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The effect of hepatitis C—associated premature deaths on labour productivity losses in Spain: a ten-year analysis

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Abstract
Hepatitis C virus (HCV) infection causes a substantial economic burden, not only in terms of healthcare costs, but also in labour productivity losses. The main objective of this study is to provide objective and comparable information about the trend in labour productivity losses caused by premature HCV-associated deaths in Spain in recent years (2009–2018). We used nationwide data from several official sources to create a simulation model based on the human capital approach and to estimate the flows in labour productivity losses due to deaths identified in the period considered. Based on a pessimistic scenario, the annual number of deaths due to HCV infections decreased by 19.7% between 2009 and 2018. The years of potential labour productive life lost (YPLPLL) decreased by 38.1%. That reduction led to a decrease in annual labour productivity losses from €236 million in 2009 to €156 million in 2018 (−33.8%). The aggregate HCV-related labour productivity losses between 2009 and 2018 ranged from €1742 million (optimistic scenario) to €1949 million (pessimistic scenario), with an intermediate estimation of €1846 million (moderately optimistic scenario). These results show a substantial reduction in annual deaths, working-age deaths, YPLPLL, and labour productivity losses associated with HCV infection over this period.

Keywords Hepatitis C · Labour productivity losses · Labour losses · Premature death · Social costs · Spain

JEL Classification I0 · I1 · I30

Introduction
Chronic hepatitis C is a lifelong liver disease caused by an RNA virus infection, whose manifestations can range from mild to severe chronic illness, with systemic involvement and liver-related complications frequently leading to cirrhosis and hepatocellular carcinoma (HCC). In recent decades, this condition has represented an important challenge to public health and healthcare systems worldwide. In fact, it is currently estimated that there are 70 million people with active hepatitis C virus (HCV) infection worldwide, representing a global prevalence of chronic infection of 1%, with a wide geographic variability [1, 2].

Although many patients with HCV remain asymptomatic for years, in many countries HCV is the most frequent cause of liver cirrhosis, HCC, and liver transplantation. In addition, many patients develop nonspecific symptoms, such as fatigue, muscle and osteoarticular pain, disturbed mental concentration and sleep, anxiety, depression, appetite changes, and digestive disorder, with different grades of severity [3, 4], affecting their health-related quality of life [5]. Between 55 and 85% of cases of acute HCV infection progress to chronic hepatitis C [6], which, without adequate treatment, may lead to advanced liver fibrosis and the above-mentioned complications [7].

The serious health effects of hepatitis C result in a heavy burden on individual and social well-being. The strong economic effect of the virus has been analysed in the literature. The perspective of the healthcare payer is more prevalent [8], although there is a notable number of works that have analysed other social costs. One of the most affected dimensions is the reduced work capacity of people infected with HCV due to the HCV-related symptoms and the progression to end-stage liver disease. HCV reduces patient productivity in the workplace through both absenteeism and presenteeism [9], as well...
as through long-term or permanent sick leave [10] and the premature death of working-age people [11]. Although the results vary widely between countries [12] and depend on the severity of the disease [13], a recent review of the literature indicates that the non-healthcare costs caused by hepatitis C could be as high as the healthcare costs [14].

A paradigm shift in the treatment of HCV infection occurred with the introduction of the second-generation Direct-Action Antivirals (DAAs) [15, 16]. These drugs, which are highly effective with virtually no side effects, have drastically improved recovery rates, survival, and quality of life; delayed or prevented the onset of severe disease complications, such as cirrhosis, decompensation, and HCC [17–21]; and helped prevent HCV transmission. These results have led to the consideration of strategies to eliminate HCV infection, and the World Health Organization (WHO) global target is a reduction of 90% in incident cases and a reduction of 65% in mortality by 2030 [22], but only a few countries are likely to reach this target [23]. Thus, improvements in HCV screening and treatment uptake are needed globally to make HCV elimination attainable.

Recent studies indicate that the second-generation DAAs are associated with lower labour productivity loss through reductions in both absenteeism and presenteeism [4, 24–27]. However, there are no studies addressing the recent changes in level of labour productivity caused by premature deaths associated with HCV.

The management of HCV in Spain is quite interesting in several respects. First, the recently estimated prevalence of HCV antibodies in the general population aged 20–80 years was 0.85% (95% CI 0.64–1.08) and that of active infection was 0.22% (95% CI 0.12–0.32) [28], a sharp contrast with the incidence rates before the introduction of DAAs (incidence rate estimated at 1.15% [29]). Spain was one of the first countries to introduce the second-generation DAAs and has treated HCV infection aggressively. In addition, these figures reflect the considerable investment in health resources directed towards HCV infection in recent years [30, 31]. However, no study has analysed the social effects of increased labour productivity loss caused by premature death [11]. Therefore, the aim of this paper is to estimate the labour productivity loss caused by premature deaths associated with HCV in Spain from 2009 through 2018.

**Methods and data**

**Theoretical framework**

The underlying theoretical framework was the Human Capital approach (HC) [32, 33]. This method considers that a person’s labour productivity can be measured by his/her earnings. It assumes that the withdrawal of an individual’s labour due to premature death or disability is a loss to society because of that individual’s future lost production.

Based on the HC theory, a simulation model was used to estimate the present and future labour production loss due to premature deaths caused by hepatitis C, considering the age of death of each individual as well as the employment rate and wage by gender and age. We restrict our estimate to labour productivity losses, and we do not consider in our estimate the productivity losses due to unpaid work or leisure time.

The number of deaths in each age group was then multiplied by the average of the remaining life expectancy for that age and gender.

Second, the number of years of potential labour productive life lost (YPLL) through the premature deaths of n individuals was calculated as follows:

\[ \text{YPLL} = \sum_{i=1}^{n} L_i \]

where \( L \) is the average remaining life expectancy for that age and gender.

Finally, the calculated YPLL was multiplied by sex- and age-specific wages, adjusting by employment rate, between age of death and retirement age. Labour productivity losses (LPL) can thus be estimated as follows:

\[ \text{LPL} = \sum_{i=1}^{n} \text{YPPLL}_i \times S_i \times e_i \]

where \( S \) is the wage adjusted by gender and age, and \( e \) is the employment rate adjusted by gender and age.

**Data**

Three different databases were used to estimate the labour productivity losses associated with premature deaths among patients with hepatitis C. The first, the Spanish Structural Wage Survey was performed by the National Statistics Institute for the period considered in this analysis (2009–2018). The purpose of this survey was to provide information about
earnings (both cash and payments in kind) for work done. The gross earnings included social security contributions made by employers and were adjusted by gender and age group.

The second database used was the Labour Force Survey which is performed by the National Statistical Institute and gives information about the employment rate. This was defined as the number of people employed (i.e. those individuals aged 16 or older who had been working for at least one hour during the reference week) expressed as a percentage of the number of working-age people. This employment rate was also adjusted by gender and age for each year considered. To obtain the employment rate of people with HIV (considered as a subcategory), the Hospital Survey on HIV-AIDS was used, provided by the General Secretariat of the AIDS Plan. This is a cross-sectional containing clinical and sociodemographic information about individuals living with HIV for the period considered.

The Death Registry, maintained by the National Statistics Institute, was used to obtain information about deaths due to hepatitis C and other HCV-related illness by cause of death. The Death Registry also indicates the age and gender of the deceased person.

**Method for estimating the number of deaths attributable to HCV**

To ascertain the direct contribution of HCV infection to liver-related deaths, we applied the attributable fraction (AF) method so that we only consider those liver-related deaths attributable to chronic hepatitis C [34–39]. The AF is the difference between overall average risk of the entire population (exposed and unexposed people) and average risk in the unexposed, expressed as a fraction of the overall average risk. One of the most frequent interpretations of the AF is the proportion of disease risk or incidence (premature deaths in our study) that could be eliminated from the population if exposure (to HCV) were eliminated [40, 41]. The AF is then calculated from the prevalence of hepatitis C infection in some specific underlying diseases such as cirrhosis, HCC, other hepatic diseases or HCV co-infection [42].

For the imputation of AF, we followed the recent work of Duarte et al. [43]. These authors appraised the quality of the data, highlighting gaps in the current data, and estimated mortality attributable to hepatitis B virus and HCV, for thirty-one EU/European Economic Area countries, including Spain, from 2010 to 2015. However, the time horizon of the chosen study did not allow the incorporation of the changes in AFs derived from the recent therapeutic improvements. Because we did not find any works updating this information, we worked with three complementary frameworks. The first of them, the pessimistic scenario, assuming that the introduction of second-generation DAAs did not involve changes in the AFs of deaths due to cirrhosis, HCC, other hepatic diseases or HCV/HIV co-infection. A second scenario, moderately optimistic, which involves assuming a favourable relative change of 25% in the AFs indicated from 2016 onwards. A third scenario, optimistic, which involves assuming a favourable relative change of 50% in the AFs indicated from 2016 onwards. Table 1 summarizes the codes from the International Classification of Diseases, Tenth Revision, that were analysed and the AFs for the diseases considered, indicating the values used from 2009 to 2015 and 2016 to 2018.

In sum, we estimated labour productivity losses by multiplying the number of premature deaths associated with HCV in the period 2009–2018 by the present value of future lifetime earnings. Estimated labour earnings consider 10 age-group classification (16–19; 20–24; 25–29; 30–34; 35–39; 40–44; 45–49; 50–54; 55–59; 60–64 years old for men and women) and estimations are adjusted by labour force participation rates for each group.

**Sensitivity analysis**

For the baseline case, an annual discount rate of 3% and an annual labour productivity growth rate of 1% were applied to the values obtained for future income. Two alternative discount rates (0% and 6%) were also applied as a sensitivity analysis, as well as two alternative productivity growth rates (0% and 2%). Monetary values were converted to constant 2018 euros (the base year), applying the gross domestic product deflator for Spain.

**Results**

**Pessimistic scenario**

Based on the pessimistic scenario associated with attributed risk fractions, there were 39,640 deaths directly attributable to HCV and to diseases directly attributable to that infection. Of these, 6942 deaths (17.5%) were recorded as being directly due to hepatitis C, 16,276 (41.1%) to HCC, 12,308 (31.0%) to cirrhosis, 3960 (10.0%) to other HCV-associated liver conditions, and 155 (0.4%) to HIV-HCV co-infection. There were 13,498 working-age deaths directly attributable to HCV and to diseases directly attributable to that infection. Of these, 2285 (16.9%) were recorded as being directly due to hepatitis C, 4772 (35.4%) to HCC, 4884 (36.2%) to cirrhosis, 1404 (10.4%) to other HCV-associated liver conditions, and 152 (1.1%) to HIV-HCV co-infection (Table 2). These deaths resulted in 146,181 YPLLPLL, of which 29,330 (20.1%) were directly attributable to hepatitis C, 45,111 (30.9%) to HCC, 32,298 (35.8%) to cirrhosis,
16,614 (11.4%) to other HCV-related hepatic disorders, and 2827 (1.9%) to HIV-HCV co-infection.

Once correction factors were applied to labour productivity losses attributable to HCV infection between 2009 and 2018, the labour productivity losses caused by premature deaths associated with hepatitis C in Spain amounted to €1949 million, ranging from €236 million in 2009 to €156 million in 2018. Of the estimated total losses, €401 million (20.6%) were recorded as being due to hepatitis C, €608 million (31.2%) to HCC, €696 million (35.7%) to cirrhosis, €213 million (10.9%) to other liver diseases, and €31 million (1.6%) to HIV-HCV co-infection (Table 2).

**Moderately optimistic scenario**

With regard to the changes in the numbers of working-age deaths, as well as the YPLPLL and the labour productivity loss associated with hepatitis C, all were evaluated favourably, having shown a decreasing trend in Spain between 2009 and 2018. More precisely, after applying the AF, the results obtained show that between 2009 and 2018 there were 37,299 deaths directly attributable to HCV and to diseases directly attributable to that infection. Of these, 6942 deaths (18.6%) were recorded as being directly due to hepatitis C, 15,061 (40.4%) to HCC, 11,457 (30.7%) to cirrhosis, 3681 (9.9%) to other HCV-associated liver conditions, and 152 (0.4%) to HIV-HCV co-infection (Table 3). There were 12,710 working-age deaths directly attributable to HCV and to diseases directly attributable to that infection. Of these, 2285 deaths were recorded as being directly due to hepatitis C (18.0% of total working-age deaths), 4409 (34.7%) to HCC, 4556 (35.8%) to cirrhosis, 1310 (10.3%) to other HCV-associated liver conditions, and 149 (1.2%) to HIV-HCV co-infection (Table 3). These deaths resulted in 138,735 YPLPLL, of which 29,330 (21.1%) were directly attributable to hepatitis C, 42,022 (30.3%) to HCC, 49,019 (35.3%) to cirrhosis, 15,592 (11.2%) to other HCV-related hepatic disorders, and 2772 (2.0%) to HIV-HCV co-infection (Table 3).

Once correction factors were applied to labour productivity losses attributable to HCV infection between 2009 and 2018, the labour productivity losses caused by premature deaths associated with hepatitis C in Spain were estimated at €1846 million, ranging from €236 million in 2009 to €122
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Of the total loss estimated, €401 million (21.7%) were recorded as being directly due to hepatitis C, €565 million (30.6%) to HCC, €650 million (35.2%) to cirrhosis, €199 million (10.8%) to other liver diseases, and €31 million (1.7%) to HIV-HCV co-infection (Table 3).

**Optimistic scenario**

Based on an optimistic scenario in relation to attributed risk fractions, there were 34,958 deaths directly attributable to HCV and to diseases directly attributable to that infection. Of these deaths, 6942 (19.9%) were recorded as being due to hepatitis C, 13,858 (39.6%) to HCC, 10,606 (30.3%) to cirrhosis, 3403 (9.7%) to other HCV-associated liver conditions, and 148 (0.4%) to HIV–HCV co-infection (Table 4). Moreover, the results show that throughout the period considered, there were 11,922 working-age deaths directly attributable to HCV and to diseases directly attributable to that infection. Of these, 2285 deaths (19.2%) were recorded as being directly due to hepatitis C, 4046 (33.9%) to HCC, 4229 (35.5%) to cirrhosis, 1216 (10.2%) to other HCV-related hepatic disorders, and 146 (1.2%) to HIV-HCV co-infection.
million (10.6%) to other liver diseases, and €30 million (1.70%) to HIV-HCV co-infection (Table 4).

**Sensitivity analysis**

Two alternative discount rates (0% and 6%) and two alternative labour productivity growth rates (0% and 2%) were also applied as a sensitivity analysis.

Considering the first sensitivity analysis (2–0%), the labour loss attributable to HCV infection between 2009 and 2018 was valued at €2559 million, ranging from €318 million in 2009 to €198 million in 2018 under the pessimistic scenario. In the case of the moderately optimistic scenario, the loss reached €2481 million, ranging from €318 million to €155 million in 2009 and 2018, respectively. Finally, under the optimistic scenario for the same period, the loss was €2302 million, ranging from €318 million to €113 million (Table 5).

Considering the second sensitivity analysis (0–6%), the labour loss attributable to HCV infection between 2009 and 2018 was valued at €1571 million, ranging from €187 million in 2009 to €129 million in 2018 under the pessimistic scenario. In the case of the moderately optimistic scenario, the loss reached €1486 million, ranging from €187 to €101 million in 2009 and 2018, respectively. Finally, under the optimistic scenario for the same period, the loss was €1401 million, ranging from €187 million to €73 million (Table 6).

### Discussion

The results show that throughout the period considered, annual deaths, working-age deaths, YPLPLL, and labour productivity losses associated with HCV infection experienced a substantial reduction. Despite that reduction, the
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Aggregate labour productivity losses associated with HVC between 2009 and 2018 ranged from €1742 million (optimistic scenario) to €1949 million (pessimistic scenario; moderately optimistic scenario, €1846 million). Under the pessimistic scenario, the total number of deaths related to HCV infections decreased by 19.7% from 2009 (with 4338 deaths attributed to HCV) to 2018 (3482 deaths). The deaths under the moderately optimistic and the optimistic scenarios decreased by 37.5% and 55.2%, respectively. The working-age HCV deaths decreased by 19.3% between 2009 and 2018 (pessimistic scenario). The reductions in working-age deaths under the moderately optimistic and the optimistic scenarios were of 37.0% and 54.8%, respectively. This represented a 38.1% reduction in YPLPLL directly attributable to HCV, especially from 2016 onwards (pessimistic scenario). The reductions in YPLPLL under the moderately optimistic and the optimistic scenarios were of 51.5% and 65.0%, respectively. These reductions translated into a decrease in labour productivity losses from €236 million in 2009 to €156 million in 2018, equivalent to a reduction of 33.8% (pessimistic scenario). The related labour productivity losses were of 48.1% and 62.4% under the moderately optimistic and the optimistic scenarios, respectively.

The theoretical framework on which this work is based is the human capital approach which assume efficient labour markets, from which the identification of the price of the labour factor (wages) with its marginal productivity is derived. But the reality is much more complex, with labour markets far from an efficiency scenario [44–47]. There is an alternative approach to assess labour productivity losses, the friction cost method [48]. In the case of premature deaths, this method restricts labour productivity losses to a “friction period”, related to the time required to employ and train a new worker, after which it is considered that there is no effect on labour productivity. As can be seen, this approach is very far from the theoretical framework of human capital.
and it has been strongly disputed in the literature [49, 50]. The methodologic debate has not been definitively settled [51, 52], although the human capital method is the most widely accepted, except in the Netherlands and Canada, where the health technology assessment agencies have postulated in favour of the friction cost method [53]. Obviously, estimates of labour losses obtained by applying the friction cost approach are notably lower than those obtained by applying the human capital method, especially in cases of premature mortality and permanent sick leave [54–64]. It is noteworthy that in the studies that have estimated labour productivity losses associated with hepatitis C, the human capital method was used in all studies that explicitly identified the approach used [14].

One of the main innovations in this study (in comparison with a previous study [11]) is a methodologic improvement in the employment data used. The employment rates used had a more precise age-group classification (10 age-group classifications compared with the four age-group classifications used in the previous study), and information was included about employed populations aged 16 years or older and working-age people. This innovation enabled us to record more robust results because employment rates are widely heterogeneous among the different age groups in Spain.

In this study we used the AFs that appear in the work of Duarte et al. for the years 2009–2015 [43]. The decision to use that study was based on its quality, on the fact that the estimated values for Spain were expressly shown, and on the recent nature of the study. However, as the authors pointed out, “The lack of a systematic literature review for AF is a limitation of our study. The convenience literature search found published estimates to be rare, and available estimates mostly predated 2000, highlighting the need for more and newer studies”. Indeed, other studies reviewed include estimates for AF that do not coincide with the values collected in our study [42]. Likewise, we found that there are important differences between the AFs estimated for different countries. In the study by Duarte et al., the mortality rate per 100,000 inhabitants due to hepatitis C in European countries ranged from 32.8 in Romania to 1.7 in Norway. The rate for Spain is 9.0, slightly above the average rate of the 30 European countries analysed. It is important to consider this when interpreting our results to avoid the mistake of extrapolating them directly to other countries.

We found no applicable information about AF estimates for Spain for the last years of the period analysed (2016–2018). However, in view of the extensive literature published in recent years on the major improvement that DAAs have brought to patient health, it was not possible to

| Table 5 | Sensibility analysis [2–0%] by different scenarios, labour productivity losses |
|----------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|          | 2009            | 2010            | 2011            | 2012            | 2013            | 2014            | 2015            | 2016            | 2017            | 2018            | Total           |
| Pessimistic |                   |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| Group 1: hepatitis C | 76,023          | 66,793          | 60,483          | 56,082          | 54,099          | 60,650          | 55,860          | 45,170          | 30,650          | 27,347          | 533,156         |
| Group 2: HCC | 83,535          | 88,578          | 80,644          | 76,362          | 78,617          | 77,681          | 82,412          | 70,014          | 56,890          | 52,455          | 747,188         |
| Group 3: cirrhosis | 112,663         | 110,310         | 101,603         | 93,792          | 87,386          | 79,536          | 85,856          | 84,327          | 75,155          | 56,367          | 870,996         |
| Group 4: other | 36,612          | 38,033          | 34,386          | 32,687          | 32,692          | 26,591          | 26,441          | 24,381          | 21,084          | 18,410          | 283,782         |
| Group 5: HIV | 9,498           | 8,438           | 7,880           | 6,483           | 4,598           | 3,294           | 2,321           | 1,202           | 1,157           | 663             | 45,536          |
| Total     | 318,330         | 312,153         | 284,996         | 265,406         | 251,391         | 247,751         | 225,094         | 212,988         | 197,874         | 195,243         | 2,568,874       |
| Moderately optimistic |                   |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| Group 1: hepatitis C | 76,023          | 66,793          | 60,483          | 56,082          | 54,099          | 60,650          | 55,860          | 45,170          | 30,650          | 27,347          | 533,156         |
| Group 2: HCC | 83,535          | 88,578          | 80,644          | 76,362          | 78,617          | 77,681          | 82,412          | 70,014          | 56,890          | 52,455          | 747,188         |
| Group 3: cirrhosis | 112,663         | 110,310         | 101,603         | 93,792          | 87,386          | 79,536          | 85,856          | 84,327          | 75,155          | 56,367          | 870,996         |
| Group 4: other | 36,612          | 38,033          | 34,386          | 32,687          | 32,692          | 26,591          | 26,441          | 24,381          | 19,551          | 18,410          | 283,782         |
| Group 5: HIV | 9,498           | 8,438           | 7,880           | 6,483           | 4,598           | 3,294           | 2,321           | 1,202           | 1,157           | 663             | 45,536          |
| Total     | 318,330         | 312,153         | 284,996         | 265,406         | 251,391         | 247,751         | 225,094         | 167,403         | 155,243         | 145,283         | 2,480,658       |
| Optimistic |                   |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| Group 1: hepatitis C | 76,023          | 66,793          | 60,483          | 56,082          | 54,099          | 60,650          | 55,860          | 45,170          | 30,650          | 27,347          | 533,156         |
| Group 2: HCC | 83,535          | 88,578          | 80,644          | 76,362          | 78,617          | 77,681          | 82,412          | 70,014          | 56,890          | 52,455          | 747,188         |
| Group 3: cirrhosis | 112,663         | 110,310         | 101,603         | 93,792          | 87,386          | 79,536          | 85,856          | 84,327          | 75,155          | 56,367          | 870,996         |
| Group 4: other | 36,612          | 38,033          | 34,386          | 32,687          | 32,692          | 26,591          | 26,441          | 24,381          | 12,190          | 12,273          | 258,938         |
| Group 5: HIV | 9,498           | 8,438           | 7,880           | 6,483           | 4,598           | 3,294           | 2,321           | 601             | 772             | 442             | 44,328          |
| Total     | 318,330         | 312,153         | 284,996         | 265,406         | 251,391         | 247,751         | 225,094         | 135,132         | 121,819         | 112,611         | 2,302,479       |

HCC, hepatocellular carcinoma

*aThousands of euros updated to 2018*
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ignore a reduction of the AF of HCV-related deaths. However, the precise effect of the new treatments on the reduction of HCV-related mortality remains unknown. For this reason, we proposed three hypothetical scenarios: one moderately optimistic; another more optimistic; and the starting point, where we assume that the AFs remain unchanged, the pessimistic scenario.

Another important matter that requires further explanation is why 2016, rather than an earlier year, was chosen as the year of change in the AFs. Although the second-generation DAAs were introduced in Spain in January 2014, the number of patients initially treated was very small. The figures published by the Spanish Ministry of Finance indicate that in 2014 hospital pharmaceutical expenditure on hepatitis C amounted to €110 million (2.1% of total expenditure on drugs for hospital use). This figure increased to €1190 million in 2015 (18.1%). After sales peaked in 2015, annual expenditure for the treatment of HCV infection decreased owing to declining volumes of prescriptions and a large reduction in the price of drugs: €408 million (6.6% of total spending on drugs for hospital use) in 2016 and €235 million (3.7%) in 2017 [31]. Thus, although the largest investment of resources was made in 2015, it could have been expected that the return on that investment would not be immediate but would take a few months to translate into results that were beneficial for health. In fact, if we observe the changes in the numbers of total deaths and working-age deaths directly caused by HCV, we notice a strong reduction from the year 2016 that continued into 2017 and 2018. It is more difficult to establish this relationship with other diseases related to the HCV because there are other elements to consider in relation to the treatments and to other causes of these illnesses [65–67]. For these reasons, we considered it appropriate to fix the year of change in the AF to HCV as 2016 and not earlier.

Overall, the results of this study should be relevant for healthcare decision-makers. We have shown that HCV had a considerable effect on labour productivity losses throughout the period analysed. Fortunately, that effect has been steadily decreasing since the beginning of the period studied, with an accelerated decrease in recent years. However, this does not mean that in 2018 (the last year of the period studied) the labour losses identified were not noteworthy: they amounted to €122 million even in our moderately optimistic scenario. When looking at the breakdown of the causes of labour losses (either by working-age deaths or by YPLLPLL), we observe that more than two-thirds are specific to HCC and liver cirrhosis. This indicates that there is still a wide margin for improvement in the detection and care of patients with active HCV.

### Table 6: Sensitivity analysis [0%-6%] by different scenarios, labour productivity losses

| Scenario, €a | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | Total |
|-------------|------|------|------|------|------|------|------|------|------|------|-------|
| Pessimistic |      |      |      |      |      |      |      |      |      |      |       |
| Group 1: hepatitis C | 43,465 | 37,733 | 35,011 | 32,526 | 33,001 | 37,141 | 34,108 | 28,015 | 19,632 | 17,613 | 318,244 |
| Group 2: HCC | 50,464 | 54,254 | 50,084 | 48,432 | 50,026 | 49,824 | 53,678 | 46,788 | 48,812 | 47,716 | 500,078 |
| Group 3: cirrhosis | 67,464 | 65,830 | 60,981 | 57,741 | 54,727 | 50,235 | 54,752 | 52,621 | 49,884 | 48,452 | 562,688 |
| Group 4: other | 20,820 | 21,163 | 18,438 | 17,055 | 16,070 | 14,768 | 14,875 | 13,974 | 14,976 | 14,976 | 167,114 |
| Group 5: HIV | 4,582 | 4,176 | 4,008 | 3,364 | 2,441 | 1,676 | 1,166 | 591 | 777 | 472 | 23,252 |
| Total | 186,797 | 183,156 | 168,521 | 159,118 | 156,266 | 153,643 | 158,578 | 141,984 | 134,081 | 129,229 | 1,571,377 |
| Moderately optimistic |      |      |      |      |      |      |      |      |      |      |       |
| Group 1: hepatitis C | 43,465 | 37,733 | 35,011 | 32,526 | 33,001 | 37,141 | 34,108 | 28,015 | 19,632 | 17,613 | 318,244 |
| Group 2: HCC | 50,464 | 54,254 | 50,084 | 48,432 | 50,026 | 49,824 | 53,678 | 39,091 | 36,609 | 35,787 | 464,249 |
| Group 3: cirrhosis | 67,464 | 65,830 | 60,981 | 57,741 | 54,727 | 50,235 | 54,752 | 39,466 | 37,413 | 36,339 | 524,949 |
| Group 4: other | 20,820 | 21,163 | 18,438 | 17,055 | 16,070 | 14,768 | 14,875 | 10,480 | 11,232 | 11,232 | 156,133 |
| Group 5: HIV | 4,582 | 4,176 | 4,008 | 3,364 | 2,441 | 1,676 | 1,166 | 443 | 583 | 354 | 22,792 |
| Total | 186,797 | 183,156 | 168,521 | 159,118 | 156,266 | 153,643 | 158,578 | 113,495 | 105,469 | 101,325 | 1,486,367 |
| Optimistic |      |      |      |      |      |      |      |      |      |      |       |
| Group 1: hepatitis C | 43,465 | 37,733 | 35,011 | 32,526 | 33,001 | 37,141 | 34,108 | 28,015 | 19,632 | 17,613 | 318,244 |
| Group 2: HCC | 50,464 | 54,254 | 50,084 | 48,432 | 50,026 | 49,824 | 53,678 | 23,394 | 24,406 | 23,858 | 428,420 |
| Group 3: cirrhosis | 67,464 | 65,830 | 60,981 | 57,741 | 54,727 | 50,235 | 54,752 | 26,311 | 24,942 | 24,226 | 487,209 |
| Group 4: other | 20,820 | 21,163 | 18,438 | 17,055 | 16,070 | 14,768 | 14,875 | 6987 | 7488 | 7488 | 145,152 |
| Group 5: HIV | 4,582 | 4,176 | 4,008 | 3,364 | 2,441 | 1,676 | 1,166 | 296 | 389 | 236 | 22,332 |
| Total | 186,797 | 183,156 | 168,521 | 159,118 | 156,266 | 153,643 | 158,578 | 85,001 | 76,857 | 73,421 | 1,401,357 |

HCC, hepatocellular carcinoma

aThousands of euros updated to 2018
In any case, the extrapolation of our results to other countries should be interpreted with caution for several reasons. First, because of epidemiological issues as higher or lower prevalence rates will have consequences on deaths caused by HCV, and hence, the results and conclusions could differ. Second, the quality of the health system can condition the results, in the sense that the higher the quality of the health system, the lower the number of expected deaths would be. And finally, labour factors can also affect the figures as the higher wages and the higher employment rates, the greater impact on lost labour productivity.

Of note, our analysis is based on labour productivity losses caused by premature deaths at working age. The lack of availability of data about other types of labour losses associated with absenteeism, presenteeism, and permanent sick leave has precluded their inclusion in the analysis. However, there is extensive literature that indicates the importance of these labour losses [4, 9, 14, 68, 69]. Similarly, recent studies indicate that this type of labour loss has been reduced in recent years because of therapeutic improvements [25, 26, 70], which is consistent with the results seen in this study for mortality-associated losses.

Focussing on labour losses associated with hepatitis C deaths, the estimated results should be interpreted as conservative values. On the one hand, we censored estimated labour productivity losses at age 65. Although it is true that a small part of the population continues in the labour market after this age in Spain (7% of men and 5% of women between the ages of 65 and 69 had a paid job in 2018; above that age, the figures drop to 1% in the case of men and 0.4% in the case of women), this methodology is common to most works with objectives similar to ours.

An issue that deserves a comment is that the Spanish Structural Wage Survey used in our analysis shows important differences between the salaries of men and women. Although this gap decreases consistently over the years, the difference in wages between men and women after adjusting for age, experience, educational level, economic sector and firm’s characteristics, stood at 12.7% in 2014 [71]. Given that our model attempts to estimate labour losses related to HCV-associated deaths, using the labour earnings/salaries of the deceased as a proxy, our estimates could vary if the wage discrimination component were eradicated from the Spanish labour market. Unfortunately, the models commonly used to estimate labour losses caused by illness do not capture all the complexity of the labour market, and even those simulation models, with both micro and macroeconomic features [72, 73], do not offer a definitive solution to these problems. We have applied a consistent approach with that adopted by most recent studies in this field. Then, we have tried to show as transparently as possible the assumptions, methods and data used to facilitate reproducibility and comparability between studies, and we recognized the limitations of these models, without claiming that such estimates are an exact and perfect reflection of economic reality.

Additionally, we focus exclusively on labour productivity losses. This does not mean that the productivity of people disappears when they leave the labour market. However, we recognize as a limitation of the analysis the fact that, due to the data availability, we cannot extend our results to labour losses derived from absenteeism or presenteeism, neither to the field of productivity losses due to unpaid work or other losses of time (leisure). The assessment of the time of unpaid care have received very little attention in the field of the economic impact of disease [74], although the instruments available to measure lost unpaid labour is increasing [75] and some recent works highlight its potential relevance [76]. In addition, another very relevant cost is the non-professional care provided to people with limitations on their autonomy, mainly by caregivers in their affective environment. With other diseases, such as neuro-degenerative disease, cancer, mental, vascular and other invalidating illnesses, the number of studies that analyse the costs associated with informal care is growing [77–84], but this subject has been scarcely studied in relation to hepatitis C. A future line of research would be to broaden the field of analysis to include other types of social costs, such as unpaid productivity and informal care.

Finally, another issue that needs to be considered is the fact that at the time of this writing, according to the WHO [85], 102.9 million confirmed cases of coronavirus disease (COVID-19) have been counted and 2.23 million people died from March 2020 to early February 2021. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is also responsible for causing another series of serious health problems, such as those derived from the delay in the care of chronic patients because of the overload in the healthcare systems. The current effect of the COVID-19 pandemic on the HCV elimination plans is still under analysis. Preliminary data suggest a delay in detecting high-risk HCV patients in Spain [86] and other European countries [87, 88]. Patients with chronic liver diseases are at higher risk of developing worse outcomes [89]. It is important to stress that people with active HCV, and especially those with greater liver damage, may be within the group of particularly affected chronic patients, so the positive trend identified in this study could be truncated in 2020. Likewise, the available studies indicate that hepatic dysfunction occurs in 14–53% of patients with COVID-19, particularly in those with severe disease [90].

In conclusion, these results should underscore the need to re-double the effort to achieve, in the medium term, the goal of eradicating hepatitis C. According to Razavi et al. [23], Spain could meet the WHO 2030 target by 2023. Because COVID-19 is an added impediment that will probably delay the achievement of that goal, we may have to
re-think existing strategies and ask ourselves what resources and organization we can provide to eradicate hepatitis C, once COVID-19 has remitted.

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Authors' contributions JOM designed the study. LMPL carried out the data preparation and the quantitative analysis. LMPL and JOM analysed the results. JOM and LMPL wrote the first draft of the manuscript. All authors contributed to the drafting and revising of the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflict of interest L. M. Peña-Longobardo and J. Oliva-Moreno declare no financial and non-financial conflict of interest. C. Fernández-Rodriguez has received fees for lectures and advisory boards consultancy from AbbVie.

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