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Research Article

Reimplementation of a hepatitis C virus national strategy plan provides a cost-effective path forward to elimination of the virus in Brazil: An update on previous implications

Alexis S. Voeller*, Devin Razavi-Shearer, Ivane Gamkrelidze, and Homie Razavi

Center for Disease Analysis Foundation, Lafayette, Colorado, United States

Abstract

Introduction: Viral hepatitis C plays a negative role in Brazilian health systems. This study highlights this role along with strategies needed to work toward elimination of the virus through a reimplementation of a cost-effective national strategy.

Methods: A mathematical modeling approach was used [1] to understand the disease burden of the hepatitis C virus (HCV) after the removal of the national strategy and [2] to demonstrate the economic burden with reinstatement. Two scenarios were addressed within the model: reusing the national strategy (working toward World Health Organization 2030 elimination goals) and the baseline case in 2021, which mirrors the current HCV situation.

Results: With removing the plan, an additional 207,000 patients will be infected along with 12,600 more liver-related deaths by 2030. These results demonstrate the need for strategies to be reinstated to improve diagnosis and screening. Scaling up interventions will increase direct costs, but these expenses will decrease annually as elimination targets are met. This reduction is a result of preventing HCV liver morbidity, mortality and indirect costs showing policy intervention is cost-effective over time.

Conclusion: For Brazil to achieve HCV elimination by 2030, a national strategy needs to be put back into place. As it currently stands, the previous Hepatitis C Elimination Plan does not meet WHO elimination targets. Therefore, additional scaling up of treatment, diagnosis, and screening is needed meet the WHO goals. Our data show that attaining WHO-decreed HCV elimination by 2030 will not be achieved without reinstating a reimagined intervention.

Keywords: viral hepatitis C; HCV elimination; WHO 2030 elimination targets; Brazil

Abbreviations

HCV, hepatitis C virus; DALY, disability-adjusted life year; GNI, gross national income; NSP, National Strategy Plan; WHO, World Health Organization; MoH, Ministry of Health

Introduction

Viral hepatitis C (HCV) is a disease that continues to negatively affect the health of the Brazilian population. Previous studies [1] have been published that examine the potential impact of elimination strategy programs, and the economic impact of said programs, within the country. One of these strategies, the Hepatitis C Elimination Plan, was created by the Ministry of Health, ratified by a contingency of government officials—the Tripartite Commission—who represent federal, state, and municipal governments. This plan was put into place in 2018. It outlined action items to be undertaken by different health and government sectors in terms of HCV prevention, treatment, and screening [2]. It was designed to work toward the World Health Organization (WHO) goal of elimination of HCV by 2030 and delineates the targets to be reached for a country to achieve elimination [3]. Although the plan started strongly within its first year of implementation, it was later revoked by the Brazilian government in 2019. This study highlights the impact of the current HCV disease burden in Brazil as a result of the removal of the plan, evaluates the economic feasibility of reinstating a similar elimination plan, and updates our previous work [1] based on what transpired in 2018.

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***Corresponding author(s):** Alexis S. Voeller, Center for Disease Analysis Foundation, Lafayette, Colorado, United States

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Materials and Methods

A mathematical modeling approach was used to quantify the current HCV disease burden in Brazil. Similar to our earlier work [1], this strategy estimates the current disease burden as well as approximates disease progression and the economic costs entailed with repurposing the previous Hepatitis C Elimination Plan.

Model Overview

A Markov model, created in Microsoft Excel® (2010, Microsoft Corp., Redmond, WA), was used to identify potential outcomes regarding HCV infection rates in Brazil within the general population [4]. The model outputs liver disease stages from

1950 to 2030 using epidemiological data as the base inputs and the means of calibration [4]. An outline of disease progression considered by the model is shown in the **Appendix** (Figure A1).

Model Inputs

Several epidemiological data inputs were necessary to populate and run our model, including HCV antibody prevalence as well as viremic prevalence. These data were collected and verified using a Delphi process (described previously [4] that considered results of literature searches and expert consensus from the leaders within the field. Prevalence data included as inputs in the current model were the same as those published earlier [1]. Prevalence among 15- to 69-year-olds was estimated to be 0.70% from unpublished data in 2016, stating 0.76% of 484,300 rapid tests used in Brazil were antibody positive and adjusted for at-risk populations, which was formerly noted [1]. The model inputs of age and sex were estimated by using data obtained from the Ministry of Health and the 2016 Boletim Epidemiologico report [5], which was unchanged from the previous report [1]. As another model input, most literature sources report antibody testing over RNA-positive cases, so we used a weighted average calculated from five studies in Brazil [6-10], demonstrated a viremic rate of 60.7% from 2016, which was crucial to quantifying the viremic caseload.

Another model input was the incidence of newly acquired HCV infections—meaning, new infections within a given year, not newly diagnosed cases, as noted in our earlier work [1]. Incidence data, updated for the 2021 base scenario with the same back calculations used in our previous study [1], were derived from the literature and expert consensus within Brazil. Other model inputs included the total number of diagnosed cases, the number of newly diagnosed cases annually, and the number of patients treated annually. These parameters were used after being reported through 2020 via expert consensus in unpublished data [11]. These data have been adjusted according to our prior work [1] and updated to reflect the 2021 base scenario. Unmet screening need was used as an input to infer any potential need for improvement in terms of surveillance in Brazil and were updated as mentioned. The number of liver transplants was also used as an annual input and was acquired from the Ministry of Health's database [12]. Genotypic distribution was considered as an input, but now that HCV treatment regimens are pan-genotypic, this input was not included in our current work. The number of treated and the number of cured patients were also included as model inputs as detailed by expert consensus.

Model Outputs: Base Scenario, 2021

The model outputs for the base scenario in 2021 included data available after the Hepatitis C Elimination Plan was halted in 2019. The outputs (total infected, number of patients diagnoses, number of patients treated, incident hepatocellular carcinoma, and liver-related deaths) reflect the drop in treatment cases along with the decrease in diagnosed and cured patients. We assumed the outputs for this scenario would be the same as in our previous work [1], because no interventions are currently in use by the Brazilian government. The outputs include epidemiological data that reflect the impact of rescinding the 2018 HCV elimination strategy.

Model Outputs: National Strategy Plan

This scenario was the plan the Ministry of Health created and implemented in 2018 to screen, diagnose, and treat the general population to make strides toward achieving 2030 WHO elimination targets and impacting HCV infection in Brazil. The outputs (total infected, number of patients diagnoses, number of patients treated, incident hepatocellular carcinoma, and liver-related deaths) represent the Hepatitis C Elimination Plan outlining universal treatment policy for all viremic cases, updated guidelines and simplified testing strategies and support for implementing interventions such as linkage to care for patients and sustainable pricing for medical costs over time [2]. While this plan is no longer used within Brazil, the outputs remained the same as mentioned in the previous study [1]. This elimination plan is denoted as the national strategy plan scenario (NSP) throughout this study.

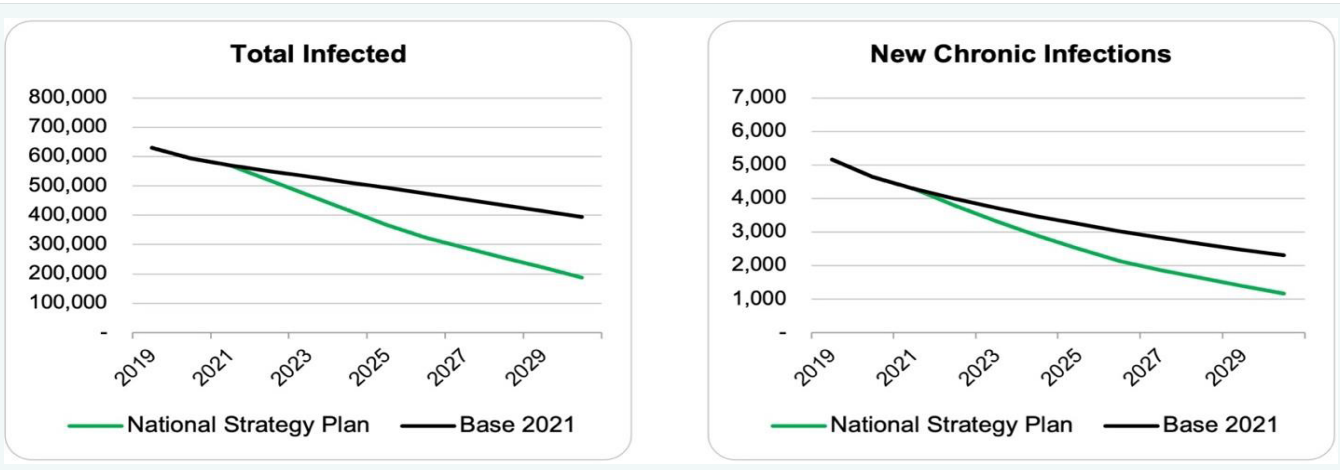

Figure 1 Total Infected Patients and New Chronic Infections Between Scenarios.

Economic Analysis

A mathematical modeling approach was also used to analyze the costs of both scenarios: no further policy changes versus reinstating the NSP/Hepatitis C Elimination Plan from 2018 with the goal of reaching the 2030 WHO elimination target. Similar to our previous study [1], data used for direct costs were collected from the Brazilian Unified Health System along with expert insight. The Delphi process was used to validate economic inputs with expert consensus. There has not been an update on economic costs since the prior work was published [1], so all input data remained constant. Price data were given in U.S. dollars and then converted at an exchange rate of 3.25 BRL at the end of 2016. We once again [1] compared direct costs (screening, treating, and diagnosis of HCV along with any related healthcare costs) to indirect costs (years of life lost [YLLs] and years living with disability [YLDs]). Expert knowledge reported in 2017 that the average cost of direct-acting antiretrovirals for a full 12-week treatment was expected to decrease from 17,000 BRL to 10,000 BRL in 2019. This value has not been updated since 2017.

For both scenarios (baseline [no change] vs. reimplementation of the elimination plan), direct costs in the economic analysis were defined as any economic burden pertaining to screening, diagnosing, and treating HCV infection along with any associated complications. The total of these costs was based off the assumption that a patient needed one anti-HCV test (screening) along with one polymerase chain reaction (PCR) RNA test (viremic confirmation) in both the baseline case and in the reinstated elimination scenario. With regard to screening as mandated by the Brazilian Ministry of Health, for the baseline scenario, a patient diagnosed with HCV underwent four PCR RNA tests, one genotyping test, and one staging/biopsy/FibroScan test. These tests comprised the total extent of screening for HCV. For the reinstated elimination scenario, we assumed each patient diagnosed with HCV needed two PCR RNA tests, one genotyping test, and one staging/biopsy/FibroScan test *per year*. (Again, although the Ministry of Health collects genotyping data, we did not include these data in our analysis.) The values associated with these tests demonstrate a conservative approach when monitoring or diagnosing patients. Indirect costs included disability-adjusted life years (DALYs), which were estimated using YLDs and YLLs. In addition, the impact disease stage has on indirect costs and how that affects productivity loss in Brazil was important for model calculations. Last, similar to our previous work [1], the value of a statistical life year was the same as the gross national income per capita in Brazil in 2015 (28,757 BRL per the World Bank [13]) and apply to DALYs for patients aged 20 to 69 years.

Results

HCV Disease Burden

Model input metrics are presented in Table 1. A 0.7% anti-HCV prevalence was used for patients aged 15 to 69 years. The anti-HCV prevalence accounting for all ages (0–85+ years) in 2016 was calculated to be 0.53%, which corresponds to the reported viremic rate of 60.7% that accounts for 670,000 HCV-/RNA-positive individuals (0.32% of the general population age 0–85+ years) [1]. These values are used in the current study because there has not been a national update regarding prevalence of HCV infection in Brazil since 2016. The highest rate of infection fell was seen in individuals 40 to 64 years old.

Table 1: Input Metrics used within the Modeling Approach.

Metrics Used in Model: Disease Burden	**Input: Disease Burden**		**Year of Estimate:**	**Source:**
Anti-HCV Prevalence in 15–69-year-olds	0.7%		2016	1
Newly Diagnosed (Annually Reported)	9,300		2020	12
Number Treated (Annually Reported)	20,200		2020	Unpublished data
Viremic Rate	60.7%		2016	1,6-10
Total Diagnosed	97,000		2016	5
Age and Sex Distribution			2016	5
Metrics Used in Model: Direct Health Costs	**Input: Annual Patient Costs for Diagnosed Patient – BRL:**		**Year of Estimate:**	**Source:**
Annual Monitoring Appointment (F0-F2)	683		2017	Expert input
Stages F3 to Compensated Cirrhosis	812			
Decompensated Cirrhosis	12359			
Hepatocellular Carcinoma	21778			
Liver Transplant	141346			
Metrics Used in Model: Diagnostic Costs	**Public:**	**Private:**		
Anti-HCV Test	11	196		
HCV RNA Test/PCR	59	709		
Genotyping	118	763		
Staging/Biopsy/FibroScan	200	623		

Other inputs (Table 1) delineate that 9,300 patients were newly diagnosed in 2020 along with 20,200 newly treated patients. The previous publication's model predicted with the national strategy plan (NSP) or Hepatitis C Elimination Plan in place compared to the base in 2017 that 37,500 patients would have been treated in 2020. Removal of the plan created a difference of nearly 18,000 patients.

When examining the current modeling scenarios, there are apparent output differences in the total number of infected patients and new chronic infections from 2019-2030 (Figure 1). The NSP shows a significant decrease in the total infected patients over time as well as a lesser burden of new chronic infections leading to fewer comorbidities resulting from HCV infection over time. These differences are presented in Table 2. Our model projections indicate that the total number of infected patients in 2030 will reach 395,000 without an HCV prevention strategy. With the NSP, the total number of people infected in 2030 decreases to 188,000. The projected number of patients diagnosed in 2021 using the NSP is 40,000 compared to the 9,300 the base case suggested. A similar trend is seen with the number of patients that could have been treated with the NSP in 2021; 50,000 patients would have been treated compared to 15,600. Other projections with the NSP conclude that the incidence of hepatocellular carcinoma, decompensated cirrhosis, and liver-related deaths would decrease by at least 50% in 2030 with the NSP compared to the baseline. The number of lives saved from liver-related death with the NSP could reach 12,600 by 2030.

Because treatment eligibility and disbursement were a large part of the original elimination plan, it is important to break down treatment numbers to highlight the gaps caused by the removal of the plan (Figure 2). When looking at the actual treated data, only 20,200 patients were treated, whereas 50,000 were supposed to be under the original plan to help attain 2030 elimination goals. The original publication [1] base case in 2017 shows that without any intervention it was predicted that there would be a low treatment rate, at only 12,500 patients in 2020—illuminating part of the rationale behind an elimination strategy in the first place.

If the Hepatitis C Elimination Plan was not removed, starting in 2019, there could have been a 53% decrease in HCV-related mortality by 2030 (Table 3). There could have also been a 51% decrease in new cases of HCV-related liver cancer along with a 50% decrease in new cases of decompensated cirrhosis by 2030. With the elimination plan in place, the reduction in the total number of infected individuals would have been by 70% along

Table 2: Model Output Data in each Scenario.

Scenarios	Base 2021	National Strategy Plan	Delta
Total Infected in 2030	395,000	188,000	207,000
Number of Patients Diagnosed in 2021	9,300	40,000	30,700
Number of Patients Treated in 2021	15,600	50,000	34,400
Incident HCC in 2030	2,900	1,200	1,700
Incident Decompensated Cirrhosis in 2030	2,300	960	1,340
Incident Liver-Related Deaths in 2030	2,700	1,200	1,500
Liver-Related Deaths	35,100	22,500	12,600

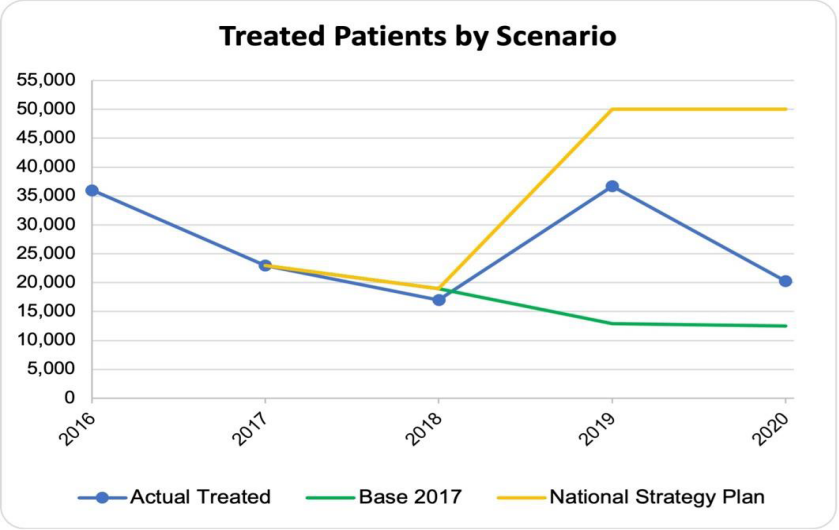

Figure 2 Treated Patients by Scenario or Actual Data Input.

with a 78% decrease in new infections by 2030. It also can be noted that with years lost due to the removal of the Hepatitis C Elimination Plan, Brazil no longer meets all the WHO 2030 relative elimination targets.

Economic Burden:

The economic burden in terms of direct and indirect costs was analyzed between the two scenarios: the base case in 2021 and the NSP. When comparing the direct medical costs between the two, Figure 3 showcases that although having the NSP in place does incur more of an upfront cost, by 2035 (Figure 3) there is a decrease in medical costs because of the decrease in disease burden. In 2025, the direct costs will peak at 724 million BRL and drop to 146 million BRL within 10 years. The indirect economic losses demonstrate that an investment in the up-front costs of the elimination program will decrease these losses starting in 2023, with 1,184 million BRL all the down to nearly 3 million BRL in 2035 as a result of the NSP. When adding both costs together, there is an overall decrease in both direct and indirect costs starting in 2023 at about 1,565 million BRL to nearly 149 million BRL with the NSP, dropping off around 2035. All the direct costs within this time frame will be devoted to healthcare costs, screening costs and treatment and lab costs. The additional screening costs will be crucial in carrying out the NSP compared to the base situation. Because the NSP affects the population positively, all these costs will decrease overtime. The economic impact of the NSP is demonstrated even further within the public health insurance budget utilization. Although the Hepatitis C Elimination Plan consume 0.43% of the budget in 2019, if the plan remained in place, it would have only utilized 0.07% of the budget by 2035.

Table 3: National Strategy Plan Projections if not Removed from Government Policy.

Impacts between 2019 to 2030:	Percentage of Decrease:
Decrease in HCV-related mortality	53%
Decrease in new cases of HCV-related liver cancer	51%
Decrease in total number infected	70%
Decrease in new infections	78%
Decrease in new cases of decompensated cirrhosis	50%

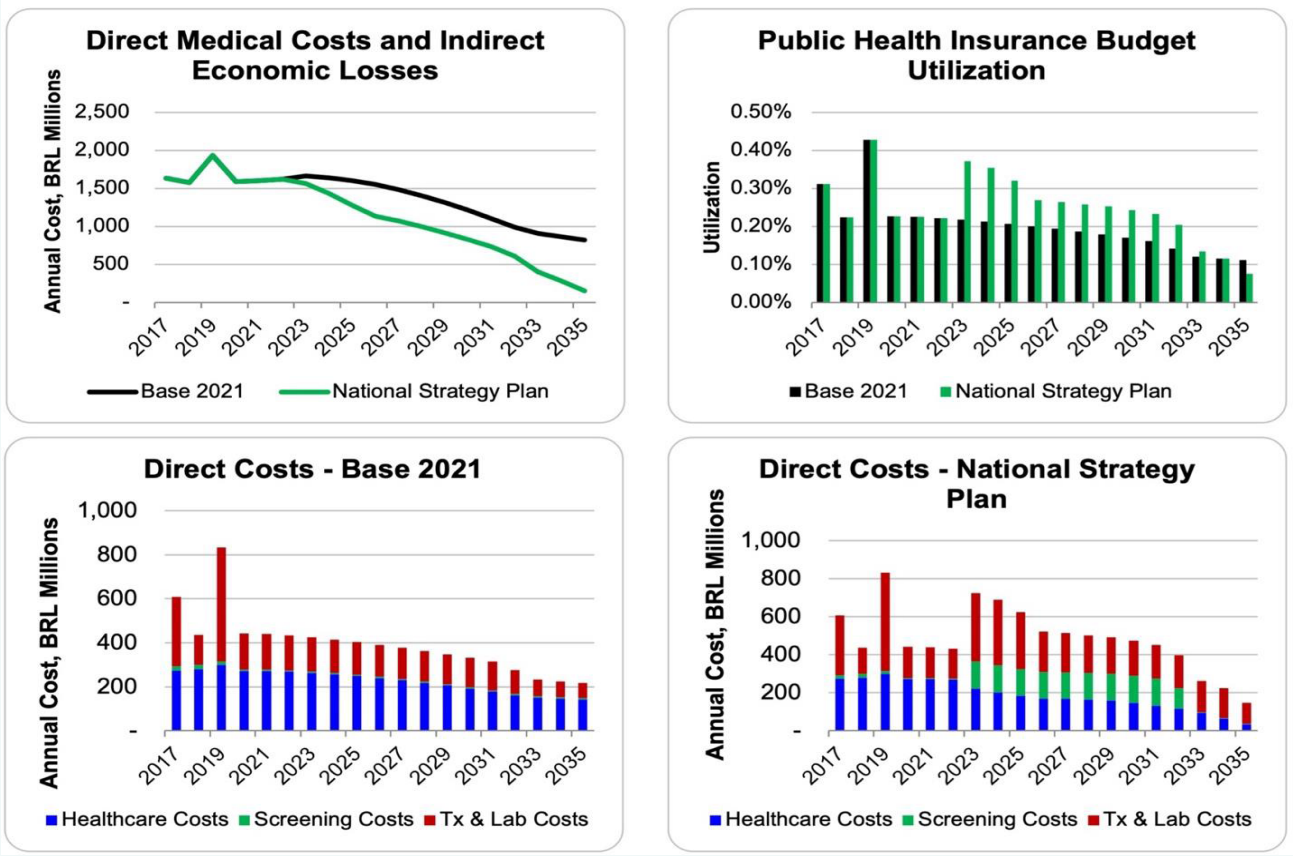

Figure 3 Impact of Costs over Time by Scenario.

The average cost per DALY averted between 2017 to 2035 with the NSP is expected to be 5,263 BRL. This value is significantly under the gross national income per capita of 28,757 BRL, making this scenario highly cost-effective. In previous work [1], the average cost per DALY averted was 1,800 BRL, demonstrating that, even now more so, the NSP/elimination plan is cost-effective in Brazil when implemented.

Discussion

Disease Burden

The national strategy plan/Hepatitis C Elimination Plan provides a steppingstone for Brazil to work toward HCV WHO elimination targets by 2030. If Brazil can treat 50,000 patients through 2024, it would be able to achieve relative WHO targets for both treatment and incidence but would not meet liver-related deaths or diagnosis targets. With the addition of absolute targets provided by the WHO [14], Brazil would meet liver-related deaths and incidence absolute targets. If the Brazilian government wishes to reach all total elimination goals, changes will need to be made to the NSP in order to account for the years lost. This can be accomplished through creating a revamped elimination strategy. Countries currently on track to reach HCV elimination targets by 2030, as noted by the Polaris Observatory [15], include Australia, Canada, Denmark, Egypt, Spain, Finland, France, the United Kingdom, Georgia, Japan, and Norway, and an additional 24 countries are actively working toward elimination. As it currently stands, the Polaris Observatory states that Brazil is not on track for achieving relative or absolute targets for elimination even through 2050 because the government is not working actively toward elimination [15].

Overall, the assumptions made within this study are in line with prior understandings and recommendations, except for the fact that we now expect liver cancer cases to increase without the robust diagnoses and treatment schedules provided by the NSP or HCV Elimination Plan. The prevalence of HCV remains around 632,000 HCV RNA-positive cases (0.31% of the general population in 2016). The model estimates there will be 395,000 total HCV-infected patients in 2030 without any type of intervention strategies, whereas the NSP scenario predicts less than half that number of patients (188,000) would be infected within the same year.

As mentioned, the modeled intervention scenario requires a robust increase in diagnosis and treatment in order to attain any elimination targets by 2030 [1]. With the implementation of such measures, the disease burden, as measured by prevalence, becomes significantly less. The model does demonstrate a greater prevalence among 40 to 64-year-olds identifying a cohort in need of priority diagnosis and treatment. This can be achieved through a reimagined hepatitis elimination strategy.

The NSP drastically impacts disease burden within Brazil. The original elimination plan had the ability to greatly impact disease progression within patients when it was first put into place and still carries that same weight if modified to account for the time lost with its removal. It is important to reconsider strategies within the country that work toward elimination targets by 2030 to make an impact on disease burden, otherwise HCV will continue to cause liver-related morbidity and mortality.

Economic Burden:

The NSP scenario requires large upfront costs economically, but savings associated with healthcare and indirect costs override this issue as the disease burden decreases significantly within the country. According to the model results, the NSP is more cost-effective than the original Hepatitis C Elimination Plan. It can be noted within the previous study, the model demonstrated a significantly more cost-effective strategy when elimination efforts were accelerated and impacted the disease burden quicker [1]. By not adopting the NSP or a similar elimination strategy, there will be an increased need for financial investment because of the high number of patients with HCV-related liver disease who need to be treated.

The recommendations being made within this study update mirror previous suggestions, acknowledging that there needs to be a scale-up of treatment and diagnosis to reach any WHO targets. This could be through reimplementation of a revamped Hepatitis C Elimination Plan or a similar strategy.

Limitations:

This study contains limitations inherent in any mathematical modeling approach. Inputs used within the model regarding the epidemiological trends of HCV within Brazil were not always readily available; the most current data were collected in 2016. Clearly, these data are different today. A Delphi process was used to alleviate data limitations by searching through peer-reviewed literature and consulting with experts in the field. Another limitation is that we assumed the number of HCV cases have not changed since 2016, and this value will remain constant moving forward. We chose this conservative approach to help account for trends in different HCV risk factors. The model is limited by its ability to identify undiagnosed patients when screening campaigns result in differing diagnosis rates. In addition, the model does not take into consideration cured patients, reinfection, comorbidities, and extrahepatic manifestations during infection. All these outstanding factors could have the potential to modify both the disease and economic burdens, regardless of the scenario. All the limitations are seen in similar modeling studies and do not have the potential to significantly change any reported results.

Conclusions

This study continues to highlight that HCV elimination is possible by 2030, in line with WHO elimination targets with the reinstatement of a renewed NSP. If the current treatment schedule, without any strategic intervention, stays in place, elimination of HCV is impossible, and an unnecessary number of lives will continue to be affected and lost. The NSP, along with the previous elimination plan instated by the government and MoH, has strict guidelines on prevention, screening, treatment and policy. With a reimagined reimplementation of this cost-effective plan, Brazil has an increased opportunity to move toward elimination and ability to decrease morbidity and mortality caused by HCV with a

strong political backing and concrete societal commitment. While there will be an increased burden economically upfront, the needed spending will drastically improve HCV infection and any associated liver diseases within the country long-term, dropping off substantially when elimination is reached. This will provide Brazil a path toward life-saving measures as well as elimination by 2030, positively impacting the lives of citizens.

Author Contributions: Alexis Voeller conducted the modeling analysis with assistance from Devin Razavi-Shearer and Ivane Gamkrelidze. Alexis Voeller prepared the first draft and Devin Razavi-Shearer, Homie Razavi, and Ivane Gamkrelidze provided feedback to finalize the manuscript. All authors verified all underlying data. All authors had full access to all the data and accept responsibility for the publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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References

1. Benzaken AS, Girade R, Catapan E, et al. Hepatitis C disease burden and strategies for elimination by 2030 in Brazil. A mathematical modeling approach. *Braz J Infect Dis* 2019; **23**(3): 182-90.
2. SAÚDE MD. PLANO PARA ELIMINAÇÃO DA HEPATITE C NO BRASIL. In: SECRETARIA DE VIGILÂNCIA EM SAÚDE DDV, PREVENÇÃO E CONTROLE DAS IST, DO HIV/AIDS E DAS HEPATITES VIRAIS, editor.; 2018.
3. World Health Organization. Combating hepatitis B and C to reach elimination by 2030. Geneva, Switzerland: World Health Organization, 2016.
4. Blach S, Terrault NA, Tacke F, et al. Global change in hepatitis C virus prevalence and cascade of care between 2015 and 2020: a modelling study. *The Lancet Gastroenterology & Hepatology* 2022; **7**(5): 396-415.
5. Boletim Epidemiológico Hepatities Virais. Brasília: Ministério da Saúde, Secretaria de Vigilância em Saúde. 2016; **Ano 5**(No. 1).
6. Puga MAM, Bandeira LM, Pompilio MA, et al. Prevalence and Incidence of HCV Infection among Prisoners in Central Brazil. *PLOS ONE* 2017; **12**(1): e0169195.
7. Costi C, Grandi T, Halon ML, et al. Prevalence of hepatitis C virus and human immunodeficiency virus in a group of patients newly diagnosed with active tuberculosis in Porto Alegre, Southern Brazil. *Memórias do Instituto Oswaldo Cruz* 2017; **112**(4): 255-9.
8. Pinto FP, Ferreira OC, Jr., Olmedo DB, et al. Prevalence of hepatitis B and C markers in a population of an urban university in Rio de Janeiro, Brazil: a cross-sectional study. *Ann Hepatol* 2015; **14**(6): 815-25.
9. Pereira LM, Martelli CM, Moreira RC, et al. Prevalence and risk factors of Hepatitis C virus infection in Brazil, 2005 through 2009: a cross-sectional study. *BMC Infectious Diseases* 2013; **13**(1): 60.
10. Silva MB, Andrade TM, Silva LK, et al. Prevalence and genotypes of hepatitis C virus among injecting drug users from Salvador-BA, Brazil. *Mem Inst Oswaldo Cruz* 2010; **105**(3): 299-303.
11. Ministry of Health Brazil. Boletim Epidemiológico: Hepatites Virais. Brasilia, Brazil, 2022.
12. Bittencourt PL, Farias AQ, Couto CA. Liver Transplantation in Brazil. *Liver Transpl* 2016; **22**(9): 1254-8.
13. The World Bank. GNI per capita, Atlas method (current US$). 2022. data.worldbank.org/indicator/NY.GNP.PCAP.CD.
14. Collaborators PO. The case for simplifying and using absolute targets for viral hepatitis elimination goals. *J Viral Hepat* 2021; **1**: 12-9.
15. CDAF. Countries on track to achieve hepatitis C and B elimination targets. 2022. https://cdafound.org/polaris-countries-maps/ (accessed December 22, 2022).