

# Strategies to manage hepatitis C virus (HCV) disease burden

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**SUMMARY.** The number of hepatitis C virus (HCV) infections is projected to decline while those with advanced liver disease will increase. A modeling approach was used to forecast two treatment scenarios: (i) the impact of increased treatment efficacy while keeping the number of treated patients constant and (ii) increasing efficacy and treatment rate. This analysis suggests that successful diagnosis and treatment of a small proportion of patients can contribute significantly to the reduction of disease burden in the countries studied. The largest reduction in HCV-related morbidity and mortality occurs when increased treatment is combined with higher efficacy therapies,

generally in combination with increased diagnosis. With a treatment rate of approximately 10%, this analysis suggests it is possible to achieve elimination of HCV (defined as a >90% decline in total infections by 2030). However, for most countries presented, this will require a 3–5 fold increase in diagnosis and/or treatment. Thus, building the public health and clinical provider capacity for improved diagnosis and treatment will be critical.

**Keywords:** diagnosis, disease burden, epidemiology, HCV, hepatitis C, incidence, mortality, prevalence, scenarios, treatment.

## INTRODUCTION

The disease burden of hepatitis C virus (HCV) infection is expected to increase as the infected population ages [1–3]. The dichotomy faced by many countries is that while the

total number of HCV infections is declining, the number of cases with advanced liver disease is expected to increase [4]. HCV infection can be cured. Historically 40–70% of the patients achieved sustained viral response (SVR) with a combination of Pegylated-interferon (Peg-IFN) and ribavirin (RBV) [5–7] with a lower SVR in genotype (G) 1 patients. More recent combinations, with protease inhibitors, led to an increased SVR in genotype 1 patients, but this also came with an increase in adverse events [8–17].

Our previous study demonstrated that the HCV disease burden increased with the current treatment paradigm [4]. Today, a number of new treatment regimens are being introduced which promise oral dosing, higher SVR, shorter duration of treatment and potentially fewer side effects. While a large proportion of patients were ineligible for antiviral therapy with previous interferon-based therapies, almost all patients should qualify for future all-oral therapies. The aim of this study was to examine the impact of different strategies on the future HCV disease burden in

Abbreviations: BASL, Belgium Association for the Study of Liver; CHC, chronic hepatitis C; DAA, direct acting antiviral agent; G, Genotype; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IDU, injection drug use; INE, National Institute of Statistics; Peg-IFN, Pegylated interferon; PHAC, Public Health Agency of Canada; PI, protease inhibitor; RBV, ribavirin; RNA, ribonucleic acid; RVR, rapid viral response; SVR, sustained viral response; UN, United Nations.

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light of new treatment options. It is important to note the objective of this work was not to prescribe the future treatment rate, SVR and required screening, but rather to analyze the impact of these changes.

## METHODOLOGY

The details of the mathematical model used to forecast HCV disease burden was described previously [4]. Input fields were provided to change the number of treated, the proportion of cases eligible for treatment, the reduction in treatment restrictions with better tolerated treatment, the average sustained viral response by genotype (G1, G2, G3, G4) and the total number of newly diagnosed and acute HCV cases at five different points in time. The year in which these changes took effect was also an input field, and it corresponded to a launch of new therapy or change in treatment algorithm. Different new therapies considered were: direct acting antivirals (DAAs) + Pegylated-interferon (Peg-IFN) + ribavirin (RBV), DAA + RBV, interferon-free all oral, second generation DAA combinations and third generation combinations. Different treatment algorithms included different segments of the infected population (e.g. F1 stage fibrosis, 70–74 year olds) in the treatment eligible population. All changes took effect immediately, and the co-existence of multiple therapies was handled by modifying the average SVR.

The future number of treated patients was capped by (i) the number diagnosed, (ii) number eligible and (iii) unrestricted cases. The size of the diagnosed population was calculated from national databases, use of analogues or expert panel input [4]. For the base case, the last year of available data was used for the annual number of newly diagnosed cases in the future. Occasionally during strategy development, the model predicted that there were not enough diagnosed cases by 2030 to see the full impact of the strategy. When this occurred, the number of newly diagnosed cases was increased, even if the new estimate was not realistically achievable. The focus of the analysis was to highlight how many cases have to be diagnosed to achieve a strategy rather than to forecast the screening capacity in a country.

According to the literature, approximately 40–60% of HCV patients are eligible for Peg-IFN/RBV treatment [18,19]. The definition of eligibility included contraindications to the drugs (e.g. psychiatric conditions) as well as patient's preference. For all countries, a treatment eligibility of 60% was used for all therapies that included Peg-IFN/RBV. When Peg-IFN could be eliminated, the eligibility was typically increased to 80%, and it was increased to 90–95% when RBV was also eliminated from the treatment regimen. Deviations from this were noted below. These assumptions could differ by genotype, and were frequently higher for G2/G3 patients. The increase in eligibility did not increase treatment in the

future. However, it did increase the pool of diagnosed and eligible patients who could be drawn upon. Any changes in treatment were implemented using a separate input.

The pool of patients who could be treated was also impacted by treatment restrictions. These restrictions included patient's age and stage of liver disease. Review of treatment guidelines and interviews with expert panels were used to identify both. In most countries, the majority of the treated patients were between the ages of 20–70, although the upper age varied between 60 in Egypt and 85+ in the Czech Republic as shown in Table 1 [4]. In addition, the stage of liver disease eligible for treatment was considered. While age restrictions were applied to all genotypes, the restrictions by the stage of liver disease were applied to specific genotypes. Patients with decompensated cirrhosis, irrespective of genotype, were considered ineligible for any treatment that involved Peg-IFN. The fibrotic stages eligible for treatment are shown in Table 1.

In this analysis, the base scenario was defined as the case when all assumptions (the number of acute cases, treated patients, percent of patients eligible for treatment, treatment restrictions, the number of newly diagnosed and the average SVR by genotype) remained the same as today. The base scenario for each country was described in detail previously [4] and summarized in Table 1. Two additional scenarios were also evaluated. In the second scenario, the impact of increasing the SVR was considered. In this case, all other assumptions remained the same as above, except that SVR and treatment eligibility were increased over time as described below. The treatment eligibility was changed when treatment regimens excluded Peg-IFN and RBV.

The third scenario included an increase in treatment as well as SVR. In most instances, the number of newly diagnosed cases has to be increased, as well as stages of disease considered for treatment, to keep up with the depletion of the diagnosed eligible patient pool. As described earlier, the number of treated patients was limited to the available diagnosed and eligible patient pool. The assumptions in this scenario were often driven by a desire to achieve a certain goal (i.e. control HCV disease burden or disease elimination). There were a number of definitions in the literature for the term disease elimination, many of which included reducing the number of new infections to zero. In this work, HCV elimination was defined as disease reduction in prevalence, morbidity and mortality to an acceptable level, which was defined as less than 10% of today's values. Reduction in prevalence was always considered among the viremic population, and reduction in HCV-related morbidity was considered for the total number of cases rather than new cases. In order to achieve some of the goals stated below, expanding access to patients with early stages of fibrosis (F0–F2) was considered.

Table 1 Summary of current treatment protocols and strategies to minimize HCV morbidity and mortality

	Australia	Austria	Belgium	Brazil	Czech Republic	Denmark	Egypt
Treatment protocols (2013)							
Treated (Annual)	2640	1100	710	11 700	880	100	65 000
Treatment rate (%)	1.1	4.2	1.1	0.6	2.1	0.5	1.1
Average SVR (%)	59	64	54	43	55	60	48
Viremic newly diagnosed (Annual)	8400	600	2900	10 000	800	700	125 000
% Treatment eligible	60	50	60	60	60	60	50
Common treatment age	20–69	15–69	15–84	15–69	15–85+	15–64	15–59
Treated stages – G1	≥ F0	≥ F1	≥ F2	≥ F2	≥ F0	≥ F2	≥ F2
Treated stages – G2	≥ F0	≥ F1	≥ F0	≥ F1	≥ F0	≥ F2	≥ F2
Treated stages – G3	≥ F0	≥ F1	≥ F2	≥ F1	≥ F0	≥ F2	≥ F2
Treated stages – G4	≥ F0	≥ F1	≥ F2	≥ F1	≥ F0	≥ F2	≥ F2
Increase efficacy only							
Max average SVR (Year)	85 (2016)	90 (2016)	90 (2016)	90 (2017)	88 (2018)	90 (2015)	90 (2014)
Max newly diagnosed (Year)							
% Treatment eligible	95 (2016)	85 (2016)	90 (2016)	95 (2017)	60 (2013)	80 (2015)	90 (2014)
Impact							
Decrease in HCV mortality (%)	5	30	10	5	10	5	15
Decrease in HCC (%)	5	30	10	5	10	5	15
Decrease in decomp cirrhosis (%)	5	40	10	10	15	5	20
Decrease in total infected (%)	5	10	5	5	10	5	10
Increase efficacy & treatment							
Max treated (Year)	14 200 (2018)	2700 (2016)	4600 (2020)	118 800 (2021)	3700 (2020)	1500 (2016)	325 000 (2018)
Treatment rate (%)	6.3	13.1	9.5	9.1	10.8	8.1	7.1
Max average SVR (Year)	85 (2016)	90 (2016)	90 (2016)	90 (2017)	88 (2018)	91 (2015)	90 (2014)
Max newly diagnosed (Year)	8400 (2013)	2400 (2016)	3400 (2016)	119 000 (2020)	4100 (2020)	700 (2013)	337 500 (2018)
% Treatment eligible	95 (2016)	85 (2016)	90 (2016)	95 (2017)	100 (2020)	80 (2015)	90 (2014)
Treatment age	20–69	15–79	15–84	15–74	15–85+	15–69	15–74
Treated stages	≥ F0	≥ F0	≥ F1 (G1/3/4) ≥ F2 (G2)	≥ F0	≥ F0	≥ F0	≥ F0
Impact							
Decrease in HCV mortality (%)	55	85	85	70	80	70	75
Decrease in HCC (%)	55	90	95	75	85	65	85
Decrease in decomp cirrhosis (%)	60	95	95	80	90	75	90
Decrease in total infected (%)	55	90	90	90	90	90	95



Table 1 (continued)

	England	France	Germany	Portugal	Spain	Sweden	Switzerland	Turkey
<b>Treatment protocols (2013)</b>								
Treated (Annual)	5400	10 100	12 700	800	9800	1100	1100	4200
Treatment rate (%)	3.8	5.2	4.7	0.7	2.1	2.8	1.4	0.8
Average SVR (%)	70	60	55	56	50	55	64	48
Viremic newly diagnosed (Annual)	5600	9000	4000	1300	15 300	1500	1100	5500
% Treatment eligible	60	60	50	65	50	60	60	20
Common treatment age	15–64	15–74	0–74	15–64	15–64	20–69	15–69	15–79
Treated stages – G1	≥ F0	≥ F2	≥ F0	≥ F2	≥ F2	≥ F2	≥ F2	≥ F0
Treated stages – G2	≥ F0	≥ F2	≥ F0	≥ F2	≥ F1	≥ F0	≥ F2	≥ F0
Treated stages – G3	≥ F0	≥ F2	≥ F0	≥ F2	≥ F1	≥ F0	≥ F2	≥ F0
Treated stages – G4	≥ F0	≥ F2	≥ F0	≥ F2	≥ F2	≥ F2	≥ F2	≥ F0
<b>Increase efficacy only</b>								
Max average SVR (Year)	93 (2018)	90 (2016)	90 (2015)	95 (2020)	90 (2018)	91 (2016)	95 (2020)	90 (2020)
<b>Max newly diagnosed (Year)</b>								
% Treatment eligible	95 (2018)	90 (2016)	95 (2015)	95 (2018)	90 (2018)	90 (2020)	60 (2013)	90 (2020)
<b>Impact</b>								
Decrease in HCV mortality (%)	15	59	40	5	15	50	10	5
Decrease in HCC (%)	10	61	45	5	15	45	10	5
Decrease in decomp cirrhosis (%)	20	56	55	5	20	60	10	5
Decrease in total infected (%)	25	11	40	5	20	10	10	5
<b>Increase efficacy &amp; treatment</b>								
Max treated (Year)	14 700 (2018)	20 200 (2014)	22 100 (2016)	8300 (2018)	16 800 (2020)	4200 (2016)	5400 (2018)	10 300 (2022)
Treatment rate (%)	14.2	10.3	9.9	8.0	4.5	12.0	7.7	2.6
Max average SVR (Year)	93 (2018)	90 (2016)	90 (2015)	95 (2020)	90 (2018)	90 (2016)	91 (2016)	90 (2020)
Max newly diagnosed (Year)	15 100 (2018)	9000 (2013)	16 400 (2020)	9700 (2018)	17 600 (2018)	1500 (2013)	3500 (2018)	5500 (2013)
% Treatment eligible	95 (2018)	90 (2016)	95 (2015)	95 (2018)	90 (2018)	90 (2020)	85 (2016)	90 (2020)
Treatment age	15–74	15–84	0–74	15–69	15–74	20–74	15–74	15–79
Treated stages	≥ F0	≥ F0	≥ F0	≥ F0	≥ F2 (G1/4) ≥ F1 (G2/3)	≥ F0	≥ F0	≥ F0
<b>Impact</b>								
Decrease in HCV mortality (%)	85	85	75	75	50	80	70	25
Decrease in HCC (%)	80	87	70	90	50	75	70	25
Decrease in decomp cirrhosis (%)	90	84	80	85	55	85	80	25
Decrease in total infected (%)	95	93	85	85	45	90	85	20

Scenario inputs, including SVR, fibrosis stage treated and medical eligibility are provided, by genotype and year, in Table 1 and Figs 1–15. Additionally, the numbers of treated and diagnosed patients necessary to achieve the desired scenario outputs are provided by year in Table 1 and Figs 1–15.

### *Birth cohort effect*

The age distribution of each country was gathered from published data and reported previously [20]. The disease progression model was used to age the HCV-infected population after taking into account mortality and SVR [4]. For this analysis, the median age in each 5-year age cohort was selected and converted to a birth year. A range of birth years were selected, which accounted for approximately 75% (or more) of the total HCV-infected population using the 2013 HCV population distribution [4].

## RESULTS

The results of the analyses are summarized in Table 1 and Fig. 16. The birth cohort effect in the HCV-infected population is shown in Fig. 18. Each bar represents the range of birth years with the value on each bar showing the percentage of the total infected population who was born between the years shown. Country specific scenario results are discussed below.

In all instances, viremic infections represented current HCV or chronic HCV infections. The term viremic was used throughout this study to highlight the presence of HCV virus. The term chronic hepatitis C (CHC) was also used to represent viremic infections. The term incidence was used for new HCV infections and not newly diagnosed. HCC referred to the total number of viremic HCV-related HCC cases, rather than new cases. Additionally, all reductions by disease stage were assumed to occur among the viremic HCV population—i.e. the effects of non-HCV-related liver disease were not considered in this analysis.

### *Australia*

#### *Increased efficacy only*

Increasing the efficacy of treatment had a significant impact on the disease burden. There will be 11 970 fewer viremic individuals in 2030 as compared to the base case, a 5% reduction. The number of HCV-related prevalent HCC cases in 2030 was estimated at 1960 cases, a 5% decrease from the base case. Similarly, the number of liver-related deaths will decrease by 5% from the base with 1670 in 2030. HCV-related decompensated and compensated cirrhosis will decrease by 5% from the base with 3970 and 36 320 cases respectively in 2030. However, under this scenario, HCV morbidity and mortality would continue to increase.

#### *Increased efficacy & treatment*

With the HCV control strategy, the total number of viremic infections was projected to decrease 55% from 2013–2030 to 103 210 thus achieving elimination of the infection. The number of HCC cases in 2030 was estimated at 900 cases, a 55% decrease from the base case. Similarly, the number of liver-related deaths will decrease by 55% from the base with 800 in 2030. Decompensated and compensated cirrhosis will decrease by 60% from the base with 1660 and 15 790 cases respectively in 2030.

### *Austria*

#### *Increased efficacy only*

There will be 1430 fewer viremic individuals in 2030 as compared to the base case, a 10% reduction. The number of HCC cases in 2030 was estimated at 110 cases, a 30% decrease from the base case. Similarly, the number of liver-related deaths will decrease by 30% from the base with 90 in 2030. Decompensated and compensated cirrhosis will decrease by up to 40% from the base with 110 and 1320 cases respectively in 2030.

#### *Increased efficacy & treatment*

There will be 12 770 fewer viremic individuals in 2030 as compared to the base case, a 90% reduction. The number of HCC cases in 2030 was estimated at 20 cases, a 90% decrease from the base case. Similarly, the number of liver-related deaths will decrease by 85% from the base with 20 in 2030. Decompensated and compensated cirrhosis will decrease by 95% from the base with 10 and 120 cases in 2030.

### *Belgium*

#### *Increased efficacy only*

There will be 2870 fewer viremic individuals in 2030 as compared to the base case, a 5% reduction. The number of HCC cases in 2030 was estimated at 580 cases, a 10% decrease from the base case. Similarly, the number of liver-related deaths will decrease by 10% from the base with 520 in 2030. Decompensated and compensated cirrhosis will decrease by 10% from the base with 1260 and 10 360 cases respectively in 2030.

#### *Increased efficacy & treatment*

There will be 42 010 fewer viremic individuals in 2030 as compared to the base case, a 90% reduction. The number of HCC cases in 2030 was estimated at 30 cases, a 95% decrease from the base case. Similarly, the number of liver-related deaths will decrease by 90% from the base with 80 in 2030. Decompensated and compensated cirrhosis will decrease by 95% from the base with 60 and 470 cases in 2030.

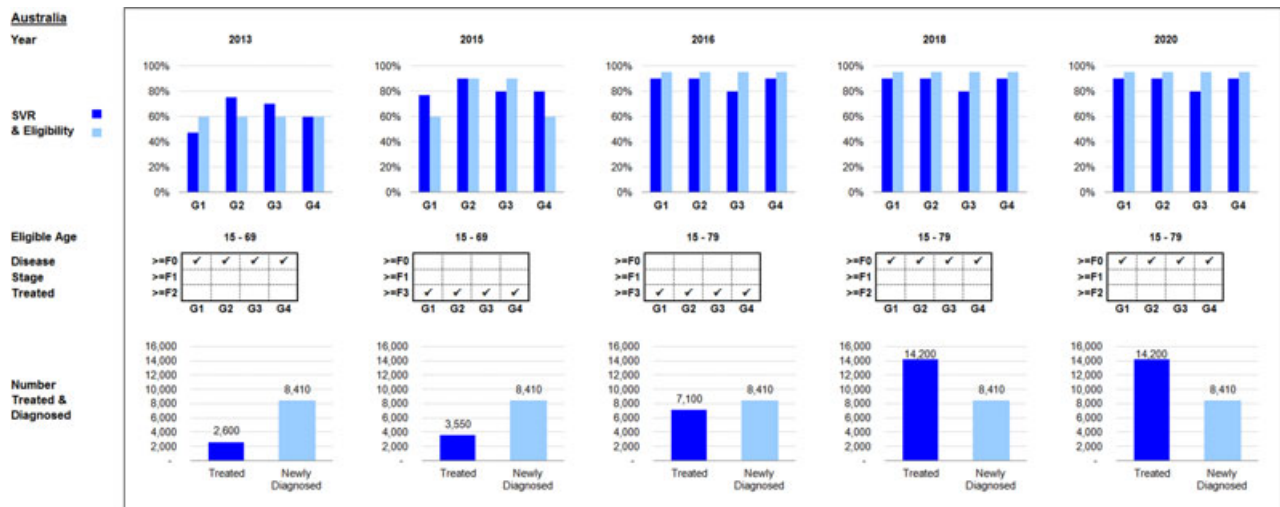


Fig. 1 Australia model inputs for increased efficacy &amp; treatment, by year.

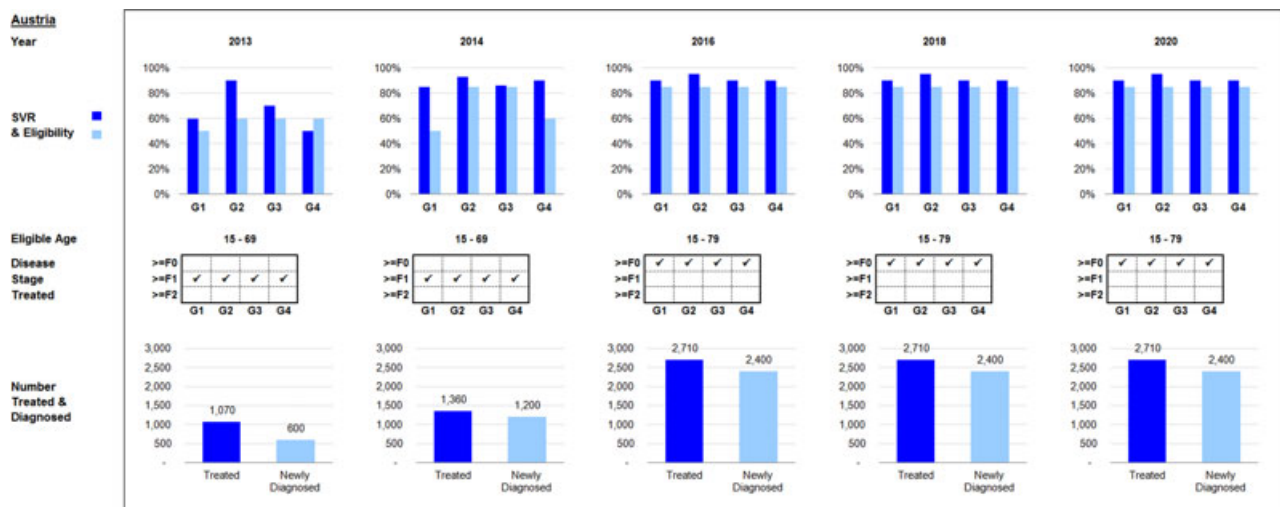


Fig. 2 Austria model inputs for increased efficacy &amp; treatment, by year.

### Brazil

#### Increased efficacy only

At the same treatment rate, the total number of HCV infection was projected to decline by 5% relative to the base cases in 2030. The number of HCC cases in 2030 was estimated at 17 860 cases, a 5% decrease from the base case. Similarly, the number of liver-related deaths will decrease by 5% from the base with 15 550 in 2030. Decompensated and compensated cirrhosis will decrease 10% and 5% respectively, from the base with 41 450 and 299 200 cases respectively in 2030.

#### Increased efficacy & treatment

In 2030, the total number of viremic infections was projected to decrease 90% from 2013–2030 to 190 570 and

there will be 1 064 060 fewer viremic individuals in 2030 as compared to the base case. With this strategy, the viremic prevalence will decline below <0.1%. The number of HCC cases in 2030 was estimated at 5140 cases, a 75% decrease from the base case. Similarly, the number of liver-related deaths will decrease by 70% from the base with 4810 in 2030. Decompensated and compensated cirrhosis will decrease by 80% with 8630 and 66 740 cases respectively in 2030.

### Czech Republic

#### Increased efficacy only

There will be 4190 fewer viremic individuals in 2030, a 10% reduction as compared to the base case. The number of HCC cases in 2030 was estimated to decline 10% or 140

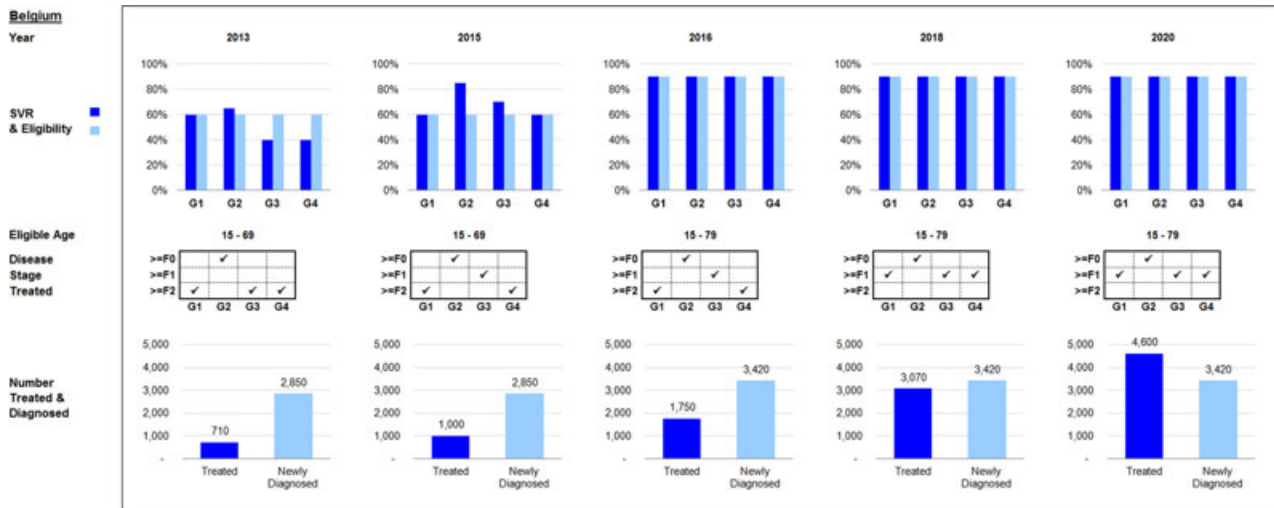


Fig. 3 Belgium model inputs for increased efficacy & treatment, by year.

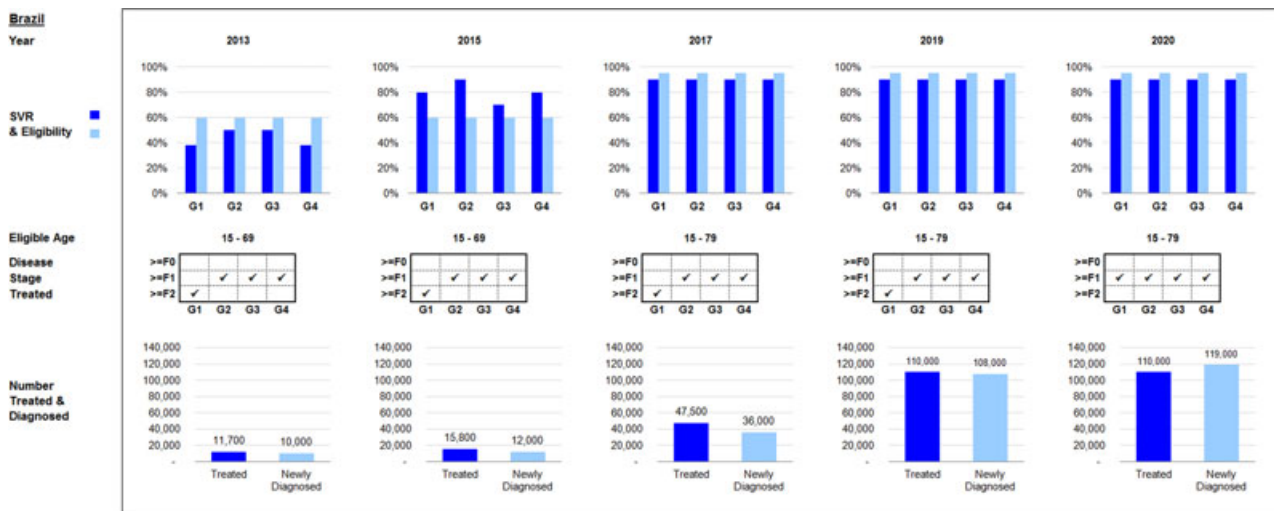


Fig. 4 Brazil model inputs for increased efficacy & treatment, by year.

cases. Similarly, the number of liver-related deaths will decrease by 10% from the base with 140 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 15% from the base with 340 and 3250 cases in 2030.

#### Increased efficacy & treatment

With an aggressive treatment and diagnosis strategy, there will be 37 600 fewer viremic individuals in 2030, a 90% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 20 cases, an 85% decrease from the base case. Similarly, the number of liver-related deaths will decrease by 80% from the base with 30 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 90% from the base with 40 and 320 cases respectively in 2030.

#### Denmark

##### Increased efficacy only

By increasing the efficacy of therapies, the number of viremic individuals will decline by 5% in 2030 as compared to the base. All associated morbidity (HCC, cirrhosis and decompensated cirrhosis) and mortality will also decline by 5% as compared to base by 2030.

##### Increased efficacy & treatment

There will be 15 090 fewer viremic individuals in 2030, a 90% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 70 cases, a 65% decrease from the base case. Similarly, the number of liver-related deaths will decrease by 70% from the base with 50 in 2030.



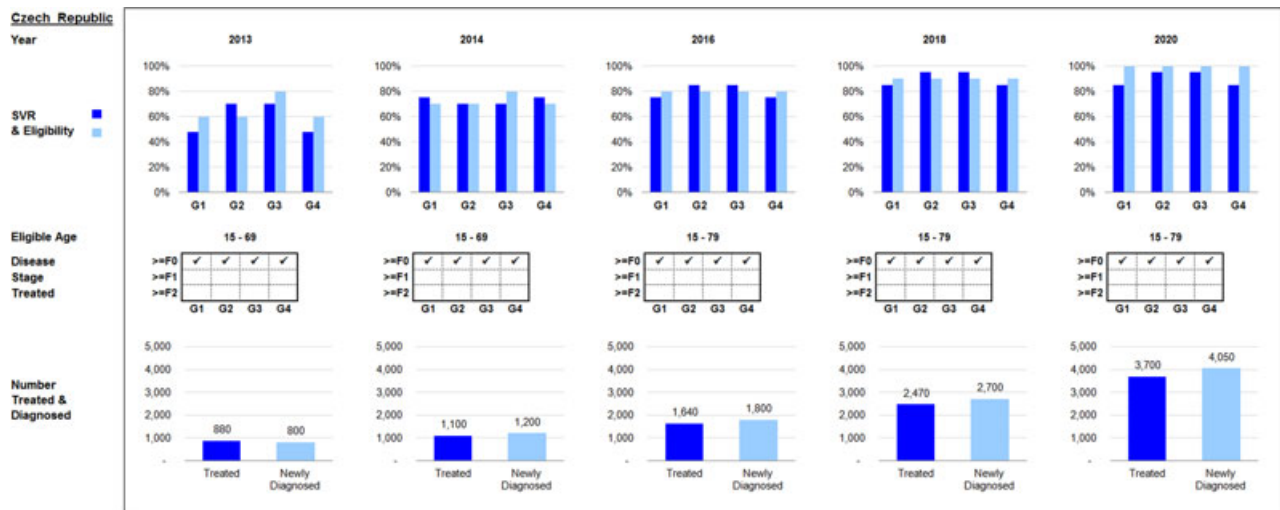


Fig. 5 Czech Republic model inputs for increased efficacy &amp; treatment, by year.

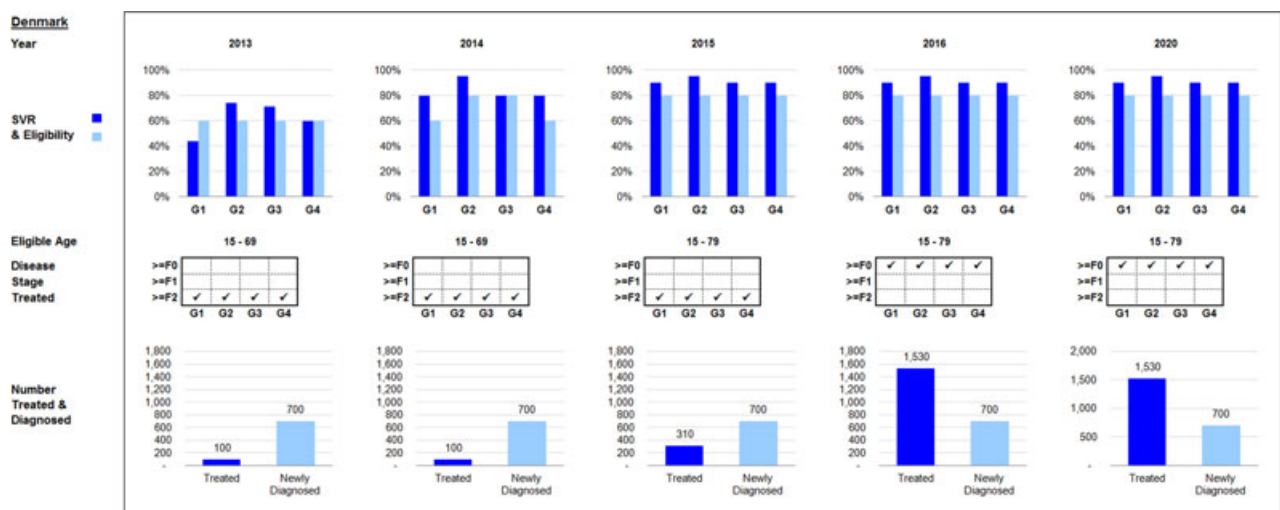


Fig. 6 Denmark model inputs for increased efficacy &amp; treatment, by year.

Decompensated and compensated cirrhosis will decrease by 75% from the base with 110 and 810 cases in 2030.

### Egypt

#### Increased efficacy only

There will be 375 550 fewer viremic individuals in 2030 as compared to the base case, a 10% reduction. The number of HCC cases in 2030 was estimated at 16 050 cases, a 15% decrease from the base case. Similarly, the number of liver-related deaths will decrease by 15% from the base with 30 730 in 2030. Decompensated and compensated cirrhosis will decrease by 20% from the base with 108 420 and 507 150 cases, respectively, in 2030.

#### Increased efficacy & treatment

There will be 4 139 770 fewer viremic individuals in 2030 as compared to the base case, a 95% reduction. By 2025,

overall viremic prevalence declines below 2%, and by 2030 viremic prevalence is estimated at 0.4%. The number of HCC cases in 2030 was estimated at 2430 cases, an 85% decrease from the base case. Similarly, the number of liver-related deaths will decrease by 75% from the base with 7500 in 2030. Decompensated and compensated cirrhosis will decrease by 90% from the base with 17 120 and 75 910 cases respectively in 2030. Finally, 1 771 650 new infections will be avoided during 2013–2030.

### England

#### Increased efficacy only

The current treatment rate is 3.8%, and changes in SVR had a noticeable impact on HCV disease burden. There will be 19 360 fewer viremic individuals in 2030 as compared to the base case, a 25% reduction. The number of HCC cases in 2030 was estimated at 810 cases, a 10% decrease



Fig. 7 Egypt model inputs for increased efficacy & treatment, by year.

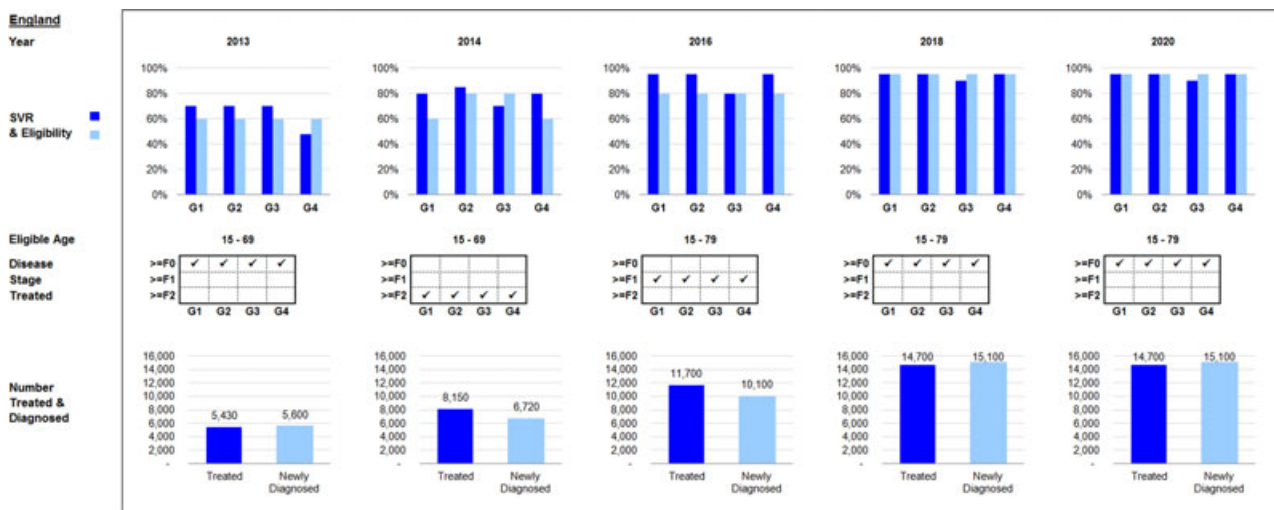


Fig. 8 England model inputs for increased efficacy & treatment, by year.

from the base case. Similarly, the number of liver-related will decrease by 15% from the base with 670 in 2030. Decompensated and compensated cirrhosis will decrease by 20% from the base with 1110 and 12 000 cases in 2030.

#### Increased efficacy & treatment

In 2030, the total number of viremic infections was projected to decrease 95% from 2013–2030 to 5300. There will be 78 330 fewer viremic individuals in 2030 as compared to the base case, a 95% reduction. The number of HCC cases in 2030 was estimated at 160 cases, an 80% decrease from the base case. Similarly, the number of liver-related deaths will decrease by 85% from the base with 120 in 2030. Decompensated and compensated cirrhosis will decrease by 90% from the base with 160 and 1700 cases respectively in 2030.

#### France

##### Increased efficacy only

In 2030, the total number of viremic infections was projected to decrease 58% from 2013–2030 to 76 000. There will be 9060 fewer viremic individuals in 2030 as compared to the base case, an 11% reduction. The number of HCC cases in 2030 was estimated at 120 cases, a 61% decrease from the base case. Similarly, the number of liver-related deaths will decrease by 59% from the base with 160 in 2030. Decompensated and compensated cirrhosis will decrease by 56% and 55%, respectively, from the base with 330 and 2580 cases in 2030.

##### Increased efficacy & treatment

In 2030, the total number of viremic infections was projected to decrease 97% from 2013–2030 to 6200. There

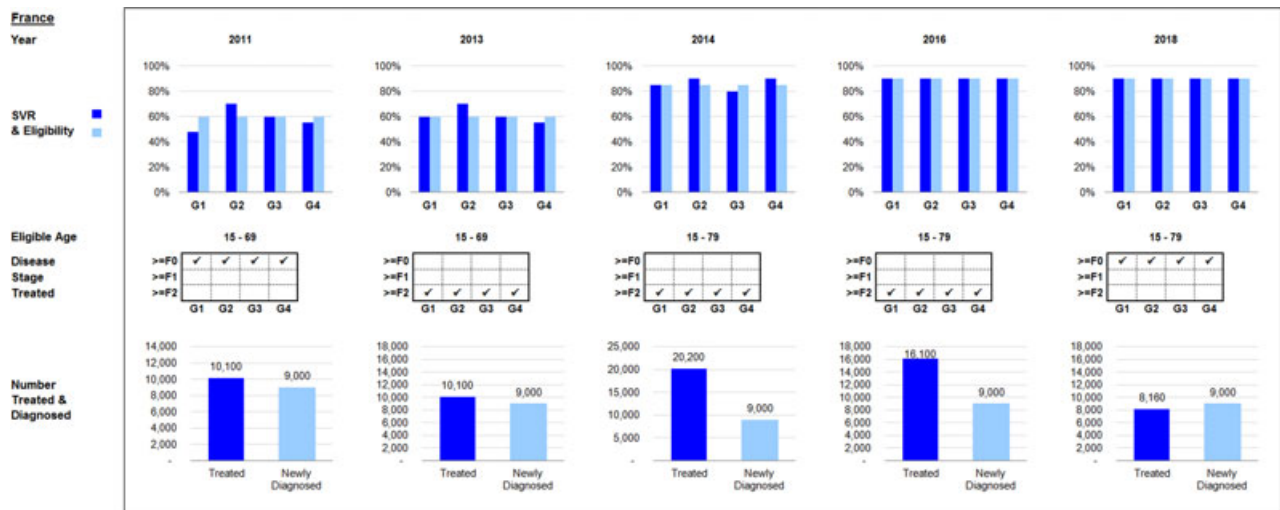


Fig. 9 France model inputs for increased efficacy &amp; treatment, by year.

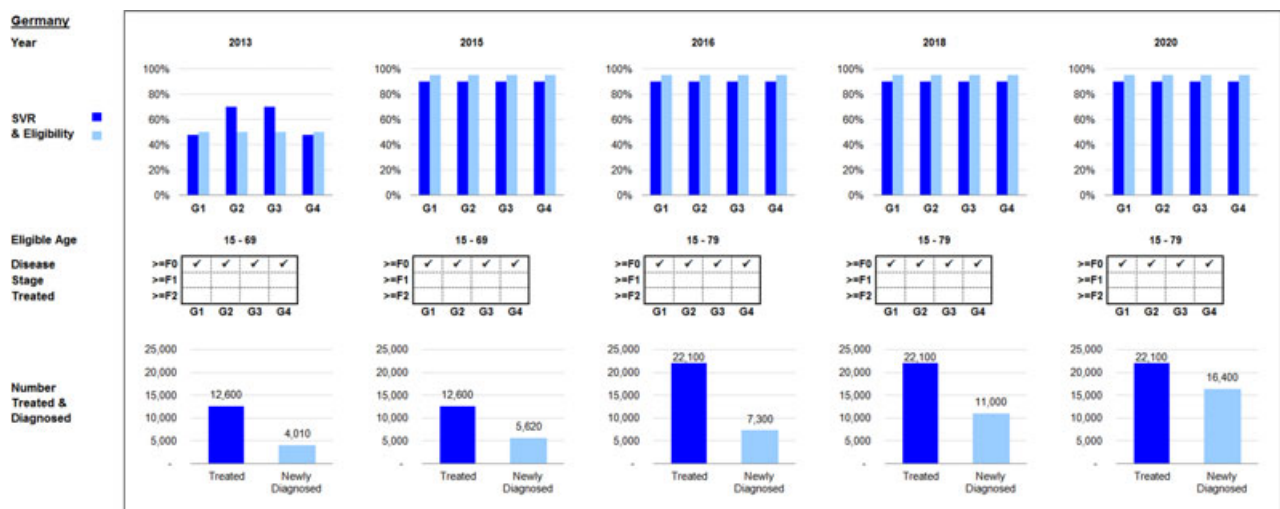


Fig. 10 Germany model inputs for increased efficacy &amp; treatment, by year.

will be 78 930 fewer viremic individuals in 2030 as compared to the base case, a 93% reduction. By 2030, the overall viremic prevalence rate was estimated at <0.01%. The number of HCC cases in 2030 was estimated at 40 cases, a 87% decrease from the base case. Similarly, the number of liver-related deaths will decrease by 85% from the base with 60 in 2030. Decompensated and compensated cirrhosis will decrease by 84% and 85%, respectively, from the base with 120 and 840 cases in 2030.

### Germany

#### Increased efficacy only

There will be 49 930 fewer viremic individuals in 2030 as compared to the base case, a 40% reduction. The number

of HCC cases in 2030 was estimated at 930 cases, a 45% decrease from the base case. Similarly, the number of liver-related deaths will decrease by 40% from the base with 840 in 2030. Decompensated and compensated cirrhosis will decrease by 55% from the base with 1030 and 11 190 cases respectively in 2030.

#### Increased efficacy & treatment

There will be 102 270 fewer viremic individuals in 2030 as compared to the base case, an 85% reduction. The number of HCC cases in 2030 was estimated at 460 cases, a 70% decrease from the base case. Similarly, the number of liver-related deaths will decrease by 75% from the base with 390 in 2030. Decompensated and compensated cirrhosis will decrease by 80% from the base with 440 and 5480 cases respectively in 2030.

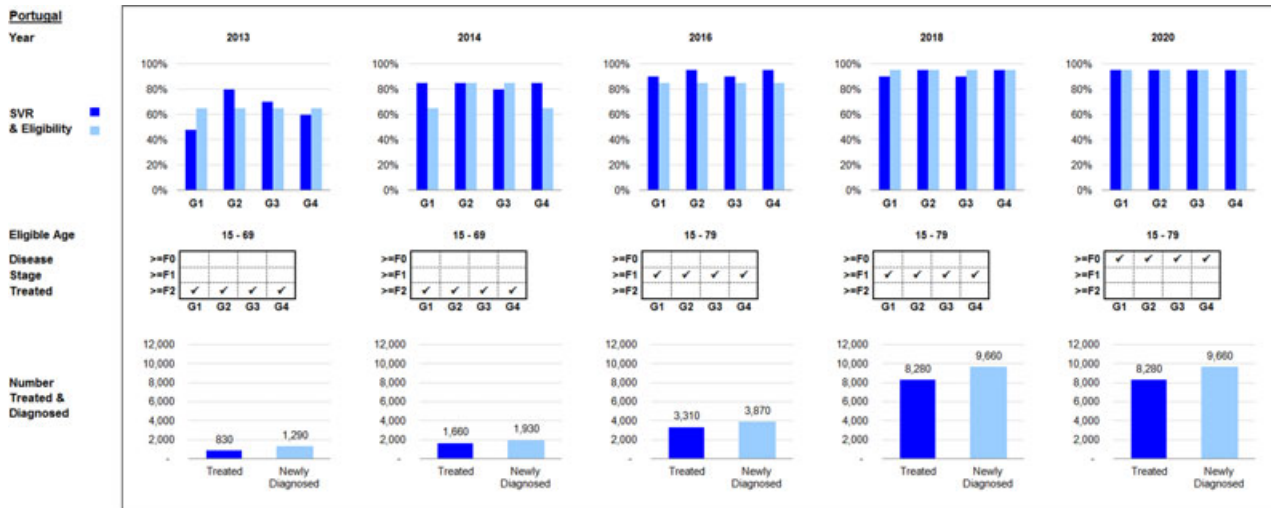


Fig. 11 Portugal model inputs for increased efficacy & treatment, by year.

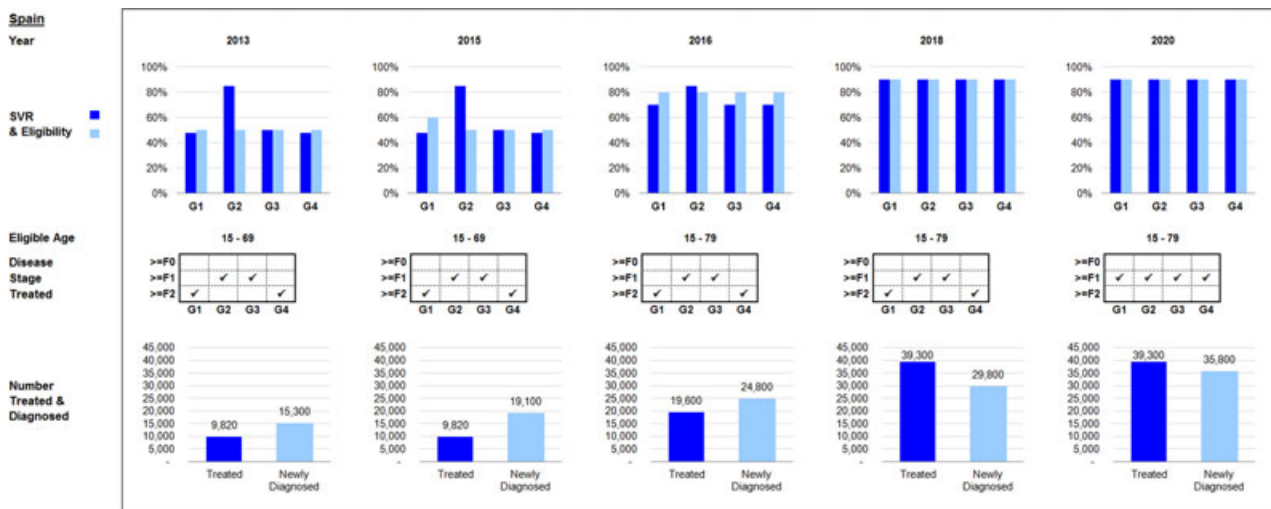


Fig. 12 Spain model inputs for increased efficacy & treatment, by year.

## Portugal

### Increased efficacy only

There will be 4160 fewer viremic individuals in 2030 as compared to the base case, a 5% reduction. The number of HCC cases in 2030 was estimated at 1910 cases, a 5% decrease from the base case. Similarly, the number of liver-related deaths will decrease by 5% from the base with 1590 in 2030. Decompensated and compensated cirrhosis will decrease by 5%, respectively, from the base with 4590 and 23 370 cases respectively in 2030.

### Increased efficacy & treatment

This scenario decreased HCV-related mortality by 8500 deaths (75%) by 2030. HCV-related liver cancers decreased by 1600 cases (90%). Cases of decompensated cirrhosis

decreased by 3600 (85%). The number of total infected declined by 75 800 (85%) as compared to the base case. By 2030, the viremic population was estimated at 11 540 with an overall viremic prevalence rate of 0.1%.

## Spain

### Increased efficacy only

There will be 50 100 fewer viremic individuals in 2030 as compared to the base case, a 20% reduction. The number of HCC cases in 2030 was estimated at 3890 cases, a 15% decrease from the base case. Similarly, the number of liver-related deaths will decrease by 15% from the base with 3190 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 20% from the base with 5310 and 58 000 cases, respectively, in 2030.





Fig. 13 Sweden model inputs for increased efficacy &amp; treatment, by year.

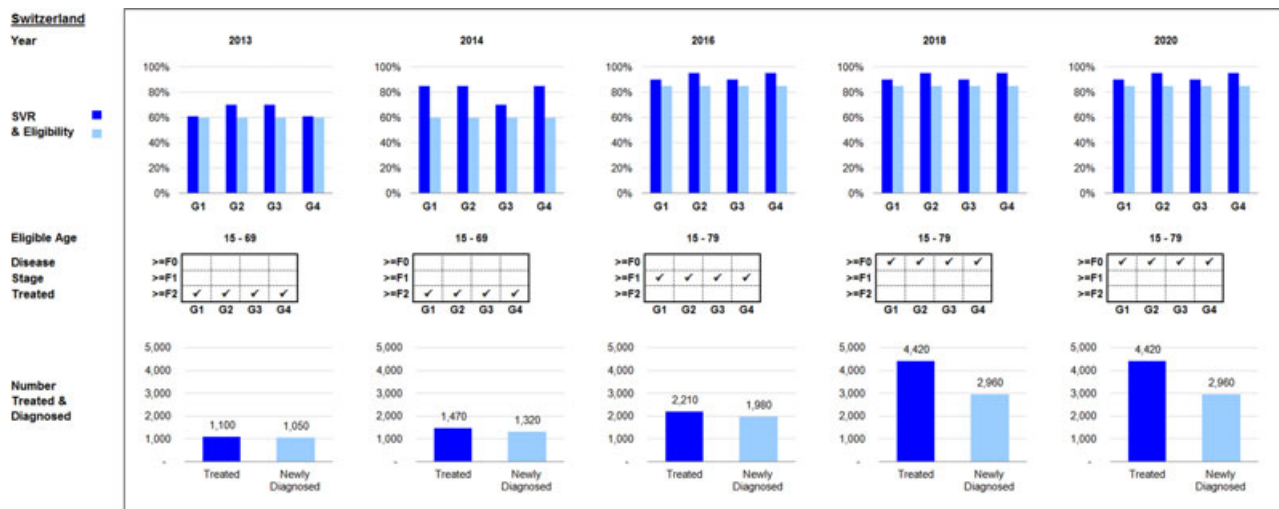


Fig. 14 Switzerland model inputs for increased efficacy &amp; treatment, by year.

### Increased efficacy & treatment

With an increase in diagnosis of 15% in 2018, there will be 128 000 fewer viremic individuals in 2030 as compared to the base case, a 45% reduction. The number of HCC cases in 2030 was estimated at 2160 cases, a 50% decrease from the base case. Similarly, the number of liver-related deaths will decrease by 50% from the base with 1930 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 60% from the base with 2780 and 30 300 cases respectively in 2030.

### Sweden

#### Increased efficacy only

There will be 3750 fewer viremic individuals in 2030 as compared to the base case, a 10% reduction. The number

of HCC cases in 2030 was estimated at 160 cases, a 45% decrease from the base case. Similarly, the number of liver-related deaths will decrease by 50% from the base with 90 in 2030. Decompensated and compensated cirrhosis will decrease by 60% from the base with 150 and 1440 cases respectively in 2030.

#### Increased efficacy & treatment

There will be 28 960 fewer viremic individuals in 2030 as compared to the base case, a 90% reduction. The number of HCC cases in 2030 was estimated at 70 cases, a 75% decrease from the base case. Similarly, the number of liver-related deaths will decrease by 80% from the base with 40 in 2030. Decompensated and compensated cirrhosis will decrease by 85% from the base with 50 and 460 cases respectively in 2030.

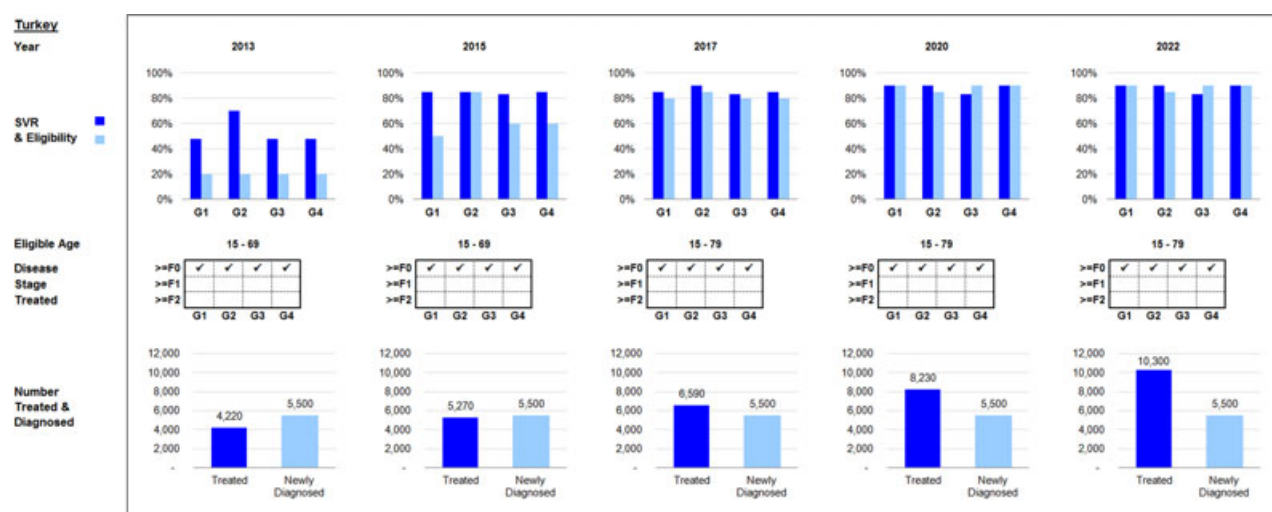


Fig. 15 Turkey model inputs for increased efficacy & treatment, by year.

## Switzerland

### Increased efficacy only

There will be 4510 fewer viremic individuals in 2030 as compared to the base case, a 5% reduction. The number of HCC cases in 2030 was estimated at 670 cases, a 10% decrease from the base case. Similarly, the number of liver-related deaths will decrease by 10% from the base with 580 in 2030. Decompensated and compensated cirrhosis will also decrease by 10% from the base with 1570 and 11 100 cases respectively in 2030.

### Increased efficacy & treatment

There will be 53 000 fewer viremic individuals in 2030 as compared to the base case, an 85% reduction. The number of HCC cases in 2030 was estimated at 210 cases, a 70% decrease from the base case. Similarly, the number of liver-related deaths will decrease by 70% from the base with 200 in 2030. Decompensated and compensated cirrhosis will decrease 80% from the base with 350 and 2360 cases respectively in 2030.

## Turkey

### Increased efficacy only

There will be 12 100 fewer viremic individuals in 2030 as compared to the base case, a 5% reduction. The number of HCC cases in 2030 was estimated at 3620 cases, a 5% decrease from the base case. Similarly, the number of liver-related deaths will decrease by 5% from the base with 3290 deaths in 2030. Decompensated and compensated cirrhosis will decrease 5% from the base, with 8450 and 68 000 cases in 2030.

### Increased efficacy & treatment

There will be 76 700 fewer viremic individuals in 2030 as compared to the base case, a 20% reduction. The num-

ber of HCC cases in 2030 was estimated at 2850 cases, a 25% decrease from the base case. Similarly, the number of liver-related deaths will decrease 25% from the base with 2640 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 25% and 30%, respectively, from the base with 6490 and 51 340 cases respectively in 2030.

## DISCUSSION

This analysis suggests that successful diagnosis and treatment of a small proportion of patients can contribute significantly to the reduction of disease burden in the countries studied. The largest reduction in HCV-related morbidity and mortality occurs when increased treatment is combined with higher efficacy therapies, generally in combination with increased diagnosis. However, for most countries presented, this will require a 3–5 fold increase in diagnosis and/or treatment. Thus, building the public health and clinical provider capacity for improved diagnosis and treatment will be critical.

Using today's treatment paradigm, the total number of HCV-infected individuals is expected to decline in Austria, Belgium, Brazil, Denmark, Egypt, England, France, Germany, Portugal, Spain, Sweden, Switzerland and Turkey and remain relatively flat in Australia and Czech Republic. However, HCV-related mortality and morbidity is expected to increase in all countries with the exception of France, which has had a high treatment rate [4]. This analysis demonstrated that with a treatment rate of approximately 10%, it is possible to achieve elimination of HCV (>90% decline in total infections by 2030) (Table 1). In addition, it was shown that switching to high SVR therapies would reduce HCV mortality and morbidity. This impact is magnified in countries which already have a treatment rate of 2.5–5.8% – Austria, England, France, Germany and Sweden (Table 1).

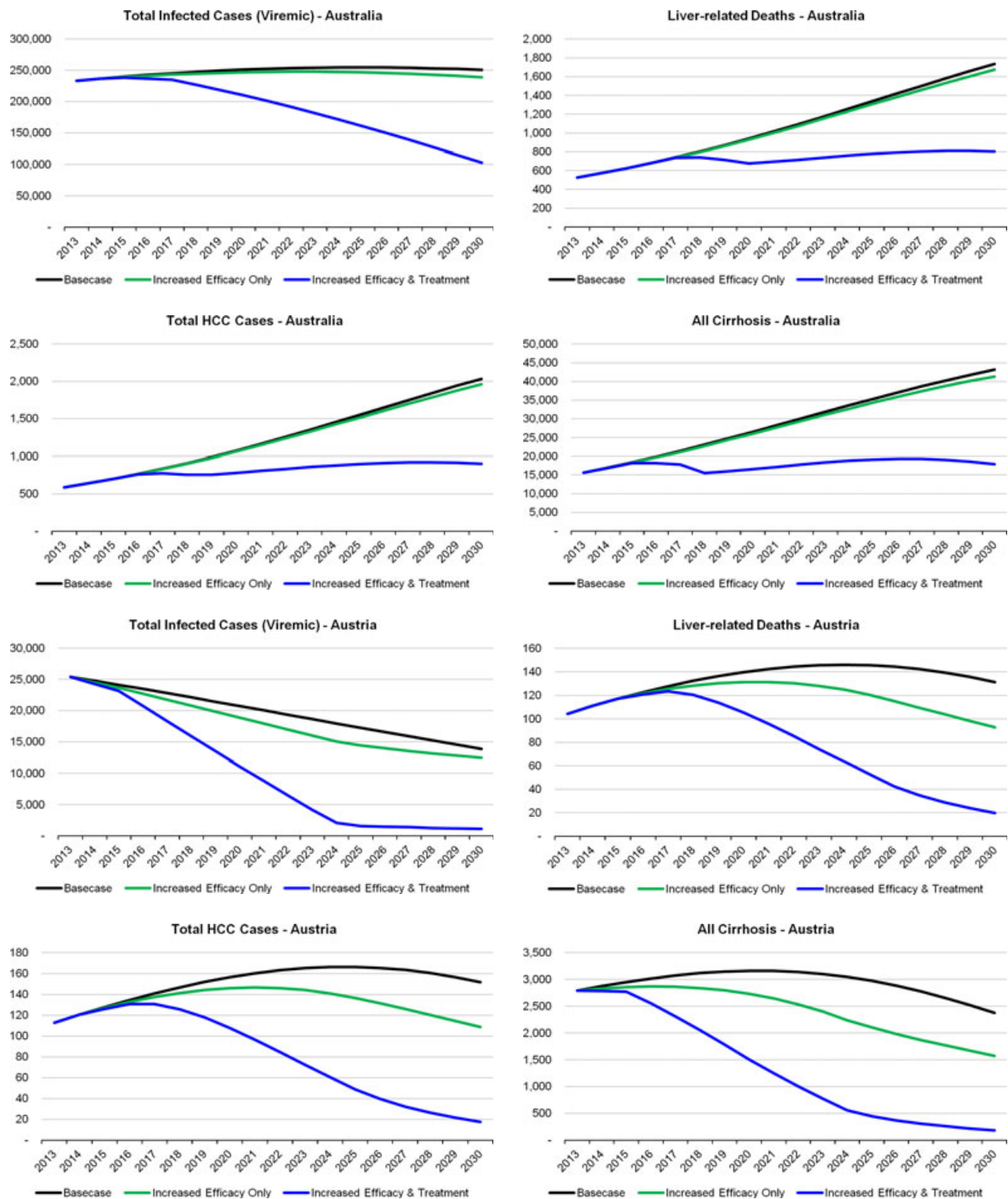


Fig. 16 Change in HCV morbidity and mortality, by scenario, 2013–2030.

As part of this analysis, two broad categories of strategies were investigated: disease control and HCV elimination. In the former case, the future SVR as well as eligible, treated and diagnosed populations were modified to keep

HCV morbidity and mortality at the same level as 2013. In the latter case, the same variables were modified to get the total number of infections below 10% of 2013 values. In several countries, (e.g. Australia and Portugal) disease con-

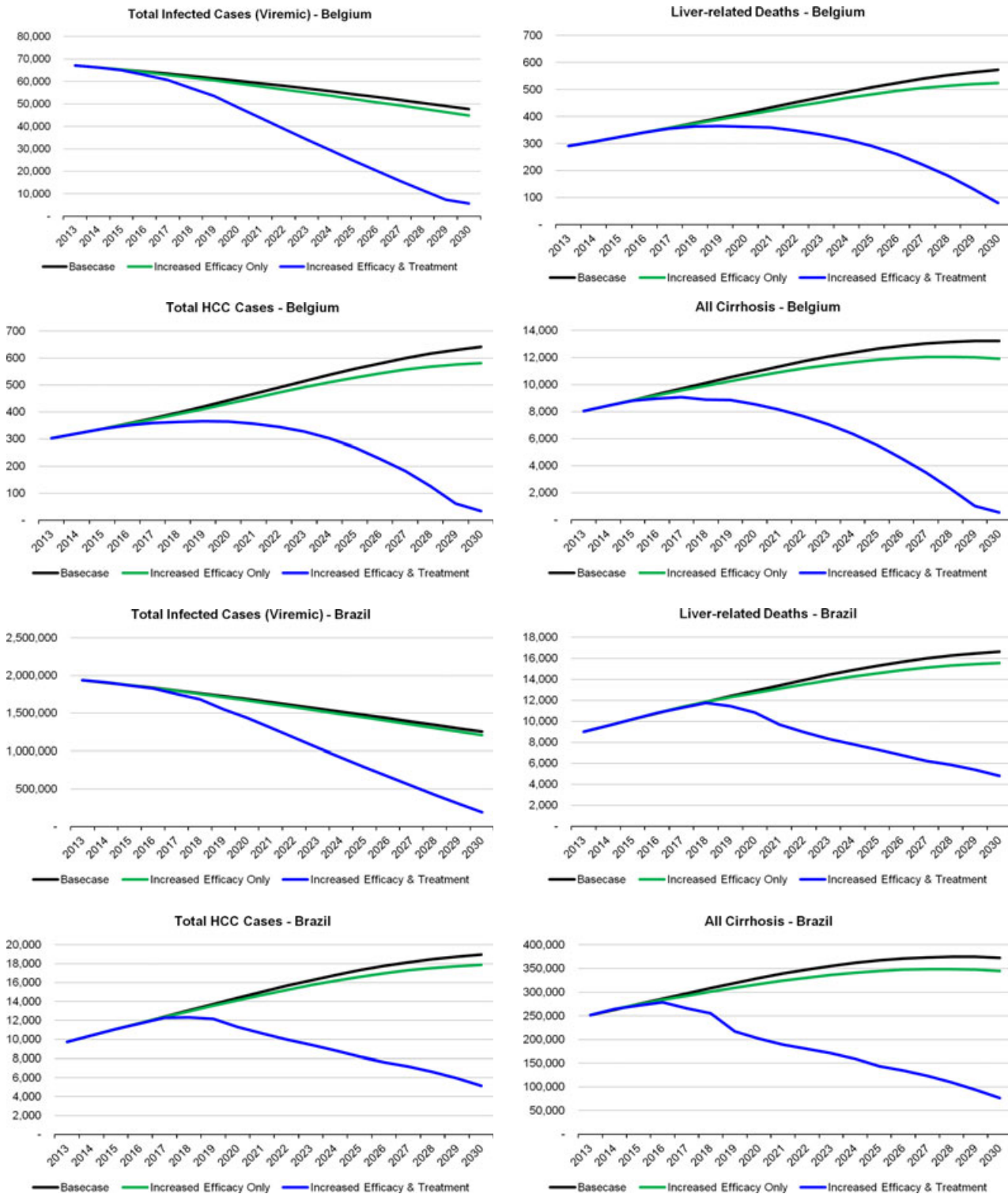


Fig. 16 (Continued).

trol had the same results as elimination, and in total all countries but Spain and Turkey were able to achieve HCV elimination. This included Egypt, which considered a strategy to achieve 2% prevalence in 10 years. The same strat-

egy projected a 96% reduction in HCV infections by 2030. Spain identified a strategy to keep the 2030 mortality and morbidity below 2013 levels and achieve HCV control. The scenarios analyzed for Turkey assessed the impact of unre-



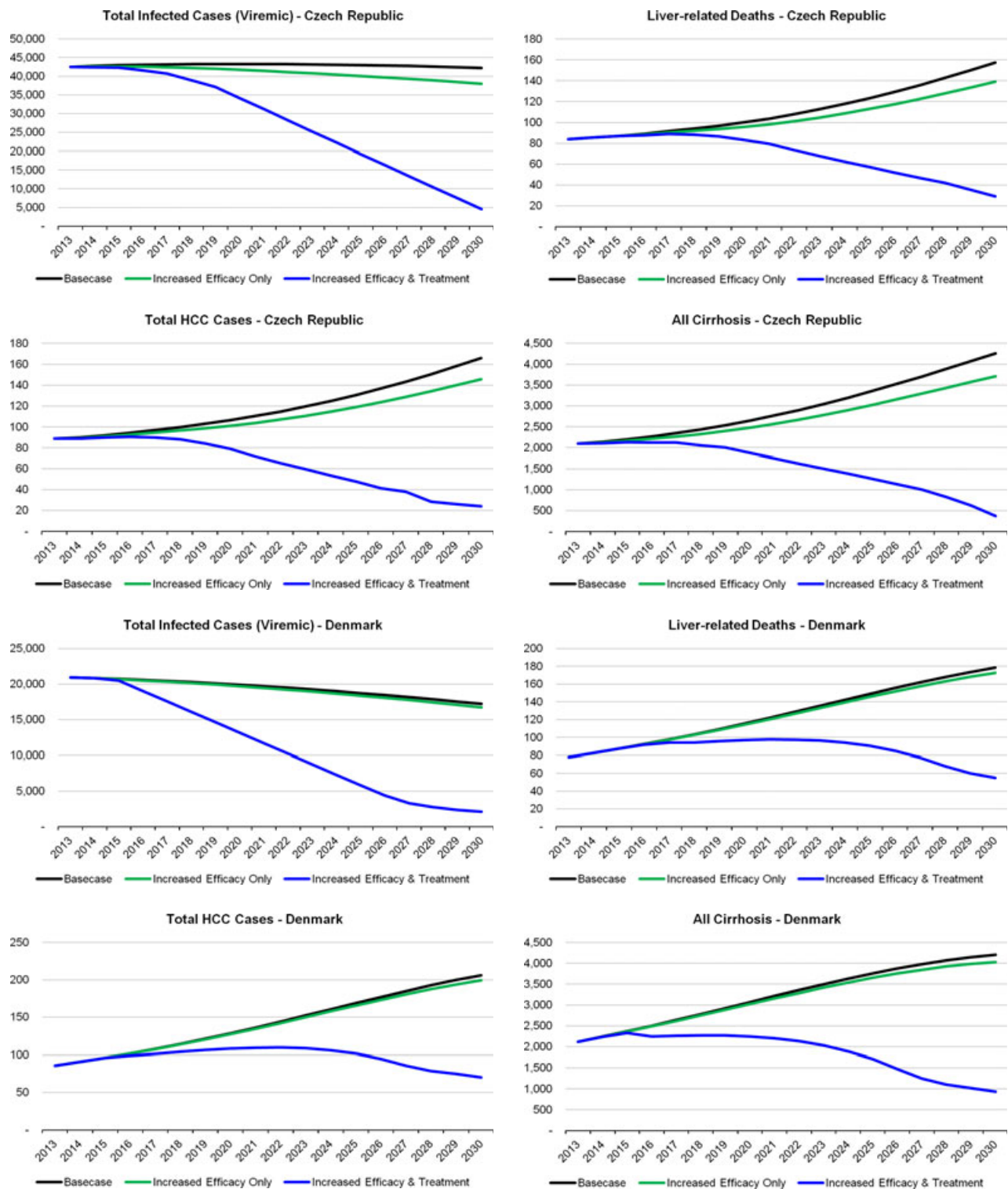


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stricted access to the new therapies combined with a 25% increase in treatment rate.

A key observation of this analysis was that increased treatment and SVR in patients who were >F2 had the largest impact in reducing morbidity and mortality. How-

ever, treating patients who were F0–F1 had the largest impact on transmission of HCV among active IDU patients, who had often contracted the virus recently. In addition, treatment of F0–F1 was necessary if the goal of the strategy were to eliminate HCV. In fact, the most

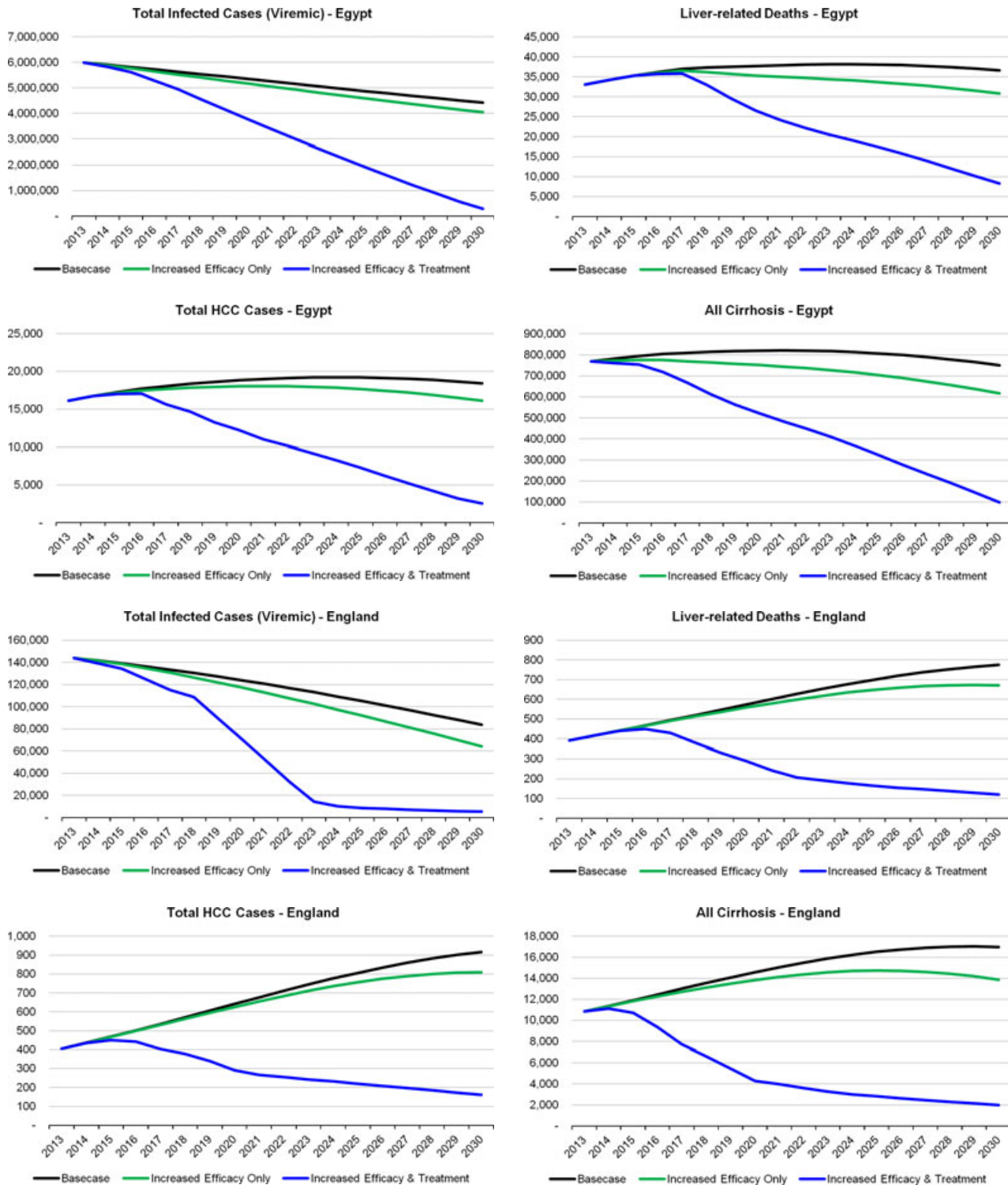


Fig. 16 (Continued).

effective strategy identified was to increase treatment in >F2 patients and once that patient pool was depleted, expand treatment to all. However, this strategy did have a major drawback. The HCV-infected population is aging, and waiting to treat early stage patients meant that some

would be too old to be treated. The age of the infected population was one of the key variables for not being able to achieve zero infections in a country. Another factor that prevented achieving zero infections was immigration. With today's mobile society, it was nearly impossible to

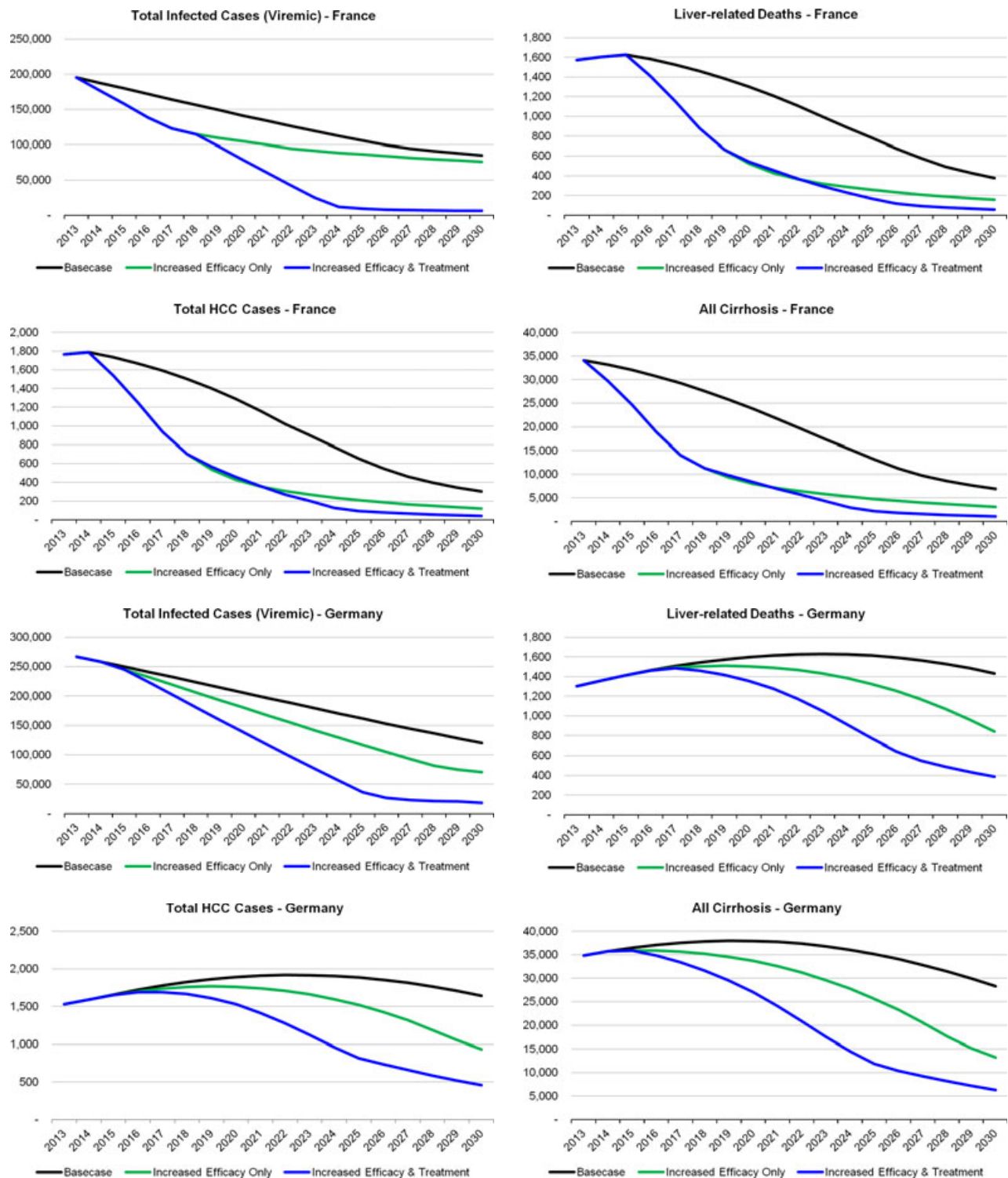


Fig. 16 (Continued).

eradicate HCV in a country. The modeling suggested that some new cases always entered the country through immigration. The long-term goal of HCV eradication will require a global effort to eliminate the virus across borders.

### Australia

The main mode of new infections was IDU, with a relatively high rate of new infections [4,20]. This meant that with current treatment rate and SVR, the total number of

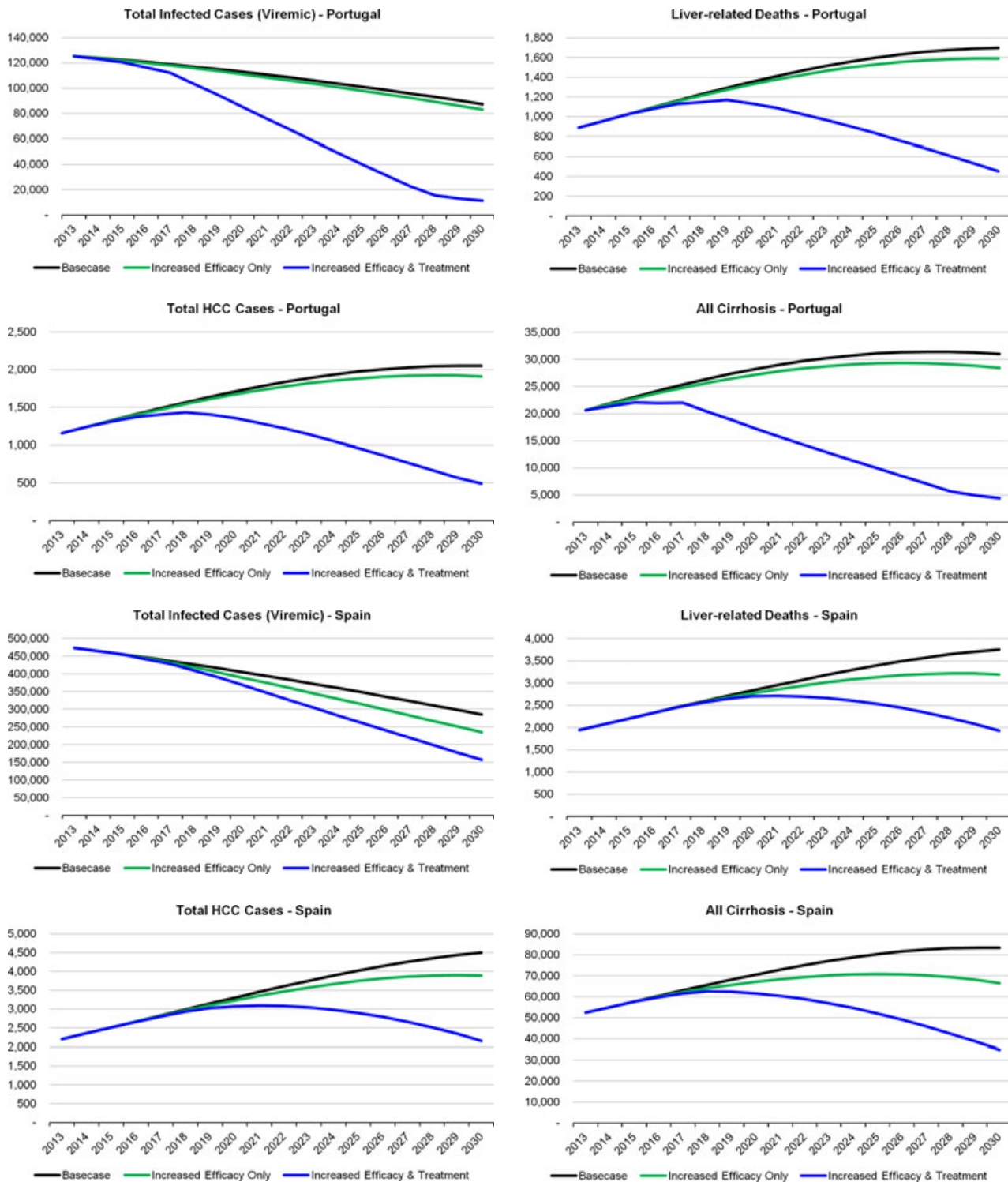


Fig. 16 (Continued).

infections will remain the same. However, the incidence of advanced liver disease will continue to increase. Liver disease already accounts for the greatest burden in hospital admissions among older HCV mono-infected adults in New

South Wales [21]. In addition, hospital admissions for HCV-related liver morbidity have recently increased [22]. A marked increase in HCV treatment uptake will be required to reduce the incidence of advanced liver disease



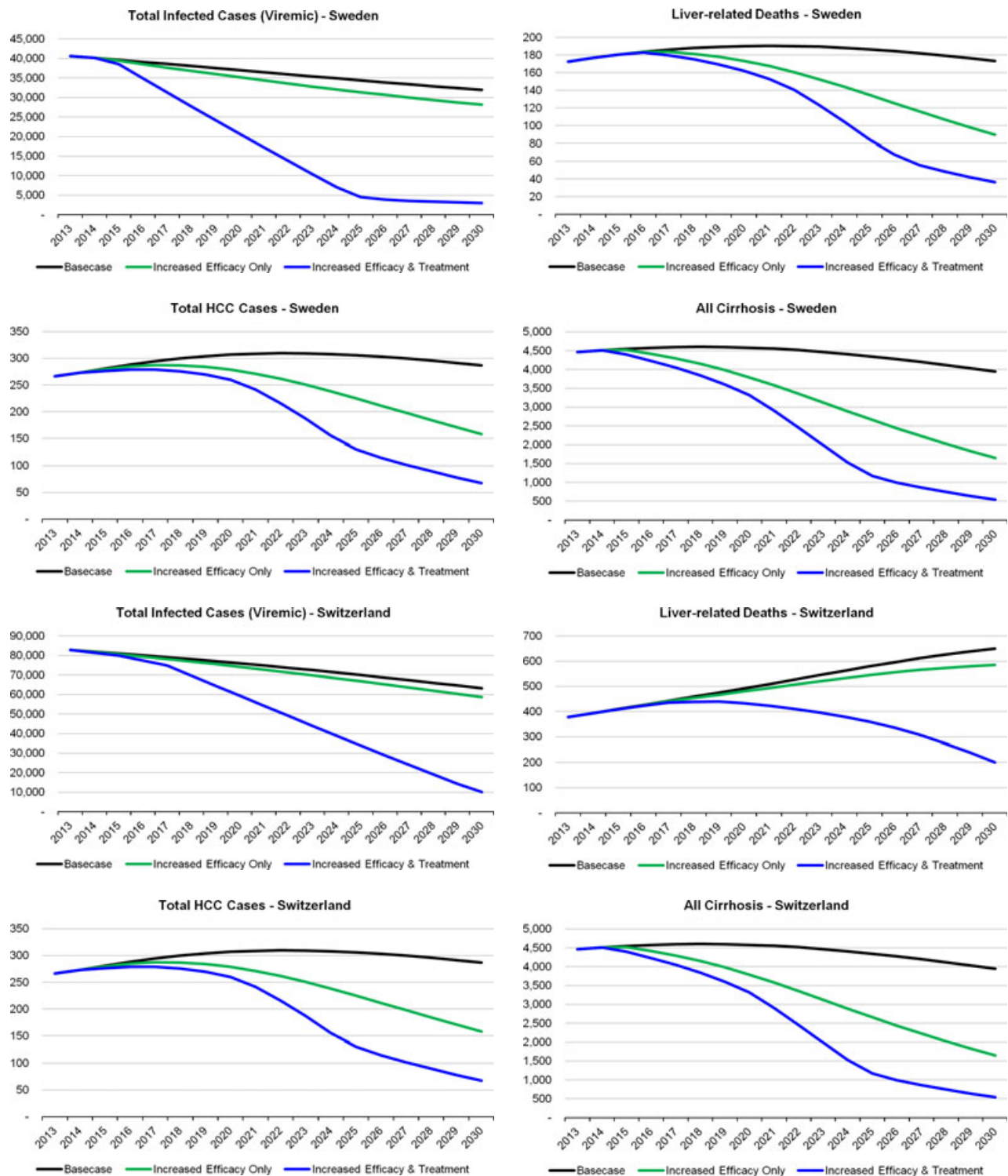


Fig. 16 (Continued).

complications and deaths. Increased treatment efficacy had a substantial impact on future disease burden. The effect of increasing the treated population along with improved efficacy was notably larger.

#### Austria

The treatment rate in Austria is currently about 4%. This meant that simply increasing SVR had a large impact (30–

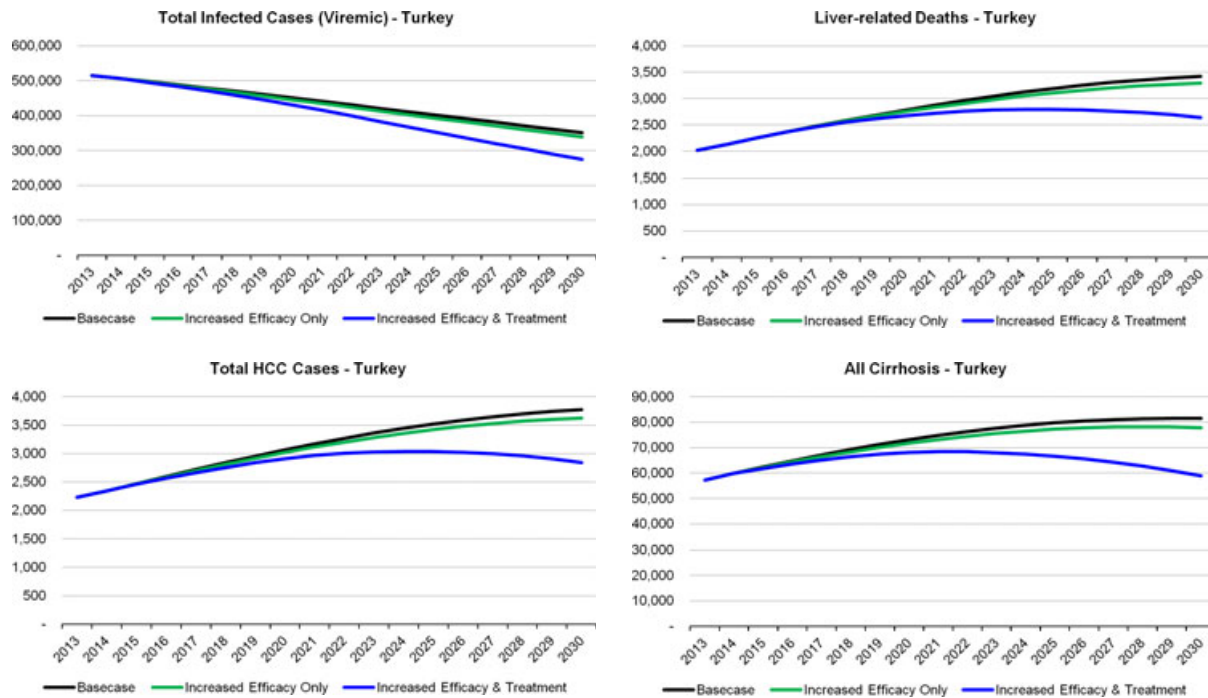


Fig. 16 (Continued).

40% reduction) on the HCV morbidity and mortality. A treatment rate of 13% (increased gradually over time) was required to achieve a 90% reduction in the total HCV infections. The increased treatment was only required until 2025 before the patient pool was depleted.

### Belgium

Increasing treatment efficacy without a concurrent increase in treatment rate had only a small impact (5–10% reduction) on total HCV infections and HCV-related morbidity. This was primarily attributable to the low treatment rate (1.1%). A dramatic impact (85–95% reduction) was achievable through an increase in the treatment rate (9.5%), which could be implemented stepwise from 2015 to 2020. Treatment at this rate was only necessary until 2030 before the patient pool was depleted.

### Brazil

Increasing treatment efficacy resulted in future decreases in HCV-related morbidity and mortality without a need to grow the diagnosed or treated population. However, the impact of treatment was much larger, demonstrating that a substantial increase in treatment (and diagnosis) was necessary to realize >90% reduction in HCV cases as well as a major reduction in HCV-related morbidity and mortality. This was driven by a relative high infection rate (1% viremic in 2013) and low treatment rate (0.6% in 2013) [4,20]. The treatment rate required to eliminate HCV was

approximately 7.8%, in line with the required treatment rate in other countries (Table 1). The increase in treatment was only required until 2029 before the pool of infected patients was depleted. Strategies to address HCV disease burden should be implemented early, through government guidelines, before patients develop liver failure or HCC. Early treatment is particularly important for improving SVR rates, which have typically been lower than those reported for other countries [23,24].

### Czech Republic

If the treatment efficacy increases, due to the use of highly effective and better-tolerated antiviral therapies, this analysis suggests a modest decrease (10%) in HCV-related mortality by 2030. Thus, to mitigate the impending burden of HCV-related liver disease in the coming years, efforts to improve screening and treatment are needed. Assuming an increase in screening and treatment, in conjunction with new DAAs, the total viremic rate was anticipated to decrease to less than 5000 infected individuals in 2030. This reduction assumed no fibrosis staging or age restrictions are added to the current SOC. Moreover, it assumed an increase in diagnosis from 800 individuals a year to just over 4000 individuals by 2020.

A reliable general screening program is crucial to HCV elimination. Without an increase in diagnosis, the number of treated patients would exceed eligible patients by 2022; thus, both factors must be implemented to achieve significant reductions in disease burden. Czech screening pro-

grams that have already been adopted have contributed significantly to a decrease in nosocomial transmission of HCV infection. For example, in patients on maintenance hemodialysis, there was a decrease in anti-HCV prevalence from 30% in the 1990s to less than 5% to date [25]. With rapidly evolving care for HCV patients and increasingly effective and tolerated all-oral antiviral regimens, all patients identified by means of screening programs could receive antiviral treatment. Based on the recommendations for birth cohort screening developed by the Centers for Disease Control and Prevention (CDC) in the United States, the most effective screening program in the Czech Republic would be to target individuals born between 1965 and 1995 [26]. This population cohort reflects 74% of the infected viremic population (Fig. 2).

Owing to a later onset of peak infectivity, the Czech Republic is in a unique situation to curb the epidemic of HCV in the country if resources are effectively mobilized. The results presented may facilitate disease forecasting and the development of rational strategies for HCV management.

### Denmark

The current treatment rate (0.5%) is reflective of conservative treatment practices as well as the warehousing of patients in anticipation of improved treatment options [27]. Improved therapies are expected to decrease the amount of time and follow-up necessary per patient, thus increasing the capacity of treating physicians. In the increased efficacy and treatment analysis, near elimination of HCV could be achieved by increasing the treatment rate to 8% in line with the requirement observed in other countries. This strategy also helps manage the disease burden and keeps the number of individuals with cirrhosis, HCC and the associated liver-related deaths at or below 2013 levels. In the absence of increased treatment, increased efficacy of new therapies has a small impact (5%) on total HCV infections as well as HCV-related morbidity. With gradual increases leading to a treatment rate of 8.1%, total HCV infections were decreased 90% from the base, and HCV-related morbidity was decreased 65–75%. Physician capacity was not expected to be a limiting factor for treatment, as evidenced by high treatment rates for HIV patients in the era of highly active antiretroviral therapy in Denmark. In the modeled scenario, increased diagnosis was not a requirement for increased treatment. Although screening efforts may not be necessary, strategies to implement this scenario should consider ways to contact previously diagnosed patients.

### Egypt

Globally, Egypt has the highest HCV prevalence. This analysis showed that while the prevalence of HCV in Egypt has already peaked, the burden of disease will continue to

grow for decades. The Egyptian National Control Strategy for Viral Hepatitis notes the importance of reducing prevalence of HCV in Egypt, as well as increasing awareness, diagnosis and treatment [28]. In addition, the national strategy highlights the importance of preventing transmission in medical settings and improving the safety of injections given in non-medical settings. The Egyptian Ministry of Health and Population implemented a program in 2001 to reduce healthcare-related HCV transmission [29]. As the majority of infected individuals in Egypt are unaware of their infection, the national control strategy also emphasizes efforts to increase awareness and testing for HCV. As part of the Viral Hepatitis National Treatment Program, 23 national treatment centers had been established by 2012, and 190 000 patients were treated from 2008–2011 [29].

The scenarios presented have the potential to reduce the burden of HCV-related morbidity and mortality in Egypt, including a reduction of viremic prevalence to <2% by 2025 in the scenario focused on increased treatment efficacy, increased treatment and reduced incidence. However, implementation of this scenario will depend upon a number of constraints. The number of diagnosed individuals needs to be increased considerably, with a similar increase in treatment. In addition, substantial reductions in prevalence are dependent upon lower numbers of new infections. Implementation would depend upon the capacity of the healthcare system to diagnose and treat new patients, as well as executing effective measures to reduce incidence.

### England

Increasing treatment efficacy resulted in moderate decreases in HCV-related morbidity and mortality (10–20% reductions). Reductions were driven by an annual treatment rate of 3.8%, but were tempered by the 4000 new infections occurring annually. Minimizing the HCV burden of disease was best achieved in England through short-term stepwise increases in treatment, to 14.2% in 2018. This treatment rate was only necessary until 2026, when the patient pool was depleted. Although F0–F4 patients are currently treated in England, this strategy was modeled to address patients with advanced disease first (F2–F4 in 2014), with increasing eligibility on a biannual basis (F1–F4 in 2016 and F0–F4 in 2018). The effect was an 85% reduction in HCV-related mortality and a 90% reduction in HCV-related decompensated cirrhosis.

### France

This analysis demonstrates that the impact of increased treatment efficacy is substantial in France, where the treatment rate is 5.2%. In addition, elimination of HCV is possible in France with an increase in treatment, as well as extension of treatment to older patients (aged 75–84 years) and those with fibrosis scores  $\geq$ F0. Because a

large proportion of infected individuals in France are older adults [30], it is necessary to treat these individuals to reduce disease burden. While the treated population is substantial, current uptake of treatment is limited by concerns about the safety of Peg-IFN/RBV/protease inhibitor regimens [17,31,32]. Given the already high treatment rate in France, increased treatment is only required until 2024 before nearly everyone who is eligible for treatment has been cured.

### *Germany*

A treatment rate of 4.7% in Germany and “treat everyone” approach were important drivers for the large impact observed with increasing SVR while keeping the treatment rate constant. In addition, in the model, close to 60% of the infected population were estimated to be already diagnosed [4]. Thus, there was a pool of available patients for any strategies that involve an increase in treatment.

HCV could be eliminated in Germany within 10–15 years, by a onetime 75% increase in the number of treated patients with high SVR. However, to reduce the total number of infections by 93%, as compared to today, a stepwise increase in the number of newly diagnosed patients was required. The combination of increased treatment and higher cured rates was forecasted to deplete the eligible population by 2027 when less than 3000 patients would need to be treated. The analysis indicated that not all patients could be treated or cured without increasing treatment age to include those above 75 years old. Modest increases in treatment have the potential to substantially reduce the burden of HCV in Germany, but this is only possible with increased screening efforts.

### *Portugal*

This study demonstrates that while the overall number of infected individuals is expected to decrease, the burden of chronic hepatitis C infection in Portugal is expected to increase substantially through 2030. Already, there is evidence suggesting that recent increases in HCC in Portugal are partially due to the increased burden of chronic HCV infection [33]. Reductions in HCV-related morbidity and mortality in Portugal are achievable, with great impact on future burden of disease, through high diagnosis and treatment rates. A scenario that includes increased treatment and efficacy demonstrates that near elimination of hepatitis C virus is achievable, with great impact on future burden of disease. By making large increases in diagnosis and treatment, the viremic prevalence rate declined to 0.1% by 2030, with fewer than 12 000 chronically infected individuals. New antiviral therapies and increased treatment can have a dramatic impact on the burden of HCV-related morbidity [34]. The results of this analysis may help public

health authorities in the design of national treatment strategies.

### *Spain*

Incidence has declined significantly since its peak in 1991 due to the implementation of HCV antibody screening in the blood supply; however, disease burden will continue to increase as the infected cohort ages. It is expected that the second-wave of DAA based therapy and, more importantly, the implementation of IFN-free regimens, and potentially ribavirin-free regimens, in the next three to four years, will yield a chance of HCV cure close to 90%. However, even with considerable enhancement of treatment response, the analysis predicts only a small impact on the burden of disease if treatment uptake remains unchanged. Thus, to mitigate HCV related liver disease in the coming years, an increase in treatment is needed.

Under current treatment, the number of patients in need of liver transplantation, independent of age restrictions, was forecasted to double by 2030, suggesting considerable need for action. With an attributable fraction of 31.6% in 2012, HCV is a leading indicator for liver transplantation. According to Organización Nacional de Trasplantes, there were 641 individuals on the transplant waiting list in 2011 [35]. Because many HCV infections have not yet progressed to end-stage liver disease, and considering a limited number of viable organs and surgical capacity, there is a pressing need for strategies to combat future trends in transplantation.

To achieve reduction goals, it is important to note that increased detection and diagnosis of HCV infection is a component of the strategies. Birth cohort screening recommendations were recently developed in the United States [26]. In Spain, the infected population is younger than in the United States, and the most effective screening programs should target individuals born between 1950 and 1980. This population cohort reflects 75% of the viremic population (Fig. 2).

This analysis demonstrated that overall HCV prevalence in Spain is in decline due to lower incidence. However, the prevalence of advanced liver disease will continue to increase as the infected population ages. It is possible to substantially reduce HCV infection through increased diagnosis and treatment in the next 10 years with new potent therapies.

### *Sweden*

A treatment rate of 2.8%, as well as focused treatment (F2–F4) for G1 and G4 patients, were significant drivers, in the model, for the large reduction in HCV-related mortality and decompensated cirrhosis (50% and 60% reductions) observed through simple increases in SVR. The total number of HCV infections was not shown to decrease as



dramatically under these conditions, only 10% reduction, due to the treatment of more advanced stage patients. When F0–F4 patients were considered for treatment alongside a treatment rate of 12%, elimination of HCV was achievable. Additionally, treatment at this rate was only required until 2025 when the pool of eligible patients depleted. Historically, high rates of diagnosis allowed for treatment at this rate without the need for increased screening to achieve the 90% reduction before 2030. These exercises indicate that a clearly defined outcome (i.e. goal of reducing mortality or goal of reducing prevalence) is important for strategy development in Sweden.

### Switzerland

Increasing treatment efficacy resulted in modest decreases (10%) in HCV-related morbidity and mortality without growing the diagnosed or treated population. This was driven by harm reduction efforts to keep new infections low and by the current focus on treating F2–F4 patients. However, the impact of increasing the diagnosed and treated population as well as unrestricting treatment was much larger, demonstrating an 85% reduction in HCV cases as well as 70–80% reductions in HCV-related morbidity and mortality. The treatment rate required for these outcomes was approximately 7.7%, with an associated threefold increase in new diagnoses. Although this treatment rate would have to be sustained past 2030, by 2030 the remaining patient pool would be predominantly 75+ years of age. In reality, this approach would require a significant expansion of the current treatment capacity as well as a screening approach to increase diagnosis. Once well tolerated and easy to administer therapies become available, a treatment indication approach (where an HCV diagnosis is followed by a treatment offer) may be possible.

### Turkey

It is estimated that the annual number of new cases peaked in 1991 and that the proportion of HCV-infected individuals peaked with 611 000 viremic infected individuals in 1998. Since then, the overall prevalence of HCV infection has been declining due to low injection drug use and an improved blood supply [36]. However, the proportion of HCV-related advanced liver disease is increasing. In 2030, the proportion of HCV-related cirrhosis and its complications, including HCC, will increase 70% from present day. In addition, we forecast that HCV-related disease morbidity and mortality will continue to increase and peak from 2029 to 2032.

HCV infection is a curable disease by therapy. Unfortunately, while approved for reimbursement in 2012, therapy with DAAs in Turkey is currently restricted to patients with advanced liver disease. The present study indicates that an unrestricted treatment approach is a feasible treatment modality for HCV infection within favorable timelines.

### HCV screening

As shown previously [4,20], diagnosis remains low in many countries, with a large number of unidentified cases. In this model, the diagnosis rate was increased to provide a sufficient patient pool to achieve the desired strategy. However, it is not clear if the number of newly diagnosed patients can be increased without a clear screening strategy.

In the United States, the Center for Disease Control and Prevention has recommended birth year screening [26,37,38]. This allows for an efficient use of resources by focusing on birth cohorts that have a higher prevalence rate. Figure 17 illustrates the number of individuals that have to be screened to identify one positive HCV person as a function of prevalence and diagnosis rate. As the diagnosis rate increases and/or prevalence decreases, the number of individuals that have to be screened goes up exponentially in order to find one newly diagnosed person. Thus, it will become more difficult (and expensive) to find new undiagnosed individuals without a clear screening strategy. By focusing on populations with high HCV prevalence (specific birth cohorts [26,37,38], IDU [39,40], HCV/HIV co-infected individuals [41] and prisoners [42–47]), new diagnosed cases can be identified in an efficient manner.

A birth cohort analysis was conducted for each of the countries, and the results are shown in Fig. 18. The analysis showed that there is, in fact, a birth cohort effect for HCV in all countries with over 70% of the infected population falling within a specific range. The range, in the countries analyzed, was more than 30 years, which is wider than the US HCV-infected population. This is likely due to variations in risk factors. The range was wider when nosocomial infection was identified as a risk factor (e.g. blood transfusion prior to blood screening in Germany and France [48–51], Egypt and Turkey). In countries where IDU was identified as a key risk factor (Australia, Czech Republic, England, France, Germany, Portugal, Sweden and Switzerland), the birth cohort range included individuals born between 1980 and 1990. The HCV epidemic is relatively young in the Czech Republic and Portugal [20], and thus the majority of the infected population was born after 1965 and 1955 respectively. The birth year cohorts, shown in this study, could provide an efficient source of identifying newly diagnosed patients as part of a national screening strategy.

There were a number of limitations with this study. For the base case, SVR of current treatments were based on data from clinical centers, which were experienced in treating patients and managing their side effects. In the real world, SVR could be substantially lower [52] than what is stated here, resulting in a larger difference between the base case and each of the scenarios. In addition, as presented previously [20], there is a large variance in HCV prevalence estimates. This effect of each of the scenarios

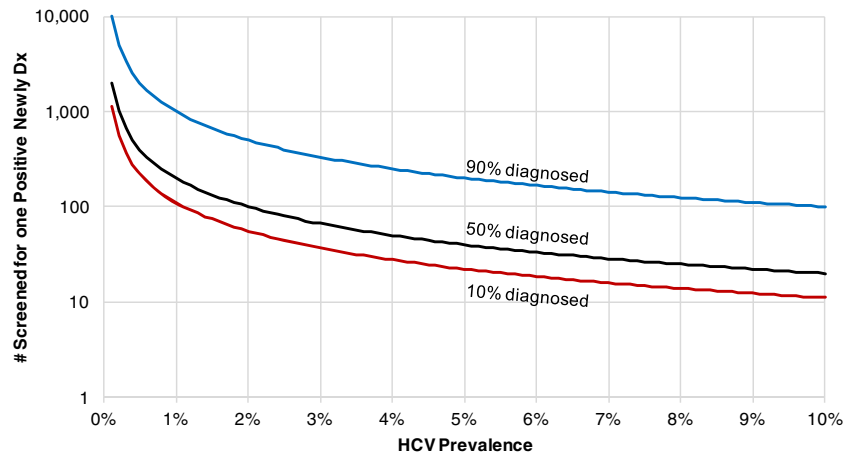


Fig. 17 Number of screened cases for one newly diagnosed person as a function of prevalence and diagnosis rate.

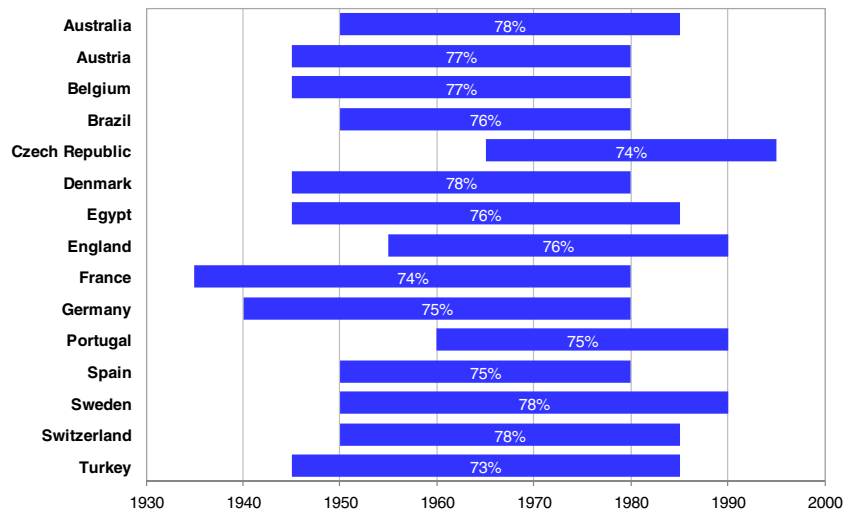


Fig. 18 Distribution of HCV-infected population by birth year cohort.

could be more or less pronounced if real prevalence is higher or lower than values assumed here.

Another limitation was that increases in treatment rate, diagnosis rate, eligibility and SVR took effect immediately without any time for an uptake. In reality, adoption of new therapies can take several years as the medical community gets familiar with the new drugs and new guidelines are developed. However, incorporation of diffusion curves required a number of assumptions (years for uptake, shape of the diffusion curve and market share of the new therapies) that would require a level of granularity that was difficult to forecast at the time of the analysis. The outputs of the model were based on the assumption that new therapies or guidelines are adopted immediately, and the model was designed to allow future modifications to incorporate treatment uptake as additional information becomes available. However, every analysis that examined the impact of accelerating or delaying increase in SVR or

treatment reached the same conclusion: the desired outcomes were more achievable when the strategy was initiated sooner rather than later.

In addition, the focus of the analysis was on HCV-infected individuals, and the disease progression was no longer followed when the patients were cured. Studies have shown that the risks for HCC, decompensation and liver-related deaths can remain, but at substantially lower rates in cured HCV patients with more advanced liver diseases [53]. This would suggest that the model overestimated the impact of curing the patients on HCV liver-related morbidity and mortality. However, it is likely that any underestimation may be small since most of the reduction in HCV morbidity and mortality came from prevention of HCV cases progressing to more advanced liver disease.

In conclusion, this analysis demonstrated that although the total number of HCV infections is expected to decline (or remain flat), HCV-related morbidity and mortality are

expected to increase in almost all countries. Reducing the HCV burden is possible with a two-pronged effort. First, active screening programs to find and identify the HCV-infected population must be implemented. Second, active management with antiviral therapy must be maintained. Through active management, it is possible to eliminate HCV infection.

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