Predicted Effects of Treatment for HCV Infection Vary Among European Countries

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CLINICAL LIVER

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BACKGROUND & AIMS: The dynamics of hepatitis C virus (HCV) infection, as well as screening practices and access to therapy, vary among European countries. It is important to determine the magnitude of the effects of such differences on incidence and mortality of infection. We compared the dynamics of infection and screening and treatment practices among Belgium, France, Germany, Italy, Spain, and the United Kingdom. We also assessed the effects of treatment with pegylated interferon and additional effects of triple therapy with protease inhibitors. **METHODS:** We created a country-specific Markov model of HCV progression based on published epidemiologic data (on HCV prevalence, screening, genotype, alcohol consumption among patients, and treatments) and reports of competitive and hepatocellular carcinoma mortality for the 6 countries. The model was used to predict the incidence of HCV-related cirrhosis and its mortality until 2021 for each country. **RESULTS:** From 2002 to 2011, antiviral therapy reduced the cumulative incidence of cirrhosis by 7.1% and deaths by 3.4% overall. Reductions in incidence and mortality values ranged from 4.0% and 1.9%, respectively, in Italy to 16.3% and 9.0%, respectively, in France. From 2012 to 2021, antiviral treatment of patients with HCV genotype 1 infection that includes protease inhibitor–based triple therapy will reduce the cumulative incidence of cirrhosis by 17.7% and mortality by 9.7% overall. The smallest reduction is predicted for Italy (incidence reduced by 10.1% and mortality by 5.4%) and the highest is for France (reductions of 34.3% and 20.7%, respectively). **CONCLUSIONS: Although HCV infection is treated with the same therapies in different countries, the effects of the therapies on morbidity and mortality vary significantly. In addition to common guidelines that are based on virologic response-guided therapy, there is a need for public health policies based on population-guided therapy.**

Keywords: Epidemiology Analysis; Ribavirin; Treatment Outcomes; Direct-Acting Antiviral Agents.

Knowledge of the natural history of hepatitis C virus (HCV) infection can help to develop models for predicting the future course of HCV infection.[1–7] Accuracy of a predictive model of spread of HCV infection requires elucidation of the dynamics of infection, the epidemiologic pattern of contamination routes, and distribution of genotypes. These parameters vary between countries and must be evaluated by robust studies at a national level.

The impact on disease progression of HCV eradication via current antiviral therapy with pegylated interferon (PEG-IFN) and ribavirin (RBV) is well known.[8,9] Future therapeutic combinations using triple therapy of directly acting antivirals, namely protease inhibitors (PIs), with PEG-IFN and RBV should form the basis of treatment of naive[10–15] and experienced[16–18] with HCV genotype 1 (G1) infection. However, no clinical studies have assessed the impact of antiviral therapy on long-term morbidity and mortality because it is unethical to maintain patients without therapy. Only a modeling approach can address this issue and predict its impact on a population.[5]

The development of country-specific models enables comparison of HCV natural history, prevalence according to fibrosis stage, and impact of therapy on HCV burden across countries. Recent studies pointed out substantial discrepancies in Europe in terms of HCV burden[19] and access to antiviral therapy.[20] Indeed, the prevalence of HCV ranged from 0.6% in Germany to 4% in Italy, and the number of patients treated ranged from 16% of HCV

Abbreviations used in this paper: CI, confidence interval; G, genotype; PEG-IFN, pegylated interferon; PI, protease inhibitor; RBV, ribavirin; SVR, sustained virologic response.

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prevalent cases in France to 3% in Italy and the United Kingdom.[19,20] Until now, the impact on HCV morbidity and mortality of differences in access to treatment in different European countries has been ignored. A modeling approach taking into account national characteristics such as epidemiologic patterns, natural history, screening, and treatment rates may help to adapt therapeutic strategies and public health policies to the national HCV burden and "population-guided therapy."

In this study, we built country-specific models for Belgium, France, Germany, Italy, Spain, and the United Kingdom. Our main objectives were to (1) compare these countries in terms of dynamics of infection, natural history, screening, and treatment practices; (2) assess, by country, the impact of pegylated bitherapy; and (3) predict the additional impact of triple therapy with PIs.

Materials and Methods

Overview

We used a country-specific back-calculation method and a state-transition Markov model to first reconstruct the past incidence of HCV infection and simulate progression of HCV disease among newly HCV-infected cohorts in Belgium, France, Germany, Italy, Spain, and the United Kingdom. Next, we projected country-specific HCV-related morbidity and mortality and assessed the impact of therapy for each country.

Natural History of Disease in Newly HCV-Infected Cohorts

Newly HCV-infected cohorts were derived from country-specific past incidence of HCV infection, with the latter estimated during a back-calculation process. Past incidence of HCV infection was assumed to follow a logistic function until a peak of infection in 1989 for all countries except Italy. For Italy, where a more intense epidemic wave occurred during the 1950s to 1960s via iatrogenic transmission due to use of unsterilized material,[21] the peak of infection was set at 1969. Past incidence of HCV infection was then assumed to decrease in the same proportions as those observed in the United States thereafter (94% decrease between 1989 and 2008),[22] except for Italy and the United Kingdom. For Italy, we used the same decrease as that estimated by Mariano et al,[21] that is, from a 21% decline in 1970 to a 98% decline in 2000. For the United Kingdom, where most HCV infections occurred in intravenous drug users, the decrease was assumed to be lower than in the United States,[23] that is, a 46% decrease between 1989 and 1998 followed by stabilization.

Newly HCV-infected cohorts in each country were characterized by age at the time of HCV infection, sex, genotype (see Supplementary Table 1), and alcohol abuse status (T. Stroffolini, personnal communication, 2010, for Italian data).[24–37] The Markov model (see Supplementary Materials and Methods) used to simulate progression of these newly HCV-infected cohorts is detailed elsewhere.[5] Death rates from causes other than HCV (competitive mortality) were assumed to be all-cause mortality from country-specific life tables.

Impact of HCV Treatment on Disease Progression

As previously determined, antiviral treatment effects were incorporated by estimating likelihood of being screened for HCV, of being treated, and of reaching sustained virologic response (SVR) after treatment according to the HCV genotype for naive and previously treated patients.

The likelihood of being screened for HCV differed between countries (see Supplementary Table 1). France was the only country for which we had 2 estimates of HCV screening: 24% in 1994 and 57% in 2004.[38] As previously determined,[5] we assumed a linear increase in HCV screening between 1994 and 2004 but assumed a lower increase in HCV screening thereafter so as to be at a 62% level in 2009. In Belgium, a study based on recall of patients after use of inactive batches of Cidex (Johnson & Johnson Medical, UK) disinfection solution in Belgian hospitals in 2000 estimated that 99 of the 265 (37%) positive patients already knew their status.[39] For Germany, based on the work of Zehnter et al,[40] we estimated that 40% of HCV-infected persons were screened in Germany in 2004, similar to data from a European report[41] (see Supplementary Materials and Methods for details). In Italy, Mariano et al estimated that, among HCV RNA–positive individuals detected on screening, 40% already knew of their infection in 2005.[21] For Spain, we extracted an HCV screening rate of 33% compatible with the estimate that 53% of HCV-related hepatocellular carcinomas (HCCs) were screened during 2008–2009 according to Varela et al[42] (see Supplementary Materials and Methods for details). For the United Kingdom, we assumed an HCV screening rate of 30% in 2004 according to estimates of diagnosed populations found in national reports.[43,44] For those 5 countries, we assumed a linear increase in HCV screening starting at approximately 3% at the beginning of treatment (1991).

The likelihood of being treated for patients aware of their infection also differed between countries and was fitted to the 2002–2005 number of treated patients extracted from PEG-IFN sales obtained from GERS (http://www.gie-gers.fr/) for France and from the IMS (http://www.imshealth.com/portal/site/imshealth) for other countries (see Supplementary Materials and Methods).

The likelihood of attaining an SVR after treatment was obtained from the literature.[8–11,13,15,17,45–47]

Procedure

During the process, the model was first fitted to reported age-specific annual HCC deaths related to HCV (see Supplementary Materials and Methods) in each country and calibrated to country-specific HCV prevalence and PEG-IFN sales in 2002–2005 (see Supplementary Tables 1–4).

Next, the model simulated HCV progression until 2021 for all HCV infections occurring until 2010, assuming that current treatment practices with pegylated bitherapy would be continued until 2021. The model also simulated HCV progression until 2021 in the absence of treatment for each country. We then assessed the availability of triple therapy with PIs starting in 2012 and leading to a higher SVR for G1-infected patients, which was 78% in F0–F2 and 62% in F3–F4 naive patients and 66% in F0–F2 and 48% in F3–F4 non-naive patients after correction for proportions of relapsers and nonresponders from the IDEAL study.[11,18,48] The 2 treatment regimens (pegylated bitherapy and triple therapy for G1-infected patients) were compared with absence of treatment.

The relative impact of treatment (either pegylated bitherapy or triple therapy) was calculated by subtracting the cumulative incidence (either HCV-related cirrhosis or HCV-related deaths) estimated with treatment from that estimated without treatment, divided by the estimated incidence without treatment. Because it is important that clinicians be able to assess the

impact of triple therapy compared with pegylated bitherapy, the additional impact of triple therapy compared with pegylated bitherapy was estimated by subtracting the relative impact of triple therapy from that of pegylated bitherapy, divided by the relative impact of pegylated bitherapy. To assess the impact of triple therapy, we first held the assumption that HCV screening rates and treatment access would remain unchanged (most conservative assumption). In an alternative scenario, we assumed that HCV screening rates and treatment access would increase for each country with the availability of triple therapy, leading to 75% of HCV-screened patients by 2015 and one patient out of two treated in 2015 with new triple therapy for G1 and pegylated therapy for other genotypes (less conservative assumption).

The 95% confidence intervals (CIs) were calculated from the estimated variance-covariance matrix of the estimated parameters. We redid the entire country-specific analyses from these lower and upper bounds to obtain a 95% CI of HCV-related morbidity and mortality.

Sensitivity Analyses

Controversies persist as to whether patients in F0 or F1 need to be treated. The group of G2/3 patients with the highest SVR is best suited for testing a strategy of withholding patients in F0 or F1. Evaluation of such a strategy requires testing 3 potential treatment scenarios with PEG-IFN and RBV: (1) never treating patients with F0 or F1, although some of them will progress; (2) not treating patients with F0 or F1 until they reach fibrosis F2; and (3) not treating patients with F0 or F1 until they reach fibrosis F3.

Given the rapid pace of HCV drug development, we integrated future regimens into the 10-year horizon (2012–2021), considering the first 5 years with dual therapy of PEG-IFN and RBV (non-G1) or triple therapy (G1) and the next 5 years with an IFN-free regimen for G2/3 treatment-naive patients and triple or quadruple therapy for other patients. However, a realistic evaluation of the future regimen requires at least a 10-year period following the year of start of this therapy, leading us to provide results for 2017–2026. We based our assumptions on results of clinical studies evaluating future treatment regimens that are nearing phase 3 testing and will probably be available in the near future.[49–53] To remain conservative, and because most studies recruited patients without extensive fibrosis, we applied a 20% reduction in efficacy for F3–F4 (see Supplementary Table 5). We first held the assumption that the HCV screening rate and treatment access would remain unchanged. To underline the urgent need for combining progress in the SVR rate with reinforcement of HCV screening and access to therapy, we performed the same scenario assuming that 75% of HCV-infected patients will be screened by 2017 and one infected patient out of two will be treated in 2017 with the future treatment regimen.

Additional sensitivity analyses were performed and can be found in the Supplementary Materials and Methods.

Results

HCV Natural History

Figure 1 shows the distribution of fibrosis stage over time using the no-treatment scenario for each country. Belgium, France, and Germany showed the same pattern of HCV natural history across fibrosis stages. For those countries, cases of cirrhosis and its complications, such as decompensated cirrhosis and HCC (F4 and its complications), would have stabilized around 2020–2024. In Spain and the United Kingdom, cases of cirrhosis and complications from the disease should continue to increase over the study period, reaching a peak in 2030 and 2033, respectively (not shown). In contrast, in Italy, due to a less recent HCV epidemic, cases of cirrhosis and complications would have already reached their peak of prevalence (2008 in the absence of treatment).

Impact of HCV Treatment on HCV-Related Cirrhosis and Mortality

Impact of pegylated bitherapy from 2002 to 2011. Table 1 shows the impact of treatment over the past 10 years (2002–2011), giving estimates of cumulative HCV-related cirrhosis and HCV-related deaths without and with treatment. Overall, HCV treatment reduced the cumulative incidence of cirrhosis from 414,400 (95% CI, 393,100–432,500) to 385,000 (95% CI, 365,600–401,200) (ie, −7.1%) during this period. The impact of treatment on reduction in HCV-related cirrhosis is shown in Figure 2*A* for each country; reduction varied from 4.0% in Italy to 16.3% in France. As expected, this reduction was higher for G2/3 (from 138,400 to 122,300 cases of cirrhosis; −11.6%) than for G1/4 (from 276,000 to 262,800 cases of cirrhosis; −4.8%). This difference was found for all countries (Figure 2*A*).

Similarly, HCV treatment reduced the cumulative incidence of deaths from 286,000 (95% CI, 273,400–298,000) to 276,400 (95% CI, 264,300–287,800) (ie, −3.4%) from 2002 to 2011. The weakest impact was obtained for Italy (−1.9%) and the strongest for France (−9.0%) (Figure 2*B*). Again, HCV treatment had a greater impact on G2/3 (from 93,000 to 87,400 deaths; −6.0%) than on G1/4 (from 193,000 to 188,900; −2.1%), and this difference was found for all countries (Figure 2*B*).

Future Impact of Antiviral Therapy Integrating Triple Therapy on G1 From 2012 to 2021. *Overall impact on patients with HCV.* Table 2 shows the impact of treatment over the next 10 years (2012–2021), with the cumulative incidence of HCV-related cirrhosis and HCV-related deaths predicted without and with treatment, including PI-based triple therapy for G1 (most conservative assumption, assuming no change in the evolution of screening rates or treatment practices for each country). Overall, HCV treatment would reduce the cumulative incidence of cirrhosis from 400,300 (95% CI, 378,300–412,600) to 318,100 (95% CI, 301,400–328,700) (ie, −20.5%) from 2012 to 2021 and the cumulative incidence of deaths from 316,200 (95% CI, 300,600–330,000) to 277,600 (95% CI, 264,200–289,200) (ie, −12.2%) from 2012 to 2021. Again, the lowest impact would be observed in Italy (12.9% and 7.5%, respectively) and the highest in France (38.9% and 25.5%, respectively) (not shown).

Specific Impact on G1 Patients With HCV. PI-based triple therapy would considerably impact the HCV-related incidence of cirrhosis in G1 patients, with relative impact varying from 10.1% (Italy) to 34.3% (France) and intermediate relative impacts of 11.7% in the United Kingdom,

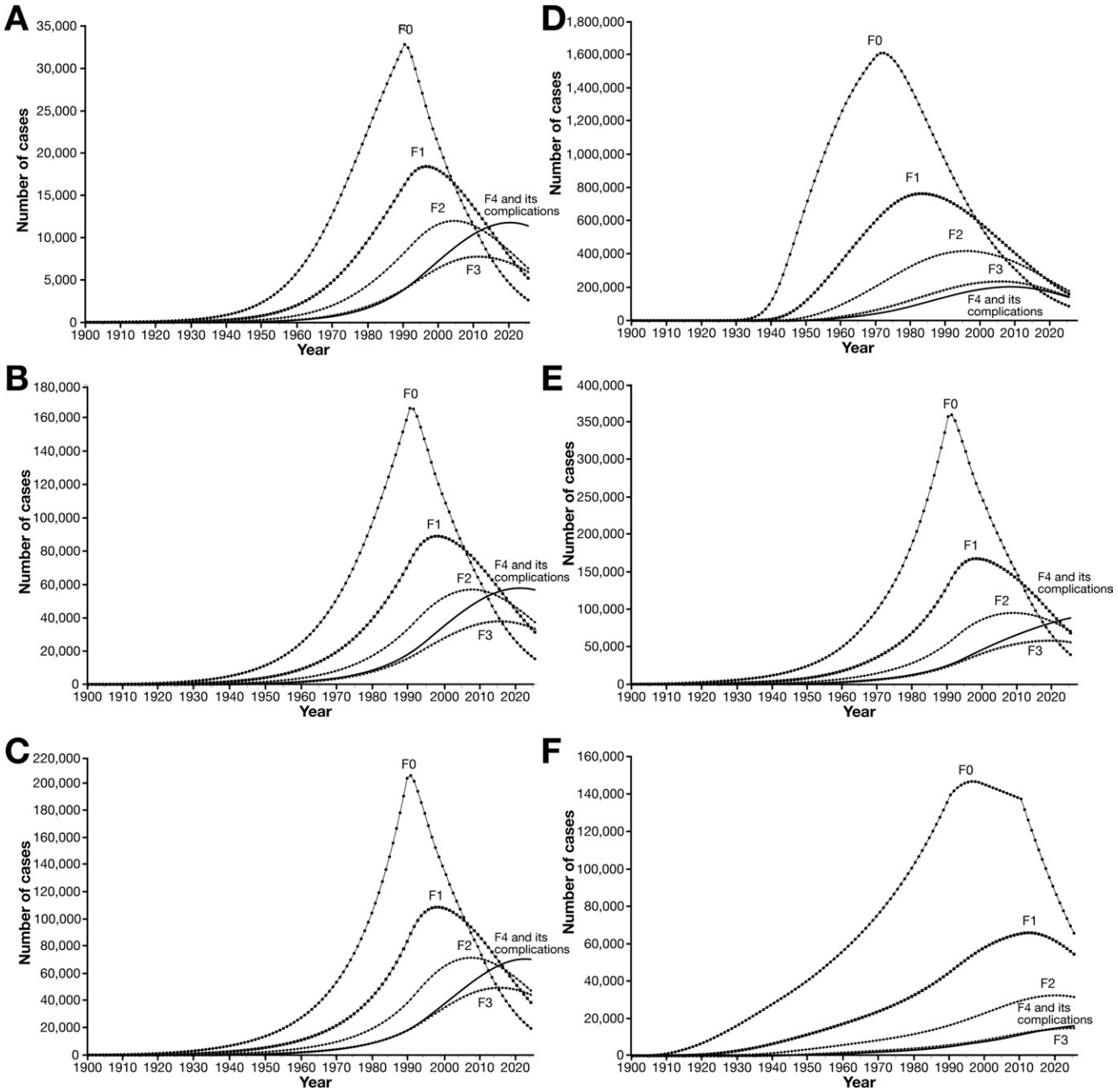

Figure 1. Distribution of fibrosis histologic stages in the absence of treatment (natural history of HCV) in persons with chronic hepatitis C (F0, *solid circles*; F1, *solid squares*; F2, *solid diamonds*; F3, *solid triangles*; cirrhosis including decompensated and HCC, *solid lines*) over time and for each specific country: (*A*) Belgium, (*B*) France, (*C*) Germany, (*D*) Italy, (*E*) Spain, and (*F*) the United Kingdom. According to HCV natural history, cases of cirrhosis and its complications would peak in 2020 in Belgium, 2021 in France, 2024 in Germany, 2008 in Italy, 2030 in Spain (not shown), and 2033 in the United Kingdom (not shown).

15.8% in Belgium, 18.4% in Spain, and 24.0% in Germany (Figure 3*A*). The additional impact of PI-based triple therapy versus pegylated bitherapy would vary between 24% in Belgium and 44% in France (Figure 3*A*). Similarly, PI-based triple therapy would affect the HCV-related incidence of deaths for G1, with relative impact varying from 5.4% in Italy to 20.7% in France (Figure 3*B*). The additional impact of PI-based triple therapy versus pegylated bitherapy would vary from 21% in Belgium to 38% in France (Figure 3*B*).

If we now consider that the availability of triple therapy will be accompanied by reinforced screening and treatment access (less conservative assumption, assuming that 75% of HCV-infected patients will be screened by 2015 and one G1-infected patient out of two will be treated in 2015 with PI-based triple therapy), the overall relative impact of PI-based triple therapy on the HCV-related incidence of cirrhosis would be 27.4% (from 19.5% in Italy to 36.7% in France) (Figure 3*A*). Moreover, the additional impact of PI-based triple therapy versus pegylated bitherapy would be dramatically increased. Similarly, in the less conservative scenario, the relative overall impact of PI-based triple therapy on the HCV-related incidence of

Table 1. Impact of HCV Treatment on 2002–2011[a] HCV-Related Cirrhosis and Death: Cumulative HCV-Related Cirrhosis and Deaths Estimated, and Their 95% CIs, Without and With Treatment

	Belgium	France	Germany	Italy	Spain	United Kingdom	Global
Cumulative HCV-related cirrhosis							
All genotypes							
Without treatment	11,600 (3900–16,300)	52,500 (50,800–54,200)	60,000 (56,500–63,500)	207,000 (205,500–208,500)	69,700 (67,900–71,500)	13,500 (8500–18,700)	414,400 (393,100–432,500)
With treatment	11,000 (3800–15,200)	44,000 (42,600–45,300)	53,300 (50,300–56,300)	198,700 (197,300–200,100)	65,100 (63,500–66,800)	12,900 (8100–17,600)	385,000 (365,600–401,200)
G1/4							
Without treatment	8600 (2900–12,000)	36,100 (35,000–37,300)	39,200 (36,900–39,300)	131,700 (130,800–132,600)	54,000 (52,600–55,400)	6400 (4000–8800)	276,000 (262,100–287,600)
With treatment	8300 (2800–11,400)	32,300 (31,300–33,300)	36,200 (34,100–36,200)	128,500 (127,600–129,400)	51,300 (50,000–52,600)	6200 (3900–8600)	262,800 (249,700–273,400)
G2/3							
Without treatment	3000 (1100–4200)	16,400 (15,900–16,900)	20,800 (19,600–22,000)	75,300 (74,700–75,900)	15,600 (15,200–16,000)	7100 (4500–9800)	138,400 (131,000–144,900)
With treatment	2800 (1000–3800)	11,700 (11,300–12,000)	17,200 (16,200–18,100)	70,200 (69,600–70,700)	13,800 (13,500–14,200)	6600 (4200–9100)	122,300 (115,900–127,800)
Cumulative HCV-related deaths							
All genotypes							
Without treatment	6700 (2800–10,000)	33,700 (32,800–34,700)	35,200 (33,200–37,200)	158,700 (157,400–160,000)	43,300 (42,300–44,300)	8300 (5000–11,700)	286,000 (273,400–298,000)
With treatment	6600 (2700–9800)	30,700 (29,800–31,600)	33,300 (31,400–35,200)	155,700 (154,400–157,000)	42,000 (41,100–43,000)	8100 (4900–11,300)	276,400 (264,300–288,800)
G1/4							
Without treatment	4900 (2000–7400)	23,300 (22,600–24,000)	23,100 (21,700–24,400)	104,100 (103,300–104,900)	33,700 (32,900–34,500)	3900 (2300–5500)	193,000 (184,900–200,600)
With treatment	4900 (2000–7300)	22,000 (21,400–22,700)	22,300 (21,000–23,500)	102,900 (102,100–103,700)	33,000 (32,200–33,700)	3900 (2300–5400)	188,900 (181,100–196,400)
G2/3							
Without treatment	1800 (800–2600)	10,500 (10,200–10,700)	12,200 (11,500–12,800)	54,600 (54,100–55,200)	9600 (9400–9800)	4400 (2600–6200)	93,000 (88,500–97,300)
With treatment	1700 (700–2500)	8700 (8400–8900)	11,000 (10,400–11,600)	52,800 (52,300–53,300)	9100 (8800–9300)	4200 (2500–5900)	87,400 (83,300–91,400)

NOTE. Overall analysis and subanalysis by genotype. Numbers have been rounded off to the nearest hundred.

[a]Corresponding to the following levels of HCV screening in 2011: 50% for Belgium, 64% for France, 48% for Germany, 46% for Italy, 35% for Spain, and 34% for the United Kingdom.

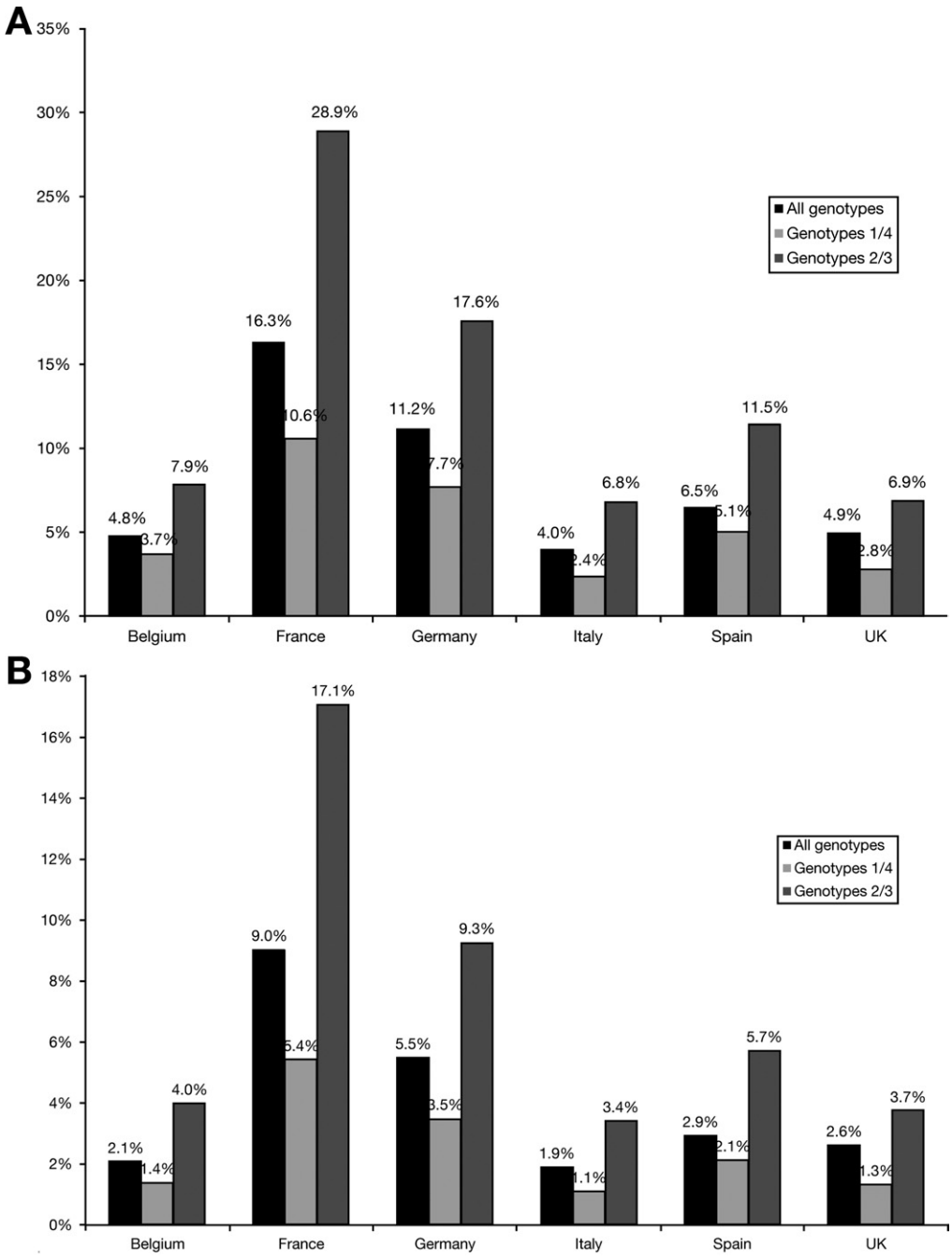

Figure 2. Treatment impact from 2002 to 2011: reduction in cumulative incidence of HCV-related (*A*) cirrhosis and (*B*) death for each country. Overall analysis and subanalysis by genotype.

death would reach 15.0% (from 10.6% in Italy to 22.5% in France) (Figure 3*B*), and the additional impact of PI-based triple therapy versus pegylated would be dramatically increased.

Sensitivity Analyses

The scenario that consists of withholding treatment until reaching F2 is more efficient than the others ("Never treating patients with F0 or F1" or "Not treating patients with F0 or F1 until they reach F3"), as shown in Supplementary Table 6.

The future expected regimen (assumed to be available in 2017) would considerably impact the overall HCV-related incidence of cirrhosis and death from 2017 to 2026, with an even greater effect with reinforcement of HCV screening and treatment access (Figure 4*A* and *B*). Detailed results are shown in Supplementary Table 7.

Additional sensitivity analyses are presented in Supplementary Tables 8–10.

Discussion

The dynamics of infection, natural history, screening, and therapeutic access are important components affecting progress in antiviral therapy in terms of morbidity and mortality. Taking into account these parameters, we show here that (1) the dynamics and natural history of HCV infection differ drastically in Belgium, France, Ger-

Table 2. Impact of HCV Treatment on 2012–2021[a] HCV-Related Cirrhosis and Deaths: Cumulative HCV-Related Cirrhosis and Death, and Their 95% CIs, Estimated Without and With Treatment

	Belgium	France	Germany	Italy	Spain	UK	Global
Cumulative HCV-related cirrhosis							
All genotypes							
Without treatment	12,200 (4000–14,100)	54,300 (52,900–55,700)	68,800 (65,600–71,800)	165,600 (164,700–166,500)	80,900 (79,100–82,700)	18,400 (12,000–24,500)	400,300 (378,300–412,600)
With treatment including PIs	10,100 (3500–11,300)	33,200 (32,500–33,900)	49,900 (47,700–51,800)	144,300 (143,600–145,000)	64,900 (63,500–66,200)	15,800 (10,500–20,500)	318,100 (301,400–328,700)
G1							
Without treatment	7400 (2400–8600)	30,700 (29,900–31,500)	41,800 (39,900–43,600)	98,500 (98,000–99,100)	53,000 (51,800–54,200)	8000 (5200–10,700)	239,500 (227,200–246,000)
With treatment including PIs	6,200 (2100–6900)	20,200 (19,700–20,600)	31,800 (30,400–33,000)	88,600 (88,200–89,000)	43,200 (42,300–44,100)	7100 (4700–9200)	197,100 (187,500–202,900)
Cumulative HCV-related deaths							
All genotypes							
Without treatment	8300 (3200–11,900)	41,600 (40,400–42,700)	47,200 (44,700–49,700)	153,000 (151,800–154,100)	54,500 (53,200–55,700)	11,700 (7300–16,000)	316,200 (300,600–330,000)
With treatment including PIs	7500 (2900–10,500)	31,000 (30,200–31,700)	39,000 (37,000–40,900)	141,500 (140,500–142,500)	48,100 (47,000–49,100)	10,600 (6700–14,000)	277,600 (264,200–289,200)
G1							
Without treatment	5000 (1900–3100)	23,600 (22,900–24,300)	28,900 (27,300–30,400)	92,100 (91,400–92,700)	35,700 (34,900–36,500)	5100 (3200–6900)	190,400 (181,700–198,100)
With treatment including PIs	4600 (1800–2600)	18,700 (18,200–19,200)	24,800 (23,500–26,100)	87,100 (86,500–87,700)	32,000 (31,300–32,700)	4700 (3000–6400)	172,000 (164,300–178,700)

NOTE. Overall analysis and subanalysis for genotype 1. Numbers have been rounded off to the nearest hundred. Results for G1 were extrapolated from those for G1–4, assuming distribution in Supplementary Table 1.

[a]Corresponding to the following levels of HCV screening in 2021: 61% for Belgium, 74% for France, 58% for Germany, 56% for Italy, 45% for Spain, and 43% for the United Kingdom.

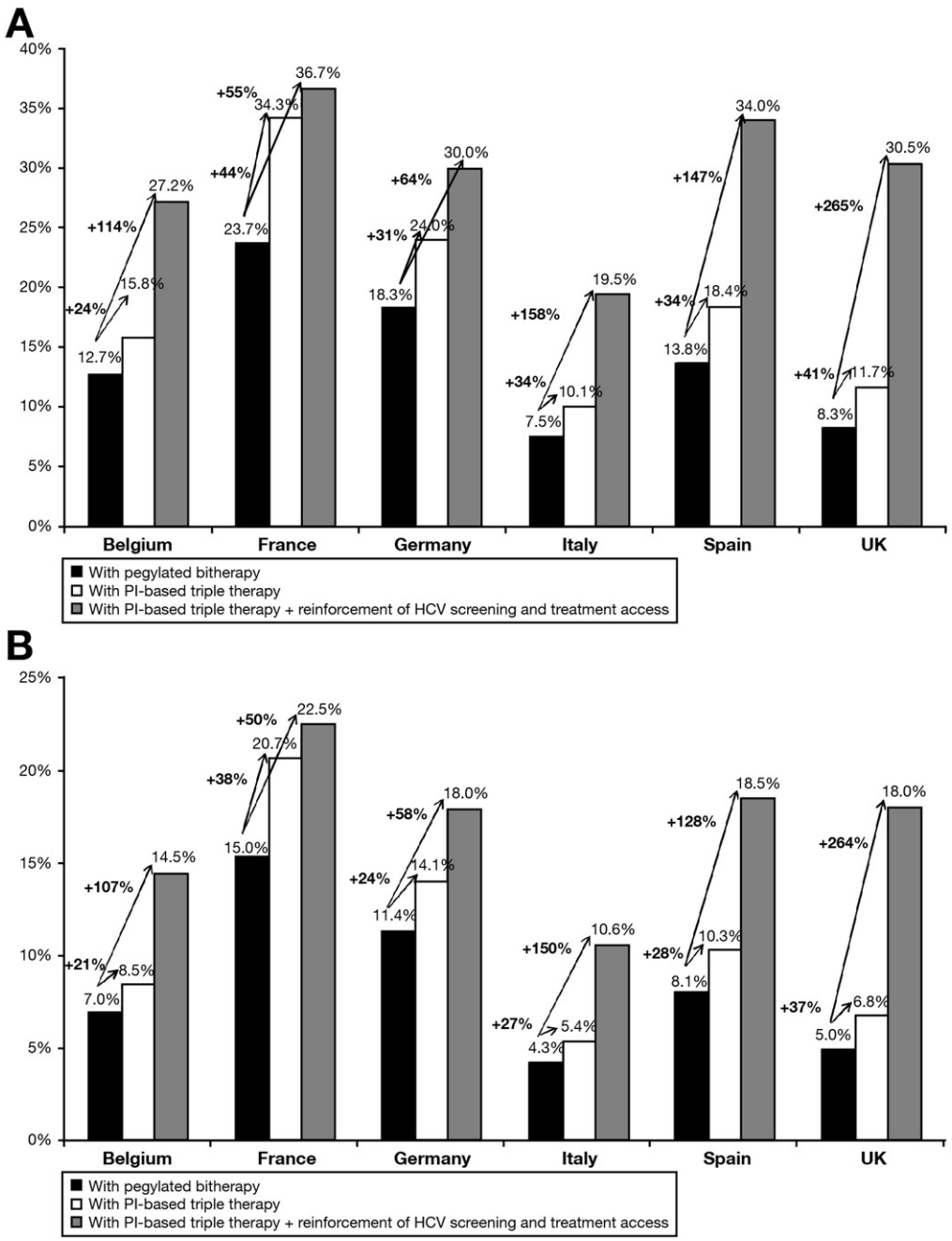

Figure 3. Treatment impact from 2012 to 2021 for G1: reduction in cumulative incidence of HCV-related (*A*) cirrhosis and (*B*) death for each country, considering pegylated bitherapy, PI-based triple therapy alone, or PI-based triple therapy and reinforcement of HCV screening and treatment access.

many, Italy, Spain, and the United Kingdom; (2) the impact of antiviral therapy in reducing the incidence of cirrhosis and deaths substantially varies across these countries; (3) for G1 patients with HCV, the impact of PI-based triple therapy from 2012 to 2021 might vary from 10.1% to 34.3% for HCV-related cirrhosis and from 5.4% to 20.7% for HCV-related mortality; and (4) ideally, 75% of HCV screening by 2015 and one patient out of two treated in 2015 (with triple therapy for G1-infected patients and pegylated bitherapy for other genotypes) in all these countries would impact HCV morbidity and mortality from 2012 to 2021 (from 19.5% to 36.7% and 10.6% to 22.5%, respectively). The present study provides a new concept that could help in creating public health policies for population-guided therapy.

The present modeling study showed significant differences in the spread of HCV infection, leading to specific patterns of natural history in these European countries. Indeed, the total number of patients with cirrhosis (including complications) is expected to peak in 2020 for Belgium, 2021 for France, 2023 for Germany, 2030 for Spain, and 2033 for the United Kingdom in the absence of treatment; for Italy, the peak was reached in 2008. These differences in fibrosis stage distribution over time are related to patterns of HCV infection. Belgium, France, and Germany present patterns similar to that predicted by Davis et al in the United States.[4] In Italy, an intensive epidemic wave appeared to have occurred during the 1950s and 1960s, mainly associated with poor hygiene during invasive procedures (eg, surgery, gynecology, den-

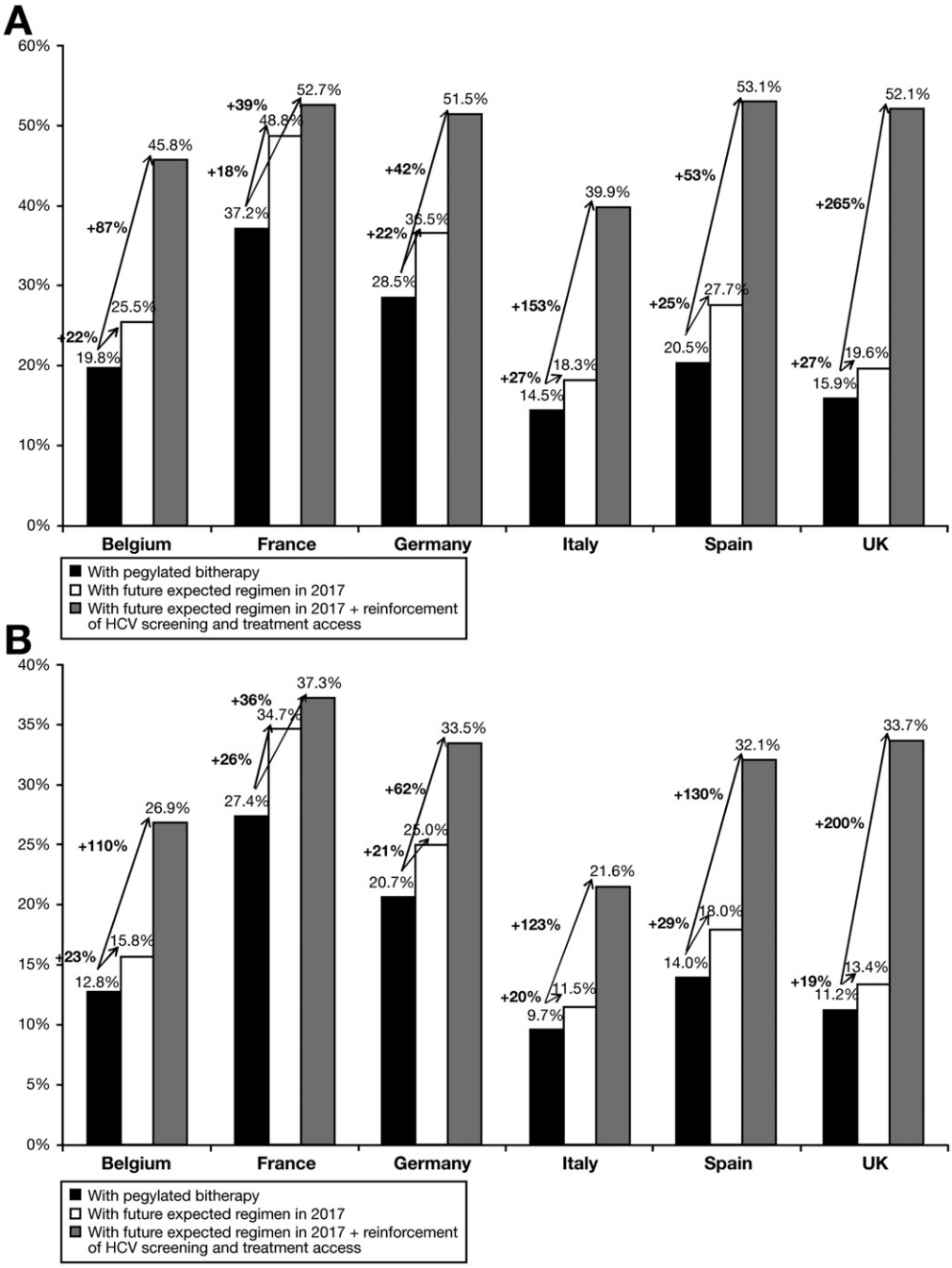

Figure 4. Treatment impact from 2017 to 2026 for all genotypes: reduction in cumulative incidence of (*A*) HCV-related cirrhosis and (*B*) death for each country, considering pegylated bitherapy, future expected regimen in 2017 alone, or future expected regimen in 2017 plus reinforcement of HCV screening and treatment access.

tistry, vaccinations, injection of antibiotics and vitamins), whereas in other countries the most intensive epidemic waves occurred during the 1980s, mainly related to transfusions and intravenous drug use. Consequently, in Italy, although antiviral therapy should reduce HCV morbidity and mortality, it will not affect the year or magnitude of the peak; in all other countries, antiviral therapy will have an impact on both (results not shown).

Our main concern was to develop country-specific models that fit "real-life" data integrating the probability of being treated based on clinicians' decisions and health policies. We used PEG-IFN sales obtained from GERS (for France) and IMS (for other countries). These data enabled us to estimate the annual likelihood of being treated among screened patients, and each country-specific model was calibrated according to the number of treated patients. These numbers are a consequence of the contraindications and side effects profile of the IFN-based regimen. Indeed, clinicians aware of the side effects profile of an IFN-based regimen adapt their decisions according to patient characteristics. For example, few patients aged 70 years in F0–F1 were treated in 2011 (from 0.8% in Italy to 4.0% in France; data not shown). Overall, estimated likelihoods depend on country, year, genotype, treatment history (naive vs re-treated patients), fibrosis (≥F2 vs F0–F1), and the presence of alcohol abuse. In addition, the proportion of prior nonresponders with F3–F4 in our model was based on clinical practice, which differs from

licensing trials. Indeed, the proportion of F3–F4 among treated patients depended on the distribution of fibrosis among screened patients, which was the result of natural history modeling, the higher likelihood of treatment among F2–F4 patients, and the fact that naive F3–F4 patients had a lower probability of SVR and therefore higher probability of being nonresponders. The latter 2 points (higher likelihood of being treated and lower SVR probability) synergistically increment the proportion of prior nonresponders with F3–F4.

During the past decade (2002–2011), the overall reduction in morbidity and mortality was much higher in France (−16.3% and −9.0%, respectively) compared with other countries (ranging from −4.0% to −11.2% and −1.9% to −5.5%, respectively). Although the use of PIs in G1 patients will increase the impact of antiviral therapy on morbidity and mortality during the next decade (2012–2021), this study also underlines the urgent need for reinforcement of HCV screening and access to therapy. Indeed, the hypothetical scenario involving use of PIs with the same targeted level of HCV screening and access to therapy for all countries indicates that all countries except Italy will catch up with France. Moreover, sensitivity analysis assuming progress expected due to drugs currently in development clearly confirmed that any progress in SVR will mainly have an impact on HCV-related morbidity and mortality if accompanied by an increase in HCV screening and access to therapy. These data reveal the complex role of the spread and natural history of HCV infection and emphasize the need for innovative public health strategies in population-guided therapy. This approach of targeted public health strategies may also be useful for countries outside of Europe but will necessitate data for country-specific models.

Until now, experts have been focusing primarily on management of patients according to virologic kinetics and disease severity. The present study shows that, although clinicians from different countries use the same drugs according to therapeutic guidelines provided by scientific organizations, the impact on morbidity and mortality across countries varies as a result of differences in the spread of HCV infection, screening, and access to therapy. Therapeutic guidelines are first set up for patient care at an individual level but do not have the tools for measuring treatment impact on morbidity and mortality at a population level. This study suggests that delaying treatment in patients with F0 or F1 until they progress to F2 is efficient. However, this strategy is difficult in clinical practice because of the need for an efficient diagnostic method to detect fibrosis progression from F0–F1 to F2 as well as optimization of the interval and frequency of diagnostic testing specifically adapted to patient characteristics. Our results should be useful to national experts when proposing therapeutic guidelines.

As expected in a modeling approach, the present work had limitations associated with data and assumptions. Country-specific models were developed after identifying at least one expert in each country so as to obtain the most accurate analyses. Moreover, the country-specific data used to adjust or calibrate each model led to constraints that made certain assumptions impossible. However, one limitation concerns the assumption of the past incidence of HCV infections. We assumed that the past incidence of HCV infections decreased from 1990 at the same proportions as those observed in the United States, except for Italy and the United Kingdom. Indeed, the same assumption was first made for the United Kingdom, but it did not enable a good fit for reported HCC deaths related to HCV. This assumption seemed valid for countries in which transfusion-induced infections were predominant before 1990, but not for the United Kingdom, with infections mainly occurring in intravenous drug users. Moreover, in an earlier work performed in France, the impact on future morbidity and mortality of the variation in the decrease of the incidence of HCV after 1990 was found to be small.[5] Secondly, we used data on PEG-IFN purchases in each country during 2002–2005 to calibrate our model. Limitations exist concerning our assumptions and parameters used to convert sales into patient figures. However, our strategy consisted of identifying experts possessing both PEG-IFN sales data and the expertise needed to convert these sales into numbers of treated patients.[20] Thirdly, liver transplantation was not considered. Indeed, liver transplantation for HCV-related liver failure or HCC represents only a small number in comparison to HCV mortality. For example, in Spain, the country with the highest liver donation rate in Europe, 378 liver transplantations for HCV-related liver failure and HCC were performed in 2009, but there were 4500 HCV-related deaths. In addition, liver transplantation does not eradicate the disease, because patients are still at risk for disease progression and 5-year survival is approximately 65%.[54,55] Thus, liver transplantation should not significantly affect results.

In conclusion, the present study clearly shows the benefit of antiviral therapy in European countries, amplified by the use of PIs. The present data should help public health authorities to optimize the impact of such therapy on morbidity and mortality.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2012.05.054.

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Conflicts of interest

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Supplementary Materials and Methods

Markov Model

Briefly, 75% of acutely infected individuals entered the first stage of chronic hepatitis (F0) during the first year after infection (Supplementary Figure 1).[1] Annual probabilities of fibrosis progression were estimated according to sex, age, and alcohol abuse status specifically for each country by the process (see Procedure). For alcohol-positive (>50 g/day) compared with alcohol-negative (≤50 g/day) patients, we assumed that fibrosis progression rates were 3 times higher between F0 and F3 and 4.5 times higher between F3 and F4.[2] Once individuals have cirrhosis (F4), they are at risk for liver failure and HCC. The annual probability of progression to liver failure depends on alcohol level: 5% in alcohol-negative and 20.6% in alcohol-positive patients[3,4] (these risks are decreased by 84% for patients who achieve SVR to treatment[5]). The annual probability of progression from cirrhosis to HCC depends on age and sex[6]: 1.7% for female subjects and 3.6% for male subjects at 57 years of age with an age effect of 1.05 by year of age (these risks are decreased by 79% for patients who achieve SVR to treatment[5]). Finally, HCV-related mortality was defined as death from liver failure, taking into account complications of cirrhosis such as ascites, variceal bleeding, and encephalopathy[7] and as death from HCC assuming period- and age-dependent probabilities.[8,9] The annual probability of death from liver failure was 39% during the first year and 11% thereafter. The annual probability of death from HCC depended on age and period: at 20–39 years of age, 70.2% during the first year and 23.1% thereafter; at 40–59 years of age, between 71.8% and 85.7% during the first year and between 23.9% and 32.3% thereafter; at 60 years of age or more, between 73.9% and 89.3% during the first year and between 29.8% and 38.3% thereafter.

HCV Screening Rate

Data on HCV screening rates are reported on Supplementary Table 1. Reliable estimates were not available for all countries. For Germany, Rossol reported that 25% of HCV-infected patients had been screened in 2005.[10] We tried to calibrate the model according to the number of patients treated between 2002 and 2005 in Germany (47,302; see Supplementary Table 2), assuming that 25% of HCV-infected patients were screened in 2005. However, this led to estimated proportions of patients treated per year that were too high (near 100%). For this reason, we adopted a different approach for estimating the HCV screening rate. Given that 41.2% of screened HCV-RNA-positive subjects are treated according to Zehnter et al[11] and that 47,302 subjects were treated from 2002 to 2005, we estimated that at least 115,000 HCV-RNA–positive patients were screened. It is reasonable to estimate that 190,000 (approximately 40%) ever-infected patients were screened, as described in a European report.[12] For Spain, data reporting that 17% of HCV-infected patients were screened in 2004 could not fit the number of patients treated between 2002 and 2005.[12,13] We therefore extrapolated the HCV screening rate from the screening rate of HCV-related HCC.[14] Indeed, the HCV screening rate increases with fibrosis stage and is higher with development of HCC. For example, in France, the 57% screening rate of the entire HCV-infected population corresponded to 55% when considering only patients in fibrosis stages <F4 and 71% when considering those in stages of cirrhosis and its complications. Thus, the reported 53% rate of screened HCV-related HCC during 2008–2009 by Varela et al[14] led to an HCV screening rate of 33% at all stages during the same period.

HCV Treatment

The main assumptions for treatment for each country were as follows: (1) patients eligible for treatment were those already screened, aged 18–70 years, F0–F4; (2) the likelihood of treatment with IFN monotherapy (from 1991 to 1998) was identical for G1/4 and G2/3; (3) the likelihood of treatment and re-treatment for patients at fibrosis stage <F2 was 80% lower than for patients at fibrosis stage ≥F2[15]; (4) patients achieving SVR were withdrawn from the number of patients at the different stages, except for those with cirrhosis (F4), who remained at risk for developing complications at lower progression rates: 84% lower for progression to decompensated cirrhosis and 79% lower for progression to HCC for patients with cirrhosis achieving SVR compared with untreated patients or those not achieving SVR[5]; and (5) treatment nonresponders or relapsers after PEG-IFN and RBV therapy might be re-treated once 3 years later. Since 2002, re-treatment has been possible for all countries except Belgium, which obtained permission to re-treat patients with HCV only in 2009. Moreover, except for France, re-treatment was only considered for patients who did not respond to IFN monotherapy.

HCC Deaths Related to HCV

The country-specific incidence of HCC deaths over time was extracted by sex and 10-year age group from the World Health Organization database (www.who.int/whosis/mort/download/en/index.html). The proportion of HCC deaths related to HCV infection was estimated for each country. For most of them, we assumed that this proportion increased linearly starting at a 0% value in 1940,[16] except for Italy and the United Kingdom (see the following text). In Belgium, the HepCar Registry reported all new cases of HCC involving consultation with physicians between January 2003 and December 2003.[17] Using these results, we assumed that 37% of HCC deaths were related to HCV in 2003. In France, a large-scale national survey estimated that 23% of HCC deaths in 2001 could be attributed to HCV.[18] In Germany, using 2 retrospective studies,[19,20] we assumed that 27% of HCC

deaths were related to HCV in 1997. In Italy, the prevalence of HCV among HCC cases from 2 large national studies was 77% in 1997 and 63% in 2008, respectively.[21,22] Two linear functions were derived from these data, one that increased until 2001 and the other that decreased thereafter, with special adjustment for age.[23] In Spain, a multicentric study of 705 cases of HCC reported that 51% were related to HCV in 2004.[14] Finally, in the United Kingdom, we extrapolated a 15% constant proportion of HCC deaths related to HCV from the percentage of HCC deaths mentioning HCV on death certificates or hospital data.[24]

Procedure

For each country, the Markov model simulates progression of HCV-infected cohorts defined by age, sex, genotype, and alcohol abuse for each year from 1900 to 2010, from onset of HCV infection to death (see Supplementary Figure 1). Unknown parameters were estimated for each country to fit age-specific annual HCC deaths related to HCV (see Supplementary Materials and Methods). In the first step of the optimization process, trial values were selected for unknown parameters on past incidence of HCV infection (2 parameters to be estimated) and annual probabilities of fibrosis progression (12 parameters to be estimated). At this point, to fit the data-based constraint of HCV prevalence, we applied a standardization factor to all estimated numbers. The number of HCV-related HCC deaths predicted by this initial model by year, age, and sex was compared with observed values. For this comparison, we used the least-squares criterion. The optimization process was repeated until a minimum value was obtained for the least-squares criterion. For this optimization, we used the SNLS1 program from the SLATEC Library, which minimizes the sum of the squares of nonlinear functions by a modification of the Levenberg–Marquardt algorithm.[25,26] This program also performed the Fisher information matrix needed to calculate the variance-covariance matrix associated with parameter estimates. The entire procedure was performed with C and C++ programming language.

The country-specific model fit (ie, observed vs predicted HCC mortality related to HCV) is shown in Supplementary Figure 2. At the end of the process, the model estimated country-specific past incidence of HCV infection and annual probability of fibrosis progression according to sex, age class, and alcohol abuse status (see Supplementary Table 3). Probabilities of fibrosis progression were country specific and back-calculated using mortality data that aggregated patients with and without all risk factors (sex, age, alcohol, and other potential risk factors). Therefore, probabilities of fibrosis were estimated from all potential risk factors, some of which were assessed individually (sex, age, and alcohol abuse) and others on an average. The importance of the other risk factors assessed on an average was confirmed by the following approach. In a first step, we tested a "unique" model with the same probabilities of fibrosis progression according to sex, age, and alcohol abuse status and distribution of those risk factors in each country. This unique model never fit observed country-specific mortality data. Indeed, it was unable to integrate the prevalence of other potential risk factors (ie, obesity, smoking, and other) or interactions between them or between sex, age, and alcohol abuse status. Indeed, the prevalence of other risk factors assessed on an average (ie, obesity, smoking, and other) differed between countries. Therefore, we had to develop a country-specific model. It is noteworthy that estimates of fibrosis progression differ between countries. They cannot be compared from one country to another because they were based on patients with country-specific characteristics.

Finally, the likelihood of being treated among patients aware of their infection was estimated so as to calibrate the country-specific 2002–2005 number of treated patients extracted from PEG-IFN sales (see Supplementary Tables 1 and 2). For example, the likelihood of being treated during 2002 and 2011 is provided in Supplementary Table 4.

Sensitivity Analyses

Additional sensitivity analyses were performed.

- We considered that treatment efficacy (PEG-IFN and RBV) decreased after age 65 years for G1 (not significant for G2 or G3) as presented by Aronsohn et al,[27] with an odds ratio of 0.61 for >65 versus ≤65 years for the age effect on SVR[27] (Supplementary Table 8).
- The proportion of prior nonresponders with F3–F4 differs in clinical practice compared with licensing trials. This bias did not affect our modeling for the following reasons. First, the proportion of F3–F4 among treated patients depended on the distribution of fibrosis among screened patients who are candidates for treatment, and this distribution of fibrosis was a result of natural history modeling. Second, the proportion of F3–F4 among treated patients also depended on the likelihood of being treated as indicated from PEG-IFN sales and clinical practice, or "real-life" data, leading to a higher likelihood of treatment among F2–F4 patients than among F0–F1 patients. Third, naive F3–F4 patients had a lower probability of SVR than naive F0–F2 patients and therefore a higher probability of being nonresponders. The latter 2 points (higher likelihood of being treated and lower SVR probability) synergistically increment the proportion of prior nonresponders with F3–F4. However, we performed a sensitivity analysis of the likelihood of being treated in G1-naive F3–F4 patients from 2002 (availability of pegylated bitherapy) to increase the pro-

portion of F3–F4 among prior nonresponder candidates for triple therapy (Supplementary Table 9).

- Our assumptions concerning future screening rates were already conservative and not optimistic; indeed, we assumed on baseline analysis that yearly screening rates will remain constant, that is, yearly screening for HCV will continue at the same rate as before triple therapy. However, we considered on sensitivity analysis that there was no additional screening of the HCV population from 2012 and thereafter (Supplementary Table 10).

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Supplementary Table 1. Epidemiologic Data Used for Each Country: HCV Prevalence, Distribution of HCV Genotype, and HCV Screening

	Belgium	France	Germany	Italy	Spain	United Kingdom
Overall population in 2011	11,000,000	65,000,000	81,500,000	61,100,000	46,800,000	62,700,000
Reference number for HCV prevalence	29	30	31, 32	23, 33	34–40	41, 42
Observed percentage (year)[a]	0.87 (1997)	0.84 (2004)	0.6 (2002)	4 (2005)	1.9 (1999)	0.7 (2004)
Estimated number in 2011[b]	72,000	360,000	460,000	2,000,000	690,000	340,000
Reference number for HCV genotype distribution (%)	43	44, 45	46	47[c]	48, 49	24, 50, 51
G1	60	56	60	62	65	44
G2/3	27	32	37	34	23	53
Other genotypes	13	12	3	4	12	3
Reference number for HCV screening	52	30	11	53	14	54, 55
Observed percentage (year)	37 (2000)	57 (2004)	40 (2004)	40 (2005)	33 (2008–2009)	30 (2004)
Estimated percentage in 2011	50	64	48	46	35	34

[a]Observed prevalence was obtained from national studies during a specific period.
[b]Number of patients ever infected with HCV estimated by the model in 2011; this number has changed over time according to national demography and modalities of HCV infection.
[c]T. Stroffolini, personnal communication, 2010.

Supplementary Table 2. 2002–2005 Treatment Data Used for Each Country-Specific Model: Number of Treated Patients, Distribution of Genotypes Among Treated Patients, and Treatment History

	Belgium	France	Germany	Italy	Spain	United Kingdom
Reference number for HCV treatment	56	57	56	56	56	56
Number	3571	54,270	47,302	63,359	36,403	11,242
Per 100 prevalent cases	4	15	9	3	5	3
Reference number for distribution of genotypes (%)	58	59	11	[a]	60	50
G1	59	53	59.5	50	67	40
G2/3	25	36	37	46	23	56
Other genotypes	16	11	3.5	5	10	4
Reference number for treatment history (%)	58	59	11	[a]	60	50
Naive	100	62	84	90	90	83
Experienced	0	38	16	10	10	17

[a]T. Stroffolini, personnal communication, 2010.

Supplementary Table 3. Country-Specific Back-Calculated Probability of Fibrosis Progression (95% CI), According to Sex and Age for Patients Without Alcohol Abuse (0–50 g/day)

	Belgium	France	Germany	Italy	Spain	United Kingdom
Women, age (*y*)						
0–40	8.4 (4.9–11.9)	5.2 (4.8–5.6)	6.6 (6.3–6.9)	2.6 (2.6–2.7)	4.3 (4.0–4.5)	2.5 (1.6–3.5)
41–50	43.5 (5.7–81.2)	5.4 (4.7–6.0)	5.6 (5.1–6.0)	2.0 (1.9–2.1)	3.0 (2.6–3.5)	4.6 (2.9–6.4)
51–60	17.4 (0.0–37.1)	5.9 (5.6–6.3)	8.8 (8.3–9.2)	7.7 (7.6–7.7)	10.8 (10.6–11.0)	1.4 (0.4–2.3)
61–70	0.0 (0.0–7.9)	9.5 (9.3–9.7)	10.7 (10.4–11.1)	6.6 (6.6–6.7)	11.5 (11.4–11.6)	10.3 (8.6–12.1)
>70	0.3 (0.0–28.5)	8.5 (8.3–8.6)	14.9 (14.3–15.5)	4.4 (4.4–4.4)	5.1 (5.0–5.1)	8.3 (7.5–9.2)
Men, age (*y*)						
0–40	3.4 (2.3–4.5)	3.5 (3.4–3.6)	3.3 (3.2–3.4)	2.5 (2.5–2.5)	2.7 (2.6–3.5)	1.6 (1.1–2.0)
41–50	3.6 (2.5–4.8)	10.0 (9.8–10.1)	5.8 (5.4–6.1)	1.2 (1.1–1.2)	11.7 (11.4–11.9)	4.1 (3.2–5.0)
51–60	13.4 (7.5–19.3)	15.4 (15.2–15.6)	15.7 (14.9–16.4)	9.8 (9.7–9.8)	9.9 (9.7–10.1)	1.2 (0.0–2.8)
61–70	13.7 (11.6–15.8)	27.3 (27.0–27.5)	15.6 (14.7–16.5)	11.8 (11.7–11.8)	45.4 (44.6–46.1)	10.3 (9.5–11.2)
>70	21.6 (5.4–37.7)	26.1 (25.2–27.1)	11.5 (10.4–12.7)	5.3 (5.3–5.3)	19.4 (19.0–19.7)	33.0 (14.1–51.9)

NOTE. All values are expressed as percentage (95% CI). For patients with alcohol abuse (>50 g/day) compared with patients without alcohol abuse (0–50 g/day), we assumed that fibrosis progression rates were 3 times higher between F0 and F3 and 4.5 times higher between F3 and F4.[2]

Supplementary Table 4. Likelihood of Being Treated During 2002 and 2011 in the Absence of Alcohol Abuse (0–50 g/day)[a] and According to Fibrosis Stage (Fibrosis ≤F2 and >F2)

	Likelihood of being treated in 2002		Likelihood of being treated in 2011	
	Naive patients	Non-naive patients	Naive patients	Non-naive patients
Fibrosis ≤F2				
Belgium	—[b]	—[c]	0.036	0.020
France	0.042	0.068	0.054	0.154
Germany	0.048	0.045	0.113	0.046
Italy	0.010	0.035	0.016	0.042
Spain	0.030	0.030	0.066	0.044
United Kingdom	0.020	0.032	0.044	0.110
Fibrosis >F2				
Belgium	0.120	—[c]	0.180	0.100
France	0.210	0.340	0.270	0.770
Germany	0.240	0.180	0.450	0.230
Italy	0.050	0.150	0.080	0.210
Spain	0.150	0.150	0.330	0.220
United Kingdom	0.100	0.160	0.220	0.550

[a]The likelihood of being treated for patients with presence of alcohol abuse (>50 g/day) was 5 times lower than that for patients with absence of alcohol abuse.
[b]No treatment of patients with F0 or F1 fibrosis in Belgium before 2005, the year in which reimbursement was obtained.
[c]No re-treatment in Belgium before 2009, the year in which reimbursement of re-treatment was obtained.

Supplementary Table 5. Assumptions of Future Regimen Efficacy

	Fibrosis F0–F2	Fibrosis F3–F4
G1		
Treatment naive	90%[61,62]	72%
Treatment experienced	90%[63,64]	72%
G2/3		
Treatment naive	100%[65]	80%
Treatment experienced	90%[a]	72%

[a]For these patients, we assumed that triple therapy with PSI-7977 (new molecule with efficacy in G2/3) would have the same efficacy as that observed in G1 treatment-experienced patients.

Supplementary Table 6. Sensitivity Analysis on 2012–2021[a] HCV-Related Cirrhosis and Death: Cumulative HCV-Related Cirrhosis and Deaths, and Their 95% CIs, Estimated Without and With Treatment Considering Baseline or Alternative Scenarios of Withholding Treatment in F0–F1 G2/3 Patients[b]

	Belgium	France	Germany	Italy	Spain	United Kingdom	Global
Cumulative HCV-related cirrhosis							
Without treatment	12,200 (4000–14,100)	54,300 (52,900–55,700)	68,800 (65,600–71,800)	165,600 (164,700–166,500)	80,900 (79,100–82,700)	18,400 (12,000–24,500)	400,300 (378,300–412,600)
With treatment (baseline scenario)	10,400 (3600–11,700)	37,100 (36,200–37,900)	52,400 (50,400–54,400)	147,000 (146,200–147,700)	67,800 (66,300–69,200)	16,100 (10,700–21,000)	330,700 (313,200–342,000)
With treatment (alternative scenarios)							
Never treating patients with F0–F1	10,900 (3700–12,500)	43,500 (42,500–44,500)	59,200 (56,500–61,600)	156,400 (155,500–157,200)	71,700 (70,100–73,200)	17,500 (11,500–23,100)	359,300 (339,900–372,200)
Not treating patients with F0–F1 until they reach F2	10,400 (3600–11,700)	37,400 (36,500–38,200)	52,700 (50,400–54,800)	147,500 (146,700–148,300)	68,000 (66,500–69,400)	16,200 (10,800–21,200)	332,200 (314,600–343,600)
Not treating patients with F0–F1 until they reach F3	10,700 (3700–12,100)	39,200 (38,400–40,100)	54,900 (52,500–57,100)	151,400 (150,600–152,200)	69,300 (67,800–70,700)	16,800 (11,200–22,100)	342,400 (324,100–354,300)
Cumulative HCV-related deaths							
Without treatment	8300 (3200–11,900)	41,600 (40,400–42,700)	47,200 (44,700–49,700)	153,000 (151,800–154,100)	54,500 (53,200–55,700)	11,700 (7300–16,000)	316,200 (300,600–330,000)
With treatment (baseline)	7600 (3000–10,700)	32,600 (31,700–33,400)	39,800 (37,700–41,800)	142,600 (141,600–143,600)	49,000 (47,900–50,100)	10,700 (6800–14,500)	282,300 (268,600–294,200)
With treatment (alternative scenarios)							
Never treating patients with F0–F1	7800 (3000–11,100)	35,500 (34,600–36,400)	42,600 (40,300–44,700)	147,400 (146,300–148,500)	50,500 (49,400–51,700)	11,300 (7100–15,400)	295,000 (280,700–307,700)
Not treating patients with F0–F1 until they reach F2	7600 (3000–10,700)	32,700 (31,800–33,500)	39,900 (37,800–41,900)	142,700 (141,700–143,700)	49,100 (48,000–50,200)	10,700 (6800–14,600)	282,700 (269,000–294,600)
Not treating patients with F0–F1 until they reach F3	7700 (3000–10,800)	33,200 (32,400–34,100)	40,700 (38,600–42,700)	144,000 (142,900–145,000)	49,500 (48,400–50,600)	11,000 (6900–14,900)	285,900 (272,100–298,000)

NOTE. Overall analysis for all genotypes. Numbers have been rounded off to the nearest hundred.

[a]Corresponding to the following levels of HCV screening in 2021: 61% for Belgium, 74% for France, 58% for Germany, 56% for Italy, 45% for Spain, and 43% for the United Kingdom.

[b]PEG-IFN and RBV treatment.

Supplementary Table 7. Impact of HCV Treatment on 2017–2026 HCV-Related Cirrhosis and Deaths: Cumulative HCV-Related Cirrhosis and Death, and Their 95% CIs, Estimated Without and With Treatment According to Future Expected Regimen

	Belgium	France	Germany	Italy	Spain	United Kingdom	Overall
Cumulative HCV-related cirrhosis							
Without treatment	11,400 (3800–11,800)	51,000 (49,900–52,100)	66,700 (64,000–69,000)	133,900 (133,200–134,600)	83,500 (81,900–85,100)	20,200 (13,500–26,200)	366,700 (346,400–378,700)
With future expected regimen							
Most conservative assumption[a]	8500 (3100–8400)	26,100 (25,700–26,500)	42,300 (40,900–43,600)	109,500 (109,000–109,900)	60,400 (59,300–61,400)	16,200 (11,200–20,500)	263,000 (249,200–270,300)
Less conservative assumption[b]	6200 (2000–5700)	24,200 (23,700–24,600)	32,300 (31,200–32,300)	80,400 (80,100–80,800)	39,100 (38,400–39,800)	9700 (6700–12,100)	191,900 (182,100–196,300)
Cumulative HCV-related deaths							
Without treatment	8500 (3200–11,800)	42,700 (41,600–43,900)	50,400 (47,900–52,800)	137,000 (136,000–137,900)	58,700 (57,300–59,900)	13,200 (8400–17,700)	310,500 (294,400–324,000)
With future expected regimen							
Most conservative assumption[a]	7200 (2800–9700)	27,900 (27,200–28,600)	37,800 (36,000–39,500)	121,200 (120,300–122,000)	48,100 (47,000–49,100)	11,400 (7400–15,200)	253,500 (240,800–264,000)
Less conservative assumption[b]	6200 (2300–8300)	26,800 (26,100–27,500)	33,500 (31,800–35,100)	107,400 (106,700–108,200)	39,800 (38,900–40,700)	8700 (7400–11,600)	222,500 (213,200–231,400)

NOTE. Overall analysis for all genotypes. Numbers have been rounded off to the nearest hundred.
[a]With assumptions on HCV screening rate and treatment access that would remained unchanged corresponding to the following levels of HCV screening in 2026: 66% for Belgium, 75% for France, 62% for Germany, 59% for Italy, 49% for Spain, and 46% for the United Kingdom.
[b]With future expected regimen and reinforcement of HCV screening and treatment access corresponding to 75% of HCV screening in 2026 for all countries.

Supplementary Table 8. Sensitivity Analysis on 2012–2021[a] HCV-Related Cirrhosis and Death: Cumulative HCV-Related Cirrhosis and Deaths, and Their 95% CIs, Estimated Without and With Treatment Considering Baseline or Alternative Scenario[b]

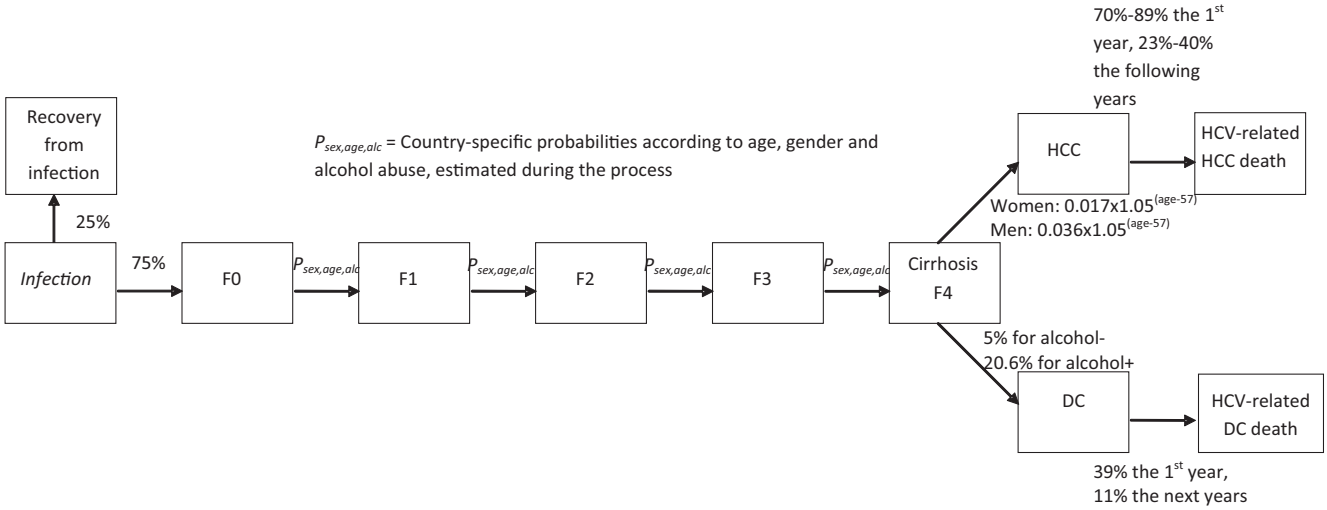
	Belgium	France	Germany	Italy	Spain	United Kingdom	Global
Cumulative HCV-related cirrhosis							
Without treatment	12,200 (4000–14,100)	54,300 (52,900–55,700)	68,800 (65,600–71,800)	165,600 (164,700–166,500)	80,900 (79,100–82,700)	18,400 (12,000–24,500)	400,300 (378,300–412,600)
With treatment[c]							
Baseline scenario	10,400 (3600–11,700)	37,100 (36,200–37,900)	52,400 (50,400–54,400)	147,000 (146,200–147,700)	67,800 (66,300–69,200)	16,100 (10,700–21,000)	330,700 (313,200–342,000)
Alternative scenario	10,400 (3600–11,700)	37,100 (36,300–38,000)	52,400 (50,200–54,500)	147,100 (146,300–147,900)	67,800 (66,400–69,300)	16,100 (10,700–21,000)	331,000 (313,500–342,300)
Cumulative HCV-related deaths							
Without treatment	8300 (3200–11,900)	41,600 (40,400–42,700)	47,200 (44,700–49,700)	153,000 (151,800–154,100)	54,500 (53,200–55,700)	11,700 (7300–16,000)	316,200 (300,600–330,000)
With treatment[c]							
Baseline scenario	7600 (3000–10,700)	32,600 (31,700–33,400)	39,800 (37,700–41,800)	142,600 (141,600–143,600)	49,000 (47,900–50,100)	10,700 (6800–14,500)	282,300 (268,600–294,200)
Alternative scenario	7600 (3000–10,700)	32,600 (31,800–33,500)	39,800 (37,800–41,800)	142,700 (141,600–143,700)	49,000 (47,900–50,100)	10,700 (6800–14,500)	282,400 (268,800–294,300)

NOTE. Overall analysis for all genotypes. Numbers have been rounded off to the nearest hundred.
[a]Corresponding to the following levels of HCV screening in 2021: 61% for Belgium, 74% for France, 58% for Germany, 56% for Italy, 45% for Spain, and 43% for the United Kingdom.
[b]Alternative scenario considered decreasing treatment efficacy with PEG-IFN and RBV after 65 years old for G1.[27]
[c]PEG-IFN and RBV treatment.

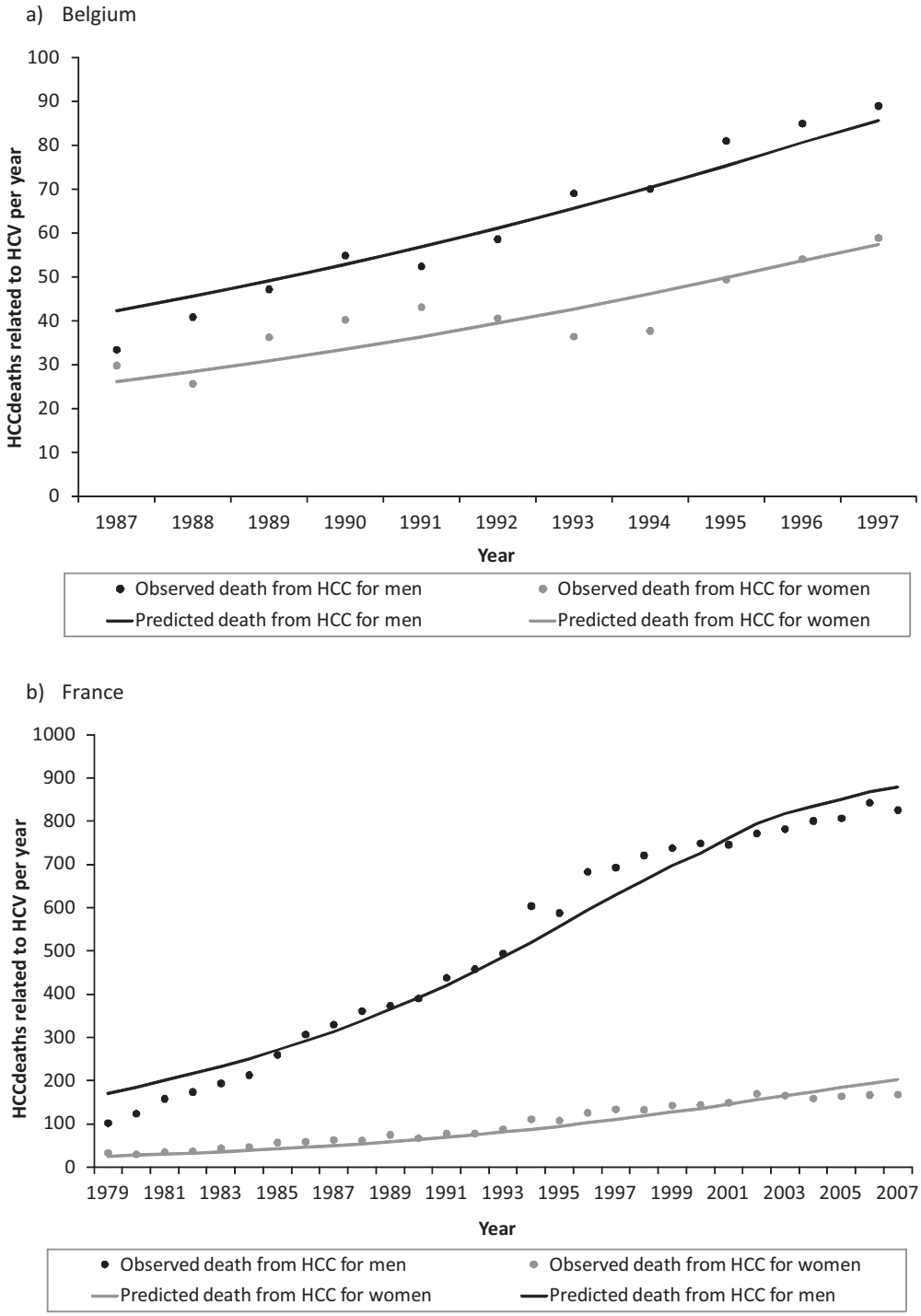
Supplementary Table 9. Sensitivity Analysis on 2012–2021[a] HCV-Related Cirrhosis and Death: Cumulative HCV-Related Cirrhosis and Deaths, and Their 95% CIs, Estimated Without and With Treatment Considering Baseline or Alternative Scenario[b]

	Belgium	France	Germany	Italy	Spain	United Kingdom	Global
Cumulative HCV-related cirrhosis							
Without treatment	12,200 (4000–14,100)	54,300 (52,900–55,700)	68,800 (65,600–71,800)	165,600 (164,700–166,500)	80,900 (79,100–82,700)	18,400 (12,000–24,500)	400,300 (378,300–412,600)
With treatment[c]							
Baseline scenario	10,100 (3500–11,300)	33,200 (32,500–33,900)	49,900 (47,700–51,800)	144,300 (143,600–145,000)	64,900 (63,500–66,200)	15,800 (10,500–20,500)	318,100 (301,400–328,700)
Alternative scenario	10,000 (3500–11,100)	32,700 (32,100–33,400)	49,500 (47,400–51,400)	143,000 (142,300–143,800)	64,400 (63,000–65,700)	15,700 (10,500–20,400)	315,400 (298,700–325,800)
Cumulative HCV-related deaths							
Without treatment	8300 (3200–11,900)	41,600 (40,400–42,700)	47,200 (44,700–49,700)	153,000 (151,800–154,100)	54,500 (53,200–55,700)	11,700 (7300–16,000)	316,200 (300,600–330,000)
With treatment[c]							
Baseline scenario	7500 (2900–10,500)	31,000 (30,200–31,700)	39,000 (37,000–40,900)	141,500 (140,500–142,500)	48,100 (47,000–49,100)	10,600 (6700–14,400)	277,600 (264,200–289,200)
Alternative scenario	7400 (2900–10,500)	30,600 (29,800–31,300)	38,700 (36,700–40,600)	140,500 (139,500–141,500)	47,700 (46,600–48,800)	10,500 (6700–14,300)	275,500 (262,200–287,000)

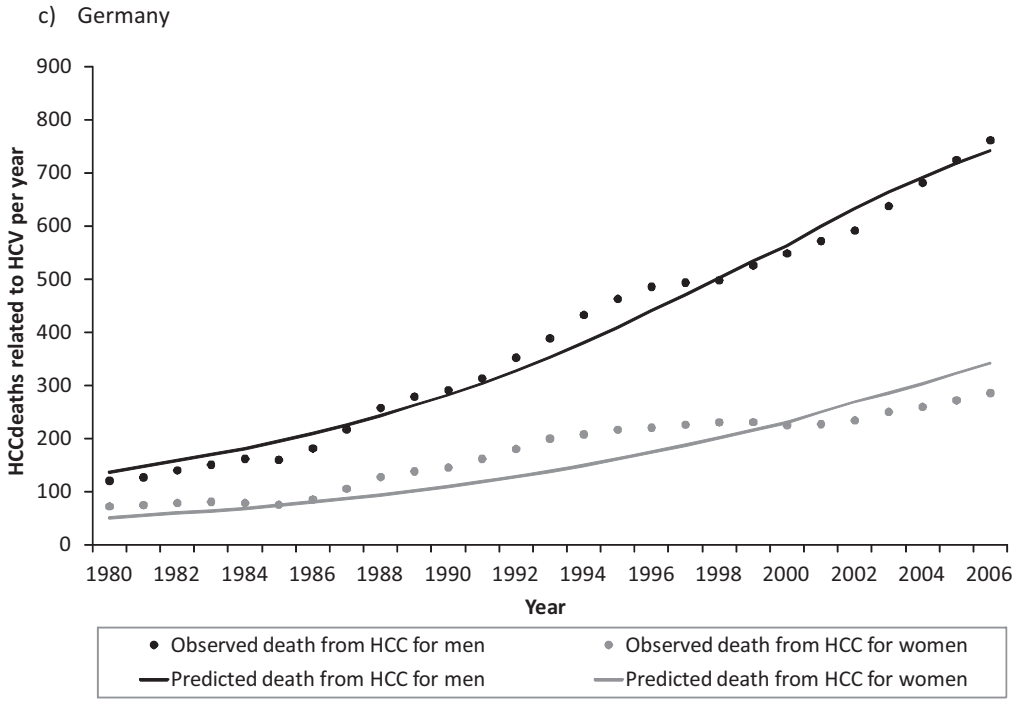
NOTE. Overall analysis for all genotypes. Numbers have been rounded off to the nearest hundred.
[a]Corresponding to the following levels of HCV screening in 2021: 61% for Belgium, 74% for France, 58% for Germany, 56% for Italy, 45% for Spain, and 43% for the United Kingdom.
[b]Alternative scenario considered higher likelihood of treating F3–F4 patients with G1 from 2002.
[c]Treatment with triple therapy for G1 and PEG-IFN and RBV for other genotypes.

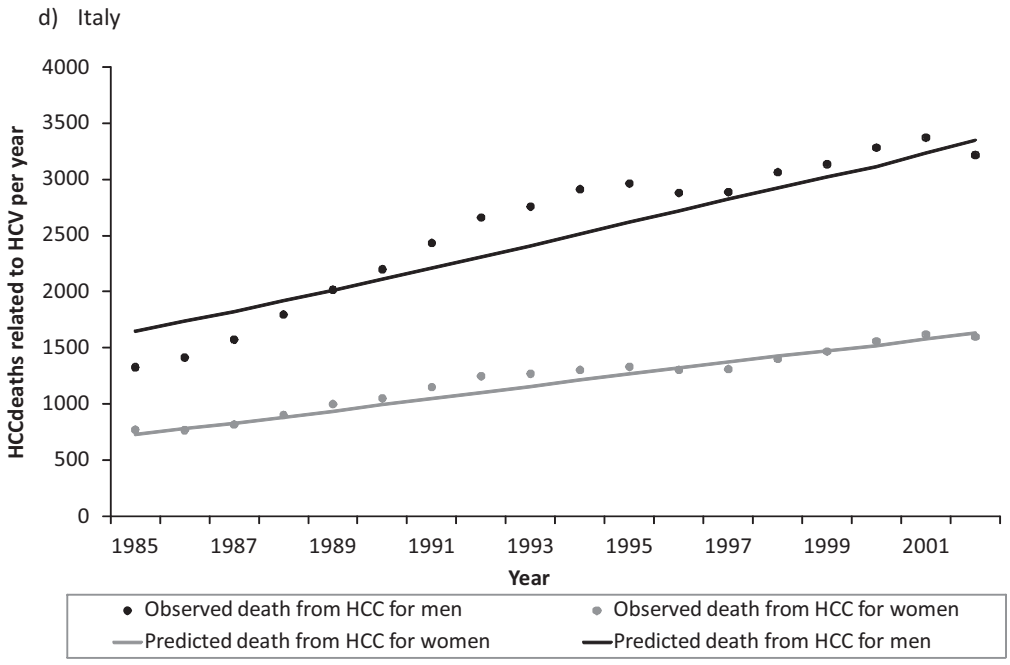


Supplementary Figure 1. Natural history of HCV disease. Annual probability of fibrosis progression, $P_{sex,age,alc}$, for each country was estimated according to sex, age, and alcohol abuse status (see Supplementary Table 3 for country-specific estimates).

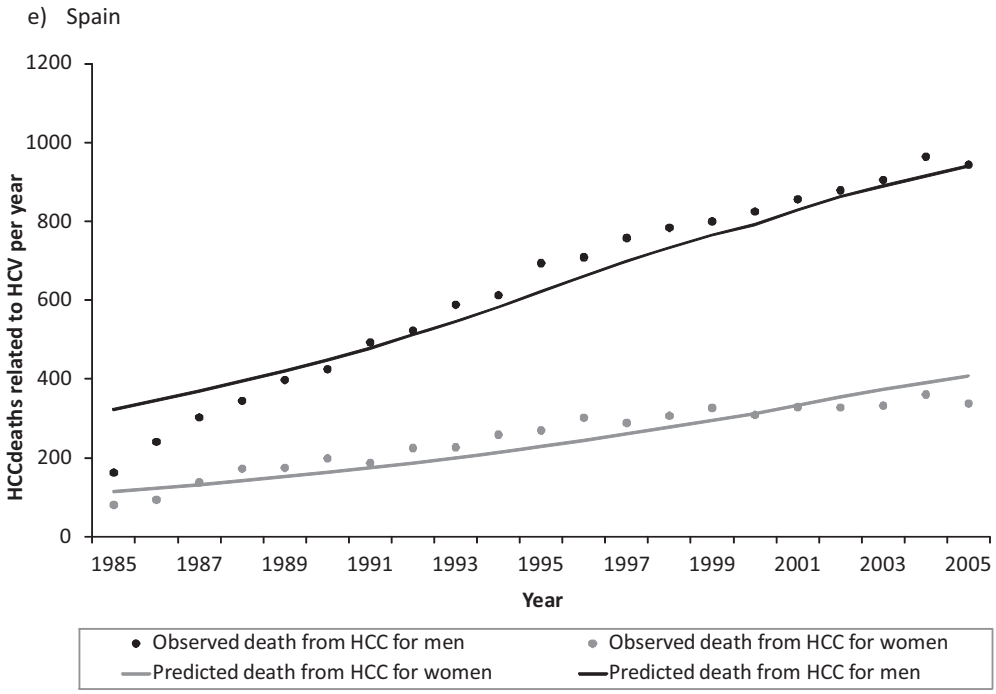


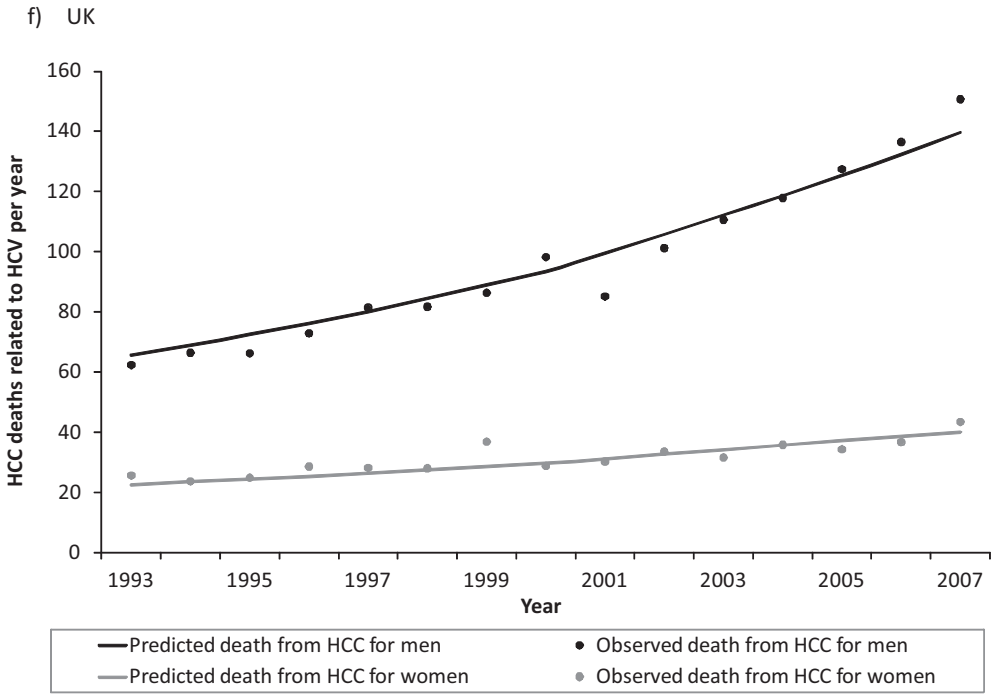
Supplementary Figure 2. Best fit between observed and predicted HCC deaths related to HCV for each specific country: (*A*) Belgium, (*B*) France, (*C*) Germany, (*D*) Italy, (*E*) Spain, and (*F*) United Kingdom. Observed HCC deaths were obtained from the World Health Organization database (www.who.int/whosis/mort/download/en/index.html). Note that the period of observed HCC deaths was not similar between countries: 1987–1997 for Belgium, 1979–2007 for France, 1980–2006 for Germany, 1985–2002 for Italy, 1985–2005 for Spain, and 1993–2007 for the United Kingdom. The proportion of HCC deaths related to HCV infection was estimated for each country.[14,16–21,23,24,28]





Supplementary Figure 2. Continued.





Supplementary Figure 2. Continued.

Supplementary Table 10. Sensitivity Analysis on 2012–2021[a] HCV-Related Cirrhosis and Death: Cumulative HCV-Related Cirrhosis and Deaths, and Their 95% CIs, Estimated Without and With Treatment Considering Baseline or Alternative Scenario[b]

	Belgium	France	Germany	Italy	Spain	UK	Global
Cumulative HCV-related cirrhosis							
Without treatment	12,200 (4000–14,100)	54,300 (52,900–55,700)	68,800 (65,600–71,800)	165,600 (164,700–166,500)	80,900 (79,100–82,700)	18,400 (12,000–24,500)	400,300 (378,300–412,600)
With treatment[c]							
Baseline scenario	10,100 (3500–11,300)	33,200 (32,500–33,900)	49,900 (47,700–51,800)	144,300 (143,600–145,000)	64,900 (63,500–66,200)	15,800 (10,500–20,500)	318,100 (301,400–328,700)
Alternative scenario	10,200 (3500–11,400)	34,100 (33,300–34,800)	51,000 (48,800–52,900)	145,000 (144,200–145,700)	66,100 (64,700–67,400)	15,900 (10,600–20,700)	322,100 (305,100–333,000)
Cumulative HCV-related deaths							
Without treatment	8300 (3200–11,900)	41,600 (40,400–42,700)	47,200 (44,700–49,700)	153,000 (151,800–154,100)	54,500 (53,200–55,700)	11,700 (7300–16,000)	316,200 (300,600–330,000)
With treatment[c]							
Baseline scenario	7500 (2900–10,500)	31,000 (30,200–31,700)	39,000 (37,000–40,900)	141,500 (140,500–142,500)	48,100 (47,000–49,100)	10,600 (6700–14,400)	277,600 (264,200–289,200)
Alternative scenario	7500 (2900–10,500)	30,300 (30,500–32,100)	39,200 (37,200–41,100)	141,700 (140,700–142,700)	48,300 (47,200–49,400)	10,600 (6700–14,400)	278,600 (265,200–290,200)

NOTE. Overall analysis for all genotypes. Numbers have been rounded off to the nearest hundred.
[a]Corresponding to the following levels of HCV screening in 2021: 61% for Belgium, 74% for France, 58% for Germany, 56% for Italy, 45% for Spain, and 43% for the United Kingdom.
[b]Alternative scenario considered no additional screening of HCV from 2012.
[c]Treatment with triple therapy for G1 and PEG-IFN and RBV for other genotypes.