCV. Patent Number: WO2015153793 A1. 8 October 2015. [cited 15 November 2021]. Available from: https://worldwide.espacenet.com/patent/search/family/052829479/publication/WO2015153793A1?q=WO2015153793A1
Sofosbuvir + Daclatasvir	SOF + DCV	Bristol-Myers Squibb (DCV) Gilead (SOF)	2008 (DCV) 2005 (SOF)	DCV: Bachand C, et al. Hepatitis C Virus Inhibitors. Patent Number: WO200802197 A2. 2008 February 21. [cited 25 March 2022]. Available from: https://patents.google.com/patent/WO2008021927A2/en SOF: Clark J. Modified Fluorinated Nucleoside Analogues.

				Patent Number: WO2005003147 A2. 2005 January 13. [cited 25 March 2022]. Available from: https://patents.google.com/patent/WO2005003147A2/en
Sofosbuvir + Velpatasvir	SOF + VEL	Gilead	2014	Yang C. Hepatitis C Treatments with Sofosbuvir. Patent Number: WO2014185995 A1. 2014 November 20. [cited 8 March 2022]. Available from: https://patents.google.com/patent/WO2014185995A1/en?oq=WO2014185995
Sofosbuvir + Ledipasvir	SOF + LDV	Gilead	2014	Chal, B., Mogalian, E., Pakdaman, R., Oliyai, R., Stefanidis, D., Zia, V. Combination Formulation Of Two Antiviral Compounds. Patent Number: WO201412098. 2014 August 7. Available from: https://patentimages.storage.googleapis.com/d5/5c

				/40/7b8fda3f9acef8/WO2014120981A1.pdf
Sofosbuvir + Ribavirin	SOF + RBV	Gilead	2013	Berrey, M. M., Hindes, R. G., Symonds, W. T., Ray, A. S., Mo, H., Hebner, C. M. (2013). Methods and Compositions for Treating Hepatitis C Virus. Patent Number: WO2013066748 A1. 2013 May 10. Available from: https://patents.google.com/patent/WO2013066748A1/en
Pegylated Interferon + Ribavirin	PEG + RBV	Hoffmann-La Roche	2006	Zahm F. Use of Peg-ifn-alpha and Ribavirin for the Treatment of Chronic Hepatitis C. Patent Number: WO199064016 A1. 2006 July 21. [cited 8 March 2022]. Available From: https://patentimages.storage.googleapis.com/31/a3/c6/ba7447c2e9ca7c/WO1999064016A1.pdf

Table 5: Patent Holder Sources by Regimen.

WHO Efficacy Data								
HCV-infected adults (≥18) without cirrhosis (Pangenotypic DAAs)								
Treatment	**G1 SVR**	**G2 SVR**	**G3 SVR**	**G4 SVR**	**G5 SVR**	**G6 SVR**	**Mixed SVR**	**Average SVR***
GLE + PIB								
All Treatment	98.00%	98.00%	95.00%	97.00%	83.00%	94.00%	97.00%	94.57%
Treatment Naive	-	-	95.00%	-	-	-	-	-
Treatment Experienced	-	-	92.00%	-	-	-	-	-
SOF + DCV								
All Treatment	98.00%	94.00%	92.00%	97.00%	88.00%	94.00%	94.00%	93.86%
Treatment Naive	98.00%	75.00%	94.00%	93.00%	83.00%	-	91.00%	-
Treatment Experienced	98.00%	75.00%	86.00%	83.00%	-	-	98.00%	-
SOF + VEL								
All Treatment	96.00%	99.00%	89.00%	99.00%	97.00%	99.00%	99.00%	96.86%
Treatment Naive	95.00%	84.00%	98.00%	-	-	-	96.00%	-
Treatment Experienced	96.00%	97.00%	85.00%	-	-	-	-	-
HCV-infected adults (≥18) with compensated cirrhosis (Pangenotypic DAAs)								
Treatment	**G1 SVR**	**G2 SVR**	**G3 SVR**	**G4 SVR**	**G5 SVR**	**G6 SVR**	**Mixed SVR**	**Average SVR***
GLE + PIB								
All Treatment	99.00%	98.00%	-	97.00%	83.00%	94.00%	93.00%	94.00%
Treatment Naive	-	-	-	-	-	-	-	-

Treatment Experienced	-	-	-	-	-	-	-	-
SOF + DCV								
All Treatment	93.00%	96.00%	63.00%	-	75.00%	93.00%	83.00%	83.83%
Treatment Naive	-	-	58.00%	-	-	-	-	-
Treatment Experienced	98.00%	-	69.00%	-	-	-	-	-
SOF + VEL								
All Treatment	90%	86%	86%	88%	-	75%	97%	87.00%
Treatment Naive	-	-	97%	-	-	-	-	-
Treatment Experienced	-	-	90.00%	-	-	-	86.00%	-
HCV-Infected adolescents (aged 12–17) or weighing at least 35 kg with chronic HCV (without cirrhosis or with only compensated cirrhosis)								
Treatment	**G1 SVR**	**G2 SVR**	**G3 SVR**	**G4 SVR**	**G5 SVR**	**G6 SVR**	**Mixed SVR**	**Average SVR***
SOF + LDV	98.00%	-	-	-	-	-	-	98.00%
SOF + RBV	-	100.00 %	97.00%	-	-	-	-	98.50%
HCV-Infected children (<12) (with genotype 2 or 3 AND severe liver disease or coinfection)								
Treatment	**G1 SVR**	**G2 SVR**	**G3 SVR**	**G4 SVR**	**G5 SVR**	**G6 SVR**	**Mixed SVR**	
PEG + RBV	-	89.00%	89.00%	-	-	-	-	

Table 6: Global SVR Data taken from the WHO's "Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection." [15]

**Note 1: Average SVR for each regimen and treatment group is assumed for impact calculations where genotype-specific SVR data is missing.*