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Hepatitis C mortality trends in Mexico from 2001 to 2017

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ABSTRACT

Introduction and Objectives: We aimed to analyze the trends of total and sex-stratified mortality from hepatitis C virus (HCV) and to estimate the proportion of non-alcoholic liver disease deaths in Mexico attributable to HCV from 2001-2017.
Materials and Methods: Using the mortality multiple-cause dataset, we selected the codes for acute HCV and chronic HCV to analyze trends from 2001 to 2017. We then estimated the proportion of HCV-related deaths out of non-alcoholic chronic liver disease deaths, by including in the denominator: other acute and chronic viral hepatitis, malignant neoplasm of the liver, liver failure, chronic hepatitis, fibrosis, and cirrhosis of the liver, and other inflammatory diseases of the liver. Average percent change (APC) for trends, overall and by sex, were estimated using Joinpoint regression.
Results: The trend in crude mortality rate significantly increased from 2001-2005 (APC 18.4%; 95%CI=12.5, 24.5; p value<0.001), and then significantly decreased from 2013-2017 (APC -6.5%; 95%CI=-10.1, -2.9; p value<0.001). Stratified by sex women experienced a more rapid decline in the 2014-2017 period than men.
Conclusions: HCV mortality seems to have started to decrease, but much remains to be done in terms of prevention, diagnosis, and timely access to treatment.

1. Introduction

Approximately 71 million people are living with chronic hepatitis C virus (HCV) infection worldwide. In 2016, it was estimated that 399,000 people died from HCV-related liver disease [1]. HCV infection is asymptomatic in its earliest stages, but up to 30% of cases progress to cirrhosis within 10 to 30 years. Once liver cirrhosis develops, the probability of developing hepatocellular carcinoma increases from 1 to 4% each year [2,3]. In Mexico, according to data from the Global Burden of Disease, the prevalence of cancer, cirrhosis, and other liver diseases caused by HCV has been increasing since 1990. In 2017, 307 disability-adjusted life years were lost per 100,000 inhabitants because of cirrhosis secondary to HCV, the second-highest rate in the Americas after Guatemala [4].

There is currently no effective vaccine against HCV, but there are multiple strategies to prevent infection, facilitate early diagnosis and provide treatment. Since 2011, HCV new treatments have been available, with up to 95% effectiveness [5]; however, their high cost remains a barrier to universal access. Eliminating the public health threat posed by viral hepatitis is one of the 2030 Sustainable Development Goals [6]. To achieve this, the World Health Organization created the *Global Health Sector Strategy against Viral Hepatitis 2016-2021* and set two specific HCV targets for 2030: an 80% reduction in new HCV infections and a 65% reduction in HCV-related mortality [7]. Several plans and strategies for HCV prevention and control at a global level [8–10] have been proposed and used for the development of national plans, such as the National Hepatitis C Elimination Program launched in Mexico in 2020 with the first step targeted at people living with HIV [11].

Analyzing the HCV mortality burden in Mexico is fundamental to defining the country's progress toward the eradication of the disease. In Mexico, since 1994, efforts have been made to prevent HCV transmission through blood transfusion [12]. In addition, programs and campaigns have been implemented to prevent sexual transmission and, to a lesser extent, syringe exchange programs for intravenous drug users [13]. Finally, in 2009, interferon and ribavirin treatments were added to the basic drug registry in Mexico.

Abbreviations: APC, average percent change; DAAD, direct-acting antivirals; HCV, Hepatitis C virus; PAHO, The Pan-American Health Organization; SD, Standard deviation

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Several studies have evaluated the trends of mortality in Mexico due to liver disease in general [14–16], considering, in some cases, the analysis of all viral hepatitis. However, no study has specifically analyzed HCV mortality or considered the role of HCV infection in mortality multiple-cause files in Mexico. We aimed to analyze the trends of total and sex-stratified mortality from HCV and to estimate the proportion of non-alcoholic chronic liver disease deaths attributable to HCV in Mexico from 2001-2017.

2. Materials and Methods

We obtained data compiled as multiple-cause files from death certificates in the Epidemiological and Statistical Deaths Registry from 2001 to 2017. Multiple-cause files consider the chain of events (diseases, injuries, or complications) that directly cause the death and include de *immediate cause* (final disease or condition resulting in death) and up to three other sequential conditions leading to the immediate cause, the *underlying cause* (illness or injury that initiated the events that resulted in death) and *other significant conditions* contributing to death but not resulting in the underlying cause [17].

HCV death can be classified as acute hepatitis C (B17.1) and chronic viral hepatitis C (B18.2) using the International Classification of Diseases-10. However, HCV infection can lead to cirrhosis, hepatic failure, or cancer. Thus, it is necessary to look for HCV across the chain of events that caused a death. The Pan-American Health Organization (PAHO) has proposed a set of basic indicators for the monitoring of viral hepatitis [18], which includes the proportion of HCV infection in deaths from cirrhosis, liver failure, and cancer. Thus, we included all the following deaths in the basic cause, B17: Other acute viral hepatitis, B18: Chronic viral hepatitis, C22: Malignant neoplasm of liver and intrahepatic bile ducts, K72: Hepatic failure (not elsewhere classified), K73: Chronic hepatitis (not elsewhere classified), K74: Fibrosis and cirrhosis of the liver, K75: Other inflammatory liver diseases. Alcoholic hepatitis (K70) and viral hepatitis A (B15) and B (B16) were excluded. We considered death attributable to HCV if HCV was the underlying cause of death (B17.1-B18.2) and if the underlying cause was non-alcoholic and non-hepatitis A or B-related liver disease (C22, K72, K73, K74, K75) and HCV were mentioned anywhere on the death certificate.

Sociodemographic variables were also retrieved from death certificates: sex, age, education level, and area of residence at the time of death (North, Center, Central West, South, another country, and not specified).

2.1. Statistical analysis

We grouped the non-alcoholic liver disease deaths (excluding hepatitis A and B) as 1) Other acute viral hepatitis (B17), 2) Chronic viral hepatitis (B18), 3) Other acute and chronic viral hepatitis (B17 +B18), and 4) Other liver diseases (K74, C22, K72, K75, K73). We then estimated the total cases and the proportion attributable to HCV in each group as follows: the *total number of deaths coded B17.1 o B18.2 anywhere on the death certificate /total number of non-alcoholic and non-hepatitis A or B-related liver disease deaths.*

The specific mortality rate attributable to HCV was estimated using the population data by the National Population Council (available at: http://www.conapo.gob.mx) for 2001-2017. We then estimated the global mortality rate, expressed as the rate per 100,000 inhabitants, using all the observations, and for sex-specific rates, the observations with missing data on sex were excluded. We analyzed the mortality trends over time at the national level and by sex, using a joinpoint regression model with the statistical program Joinpoint Regression (version 4.7.0.0). This model identifies the points where the direction or magnitude of the trend changes significantly over a period and reports average percent change (APC). A p value of less than 0.05 was considered statistically significant.

2.2. Ethical statement

Ethics approval was not required for this study.

3. Results

From 2001 to 2017, 410,739 deaths due to non-alcoholic liver disease were registered, of which 14,570 (3.5%) included HCV infection anywhere in the death certificate. Of the percentage with HCV infection, 46.9% were classified as “Chronic viral hepatitis” (B18) as the underlying cause of death, 38.7% as “Other acute viral hepatitis” (B17), 7.8% as “Malignant neoplasm of liver and intrahepatic bile ducts” (C22), 5.4% as “Fibrosis and cirrhosis of the liver” (K74), and 1.2% as “Hepatic failure (not elsewhere classified)” (K72). There were only four cases coded K73, “Chronic hepatitis (not elsewhere classified),” and K75, “Other inflammatory liver diseases.” Table 1 shows the sociodemographic characteristics of deaths attributable to HCV in all the periods. The mean age was 60 years (± 13.3), over 80% were in the 40-79-year-old group, 62.8% were women, 66.9% had a primary or lower education level, and 69.2% lived in the center and north region of the country.

Figure 1 shows the different causes of death associated with liver disease and those HCV-related. Panel A shows that deaths from viral hepatitis (B17) increased from 2001 to 2006 but decreased from 2007 to 2017; the proportion of deaths attributable to HCV increased linearly from 2001 to 2013, remaining over 85% in that period and then decreasing rapidly from that year onwards. Panel B shows that deaths from chronic hepatitis (B18) remained stable from 2001 to 2005 to increase rapidly from 2006 to 2015, to then decrease slowly; the proportion of cases attributable to HCV increased linearly from 2005 to 2014, reaching over 90% and then slowly decreased from that year onwards. Panel C shows the total of acute and chronic hepatitis, which increased rapidly from 2001 to 2007, stabilized until

Table 1
Sociodemographic characteristics of the total deaths attributable to HCV from 2011 to 2017. (n=14,570).

Sociodemographic characteristics		Frequency (%)*
Age, mean (SD[a])		60.0 (13.3)
	Men	54.7 (13.8)
	Women	63.1 (11.9)
Age group (years)		
	0 to 19	55 (0.4)
	20 to 39	929 (6.4)
	40 to 59	5925 (40.7)
	60 to 79	6768 (46.5)
	80 and more	893 (6.1)
Sex		
	Men	5419 (37.2)
	Women	9146 (62.8)
	Not specified	5 (0.0)
Education level[b]		
	Primary or less	9456 (66.9)
	Secondary/ High-school	2860 (20.2)
	Graduate or more	1428 (10.1)
	Not specified	383 (2.7)
	Not applicable	12 (0.1)
Country region of residency[c]		
	North	4127 (30.6)
	Center	5204 (38.6)
	Central west	3094 (22.9)
	South	1023 (7.6)
	Another country	27 (0.2)
	Not specified	26 (0.2)

* Unless stated otherwise.
[a] Standard deviation.
[b] Excluding missing values (n=431).
[c] Excluding missing values (n=1,069), distribution of states based on the classification of National Health and Nutrition Survey, 2012 [19].

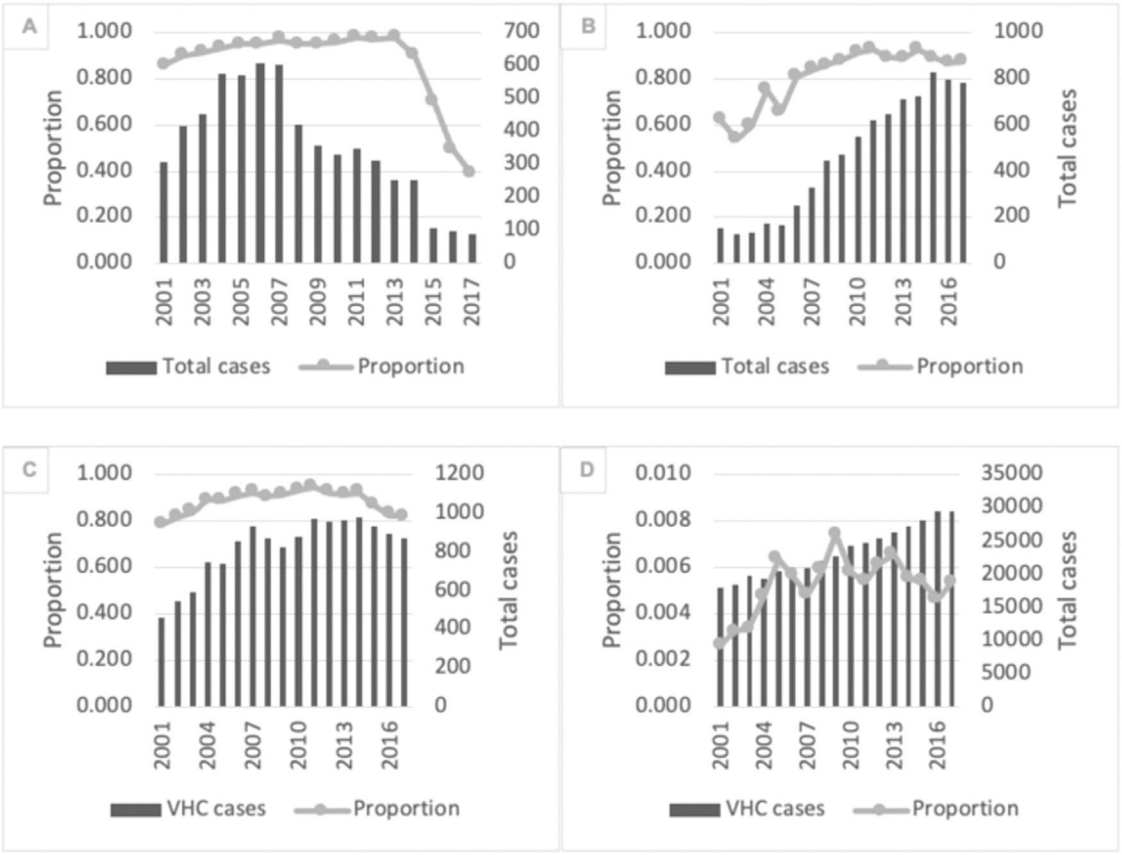

Figure 1. Total cases of mortality by non-alcoholic liver disease and proportion of attributable cases to HCV. Panel A. Other acute viral hepatitis (B17), Panel B. Chronic viral hepatitis (B18), Panel C. Other acute and chronic viral hepatitis, Panel D. Malignant neoplasm of liver and intrahepatic bile ducts (C22), Fibrosis and cirrhosis of the liver (K74), Hepatic Other inflammatory liver diseases (K75), and Chronic hepatitis (K73). The left y-axis represents the proportion of cases attributable to HCV (line), and the right y-axis, the total cases for each disease code (bars).

2014, and decreased slowly until 2017; the proportion of cases attributable to HCV remained over 80%. Panel D shows the total of deaths of other liver diseases; there is a sustained increase of these cases over time, with a low HCV-related proportion.

Figure 2 shows the joinpoint analysis of the HCV mortality rate. We observed an overall 3.3% annual increase from 2011-2017 (95%CI 1.7, 4.9; p-value<0.001); however, we can observe three trends across time. From 2001 to 2005 there is a mean 18.4% increase per year (95%CI 12.5, 24.5; p value<0.001), followed by a stabilization period from 2005 to 2013 (1.5%; 95%CI -0.1, 3.2; p-value =0.100) and, finally, a decreasing period from 2013 to 2017 (-6.5%; 95%CI -10.1, -2.9; p-value<0.001).

Figure 3 shows the mortality rate trends stratified by sex. In men, three points of inflection were identified with two periods of increase in HCV mortality (from 2001 to 2005 and from 2009 to 2012); in women, there was an increase from 2001 to 2006, stabilization from 2007 to 2014, and then a decrease from that year on. We observed differences in mortality reductions by sex; in women, the decrease

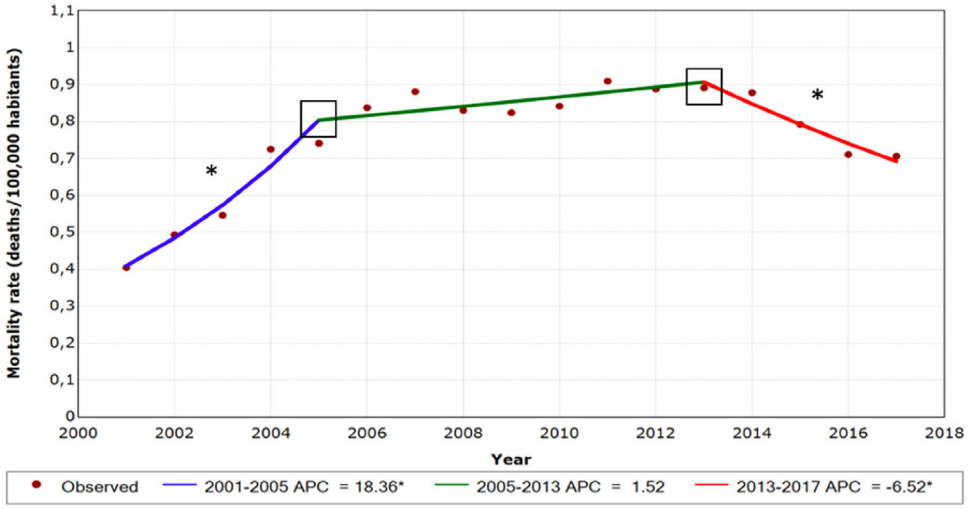

Figure 2. Trends of mortality rates of liver disease attributable to HCV from 2001-2017, Mexico. APC: average percent change. *Indicates that APC is significant at α=0.05.

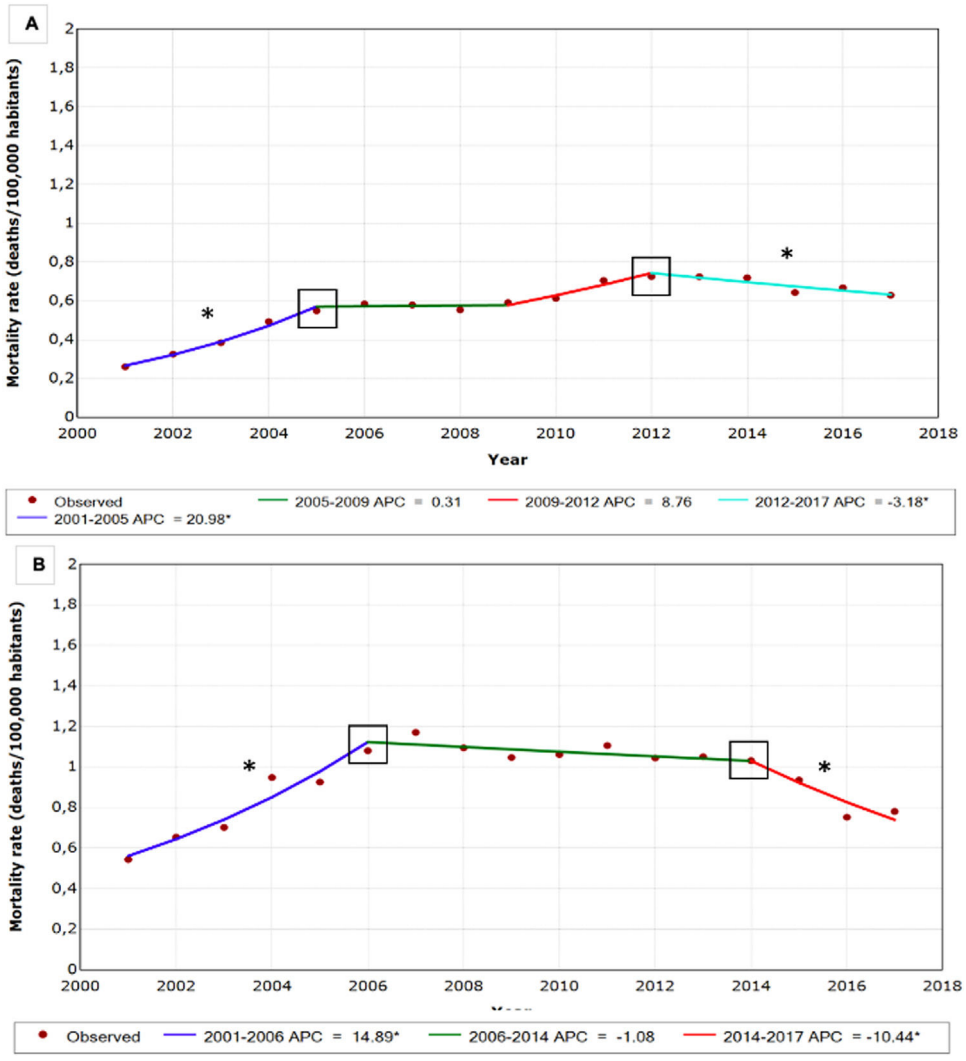

Figure 3. Trend in the crude mortality rate for HCV-attributable liver disease by sex, 2001-2017, Mexico. Panel A shows the trend in men and panel B, in women. APC: average percent change. * Indicates that the APC is statistically significant at α=0.05.

began in 2014 with an average 10.4% annual reduction (95%CI -18.7, -1.3; p-value<0.001), while in men, it began in 2012 with an average 3.2% annual reduction (95%CI -5.2, -1.2; p-value<0.001).

4. Discussion

This study aimed to analyze the trends of total and sex-stratified mortality from HCV and to estimate the proportion of non-alcoholic liver disease deaths attributable to HCV in Mexico from 2001-2017. We found that 3.5% of deaths due to non-alcoholic liver diseases were HCV-related; of these, 85.3% were registered with the virus as the underlying cause of death and 14.7% were recorded elsewhere on the death certificate. From the 2001 to 2017 period, we found a phase of a rapid increase in mortality from 2001 to 2005, followed by a period of stabilization and finally a period of decline from 2013 to 2017.

Mexico has implemented actions over the past years that could explain the changes in HCV mortality trends, which are summarized in Figure 4**.** According to the natural history of the disease [2,20], deaths observed between 2001 and 2017 may reflect infection up to 20 years earlier, corresponding to the period from 1981 to 1997. The first blood banks were founded in the country in the 1940s and safe blood guidelines were established until 1994, with the publication of the Mexican Official Standard NOM-003-SSA2-1993 [12]. It is likely that the decrease that we observed in the period from 2013 to 2017 is associated with blood guidelines as observed in other countries [21], since it is precisely in those years that its impact would be expected to be observed given the natural history of hepatitis C.

One interesting finding was the higher mortality rate in women than men, which is consistent with other studies in Mexico [15,22]. There could be several explanations for this finding. One possible explanation could be that men die from other causes of HCV non-related or even before getting cirrhosis or hepatocellular cancer attributed to HCV. Another explanation could be that women receive more blood transfusions than men [23], which would mean a higher incidence in women than men early on due to unsafe blood transfusions as observed with HIV infection by blood transfusion [24]. The lack of available treatment, would translate in higher mortality rates compared to men; therefore, the HCV prevalence in men would be higher compared to women because of higher survival, as observed on the National Health and Nutrition Survey 2018 [25].

The observed trends in mortality can be explained by several factors. The first period of accelerated increase may be related to the beginning of epidemiological surveillance of the HCV virus in 2000. Before this year, there was no precise diagnosis, and after surveillance started, HCV occupied the second place in prevalence among all viral hepatitis in the country (79% virus A, 3.3% virus B, 6.0% virus C, and 11.7% hepatitis without an etiological agent for the period 2001

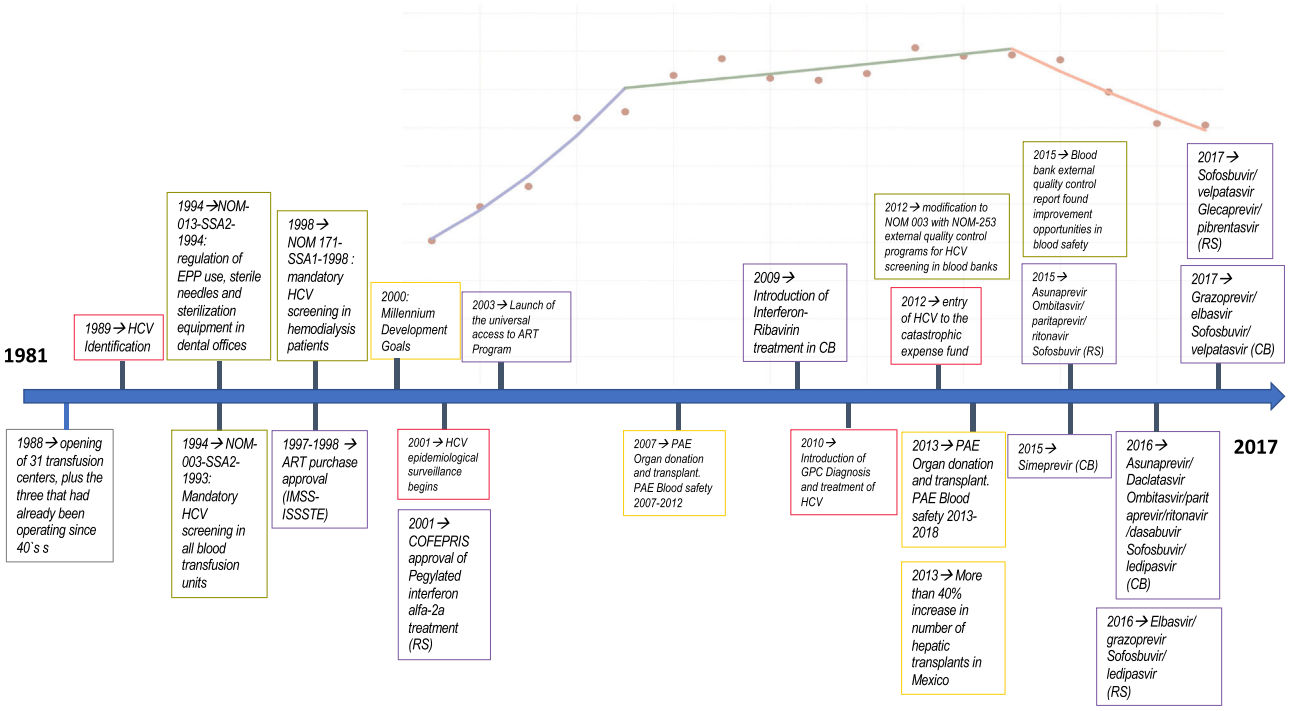

Figure 4. Timeline of events in Mexico that may have affected the trend of HCV-related liver disease in the period 2001-2017. The red dots indicate the observed HCV-related mortality and blue, green, and red lines are the fitted trend over time. HCV: hepatitis C virus; EPP: Personal protection equipment; NOM: Official Mexican Standard; ART: antiretroviral treatment; IMSS: Mexican Social Security Institute; ISSSTE: Institute of Security and Social Services for State Workers; anti-HCV: HCV antibody test; PAE: Specific Action Program; RS: Health Registry of the Federal Commission for Protection against Health Risks (COFEPRIS); CB: Basic List and Catalog of Medicines; GPC: Clinical Practice Guideline.

to 2007) [26]. Subsequently, the period of deceleration of the trend observed between 2005 and 2013 may correspond to different interventions: lagged declines resulting from the improved safety of blood transfusion, the efforts that followed the establishment of the Millennium Development Goals in the year 2000, the creation of specific action programs for organ donation and transplantation [27] and the establishment of the Clinical Practice Guideline for the diagnosis and treatment of hepatitis C [28]. HIV/HCV coinfection is not rare, given their common causes of transmission [29]. People with coinfection have a higher risk of progression of hepatitis C to cirrhosis or decompensated liver disease [30]. The introduction of new antiretroviral therapies against HIV in 1997 and the universalization of treatment in 2003 [31] improved overall survival and reduced mortality in coinfected patients, delaying progression towards cirrhosis and lowering rates of hepatic decompensation [32] and improving early diagnosis and follow-up.

A possible alternative hypothesis to the reduction in mortality observed in the period from 2013 to 2017 is the increase in installed capacity for performing liver transplants, reflected in a 41% increase in the number of transplants performed in the country. According to data from the National Transplant Center, in the period 2000 to 2017, 1,966 liver transplants were performed in the country [33,34], assuming all the transplants were performed in patients with HCV, this could mean a high reduction in mortality since it represents 13.5% of all deaths in that period. It is also to be expected that during this period, all efforts for the prevention and control of infections secondary to health care, regulated in *NOM-013-SSA2-1994-For the prevention and control of oral diseases* [35] and *NOM 171-SSA1-1998-For the practice of hemodialysis* [36], will be reflected.

Finally, the evolution of HCV treatment in Mexico may have synergized with all the aforementioned factors and led to the last period of significant deceleration observed. In 2001, peginterferon alfa was registered; however, it was not until 2009 when the combination of interferon with ribavirin was considered a basic drug in the public health system in Mexico, which allowed for the first cases to be treated for free, even if with limited effectiveness and many adverse effects [37]. By 2015, direct-acting antivirals (DAAD) entered the country, drugs with effectiveness of more than 95%, and were progressively included in the basic drug registry [38]. In addition to the above, the disease was covered by the fund for protection against catastrophic expenses of the Seguro Popular in 2012 [39] and reported treating 108 people in 2017 [40]. The Mexican Institute of Social Security started DAAD treatment in 2017, and by 2018, they had treated 1,500 patients [41] and over 10,000 by 2022 [42]. However, this increase in treatment is unlikely to explain the stabilization of trends observed from 2012 to 2017, as their impact should start to be noticeable later on.

In Mexico, the officially published mortality data are based on the underlying cause of death; if we had estimated HCV mortality based on it, we would have lost 14.7% of HCV-related deaths. PAHO provides step-by-step coding instructions to correctly identify HCV as the underlying cause of death [43]. Future research projects should undertake the analysis of HCV mortality using multiple-cause files, following PAHO's recommendations to improve comparability and provide adequate coverage. Still, researchers should be aware that in the specific case of hepatocellular carcinoma, the coding rules do not accept HCV as a cause, which could lead to the underestimation of HVC-related mortality. This highlights the need to further separate HCV-related hepatocellular carcinoma and non-related hepatocarcinoma.

Some limitations should be mentioned. First, the present study is of an ecological and observational nature, which allowed us to analyze how HCV-related mortality has evolved over time and propose some hypotheses as to which processes could have influenced it; hence, it is not a formal evaluation of the effectiveness of the interventions that have been implemented. Second, data were obtained through administrative registries, which were subject to information bias, such as the improvement in the diagnosis of hepatitis C, the availability of diagnostic tests, changes in the coding of death certificates, or other errors in the classification system. In addition, we had

no information on the type of test used to determine HCV, which could lead to misclassification if only antibodies were present and not RNA, and we also lacked information on HCV treatment, which did not allow us to assess if anti-HCV therapy was implemented in some of the cases. When analyzing trends over time, we assumed these errors have been constant, but this might not be the case, especially for the resources available for the diagnosis of HCV. Finally, underdiagnosis is a problem that has already been reported in other countries as the largest gap in the cascade of the continuum of care in HCV; fewer than half of those infected with HCV may be aware of their infection [44,45]. According to the 2018 National survey, people aged 20-49 years without a previous HCV diagnosis had a 0.23% prevalence of HCV antibodies and 0.62% in 50 and older [25]. So, it is likely to be an under-registry of HCV infection in death certificates.

5. Conclusions

The analysis of HCV mortality in Mexico shows encouraging signs, with a steady and progressive decrease in the rate since 2013. The establishment of the National Program for the Elimination of Hepatitis C in Mexico should accelerate the negative trend observed in the most recent period, helping to reduce the toll of HCV deaths in the country.

Author contributions

María Carolina Martínez-Bohórquez: Conceptualization, Formal analysis, Visualization, Writing original draft. Martha Carnalla: Visualization, Writing review & editing. Norberto Chávez-Tapia: Writing review & editing. Tonatiuh Barrientos-Gutiérrez: Methodology, Visualization, Writing review & editing. All authors approved the version to be published.

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Conflicts of interest

None.

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