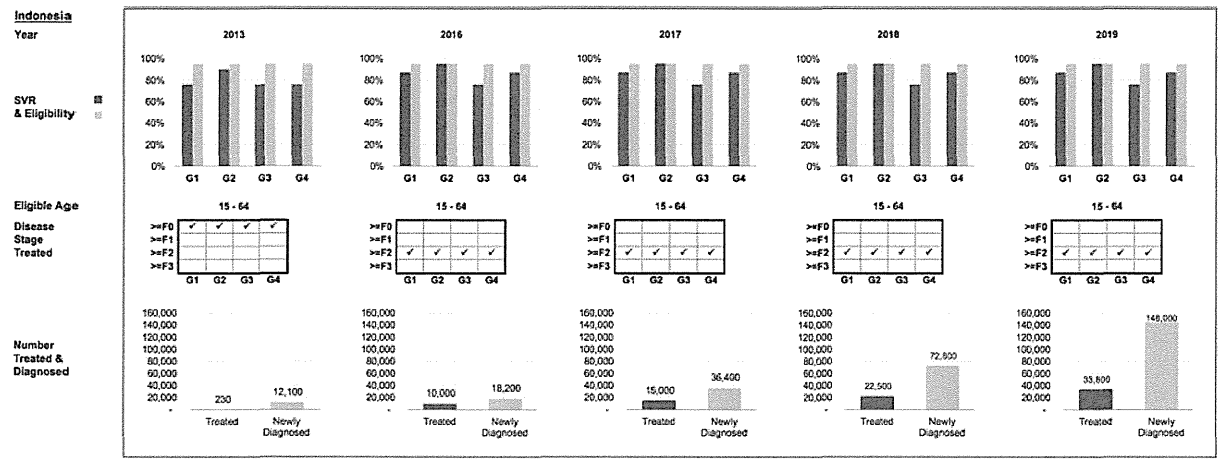

Fig. 4 Indonesia model inputs, by year.

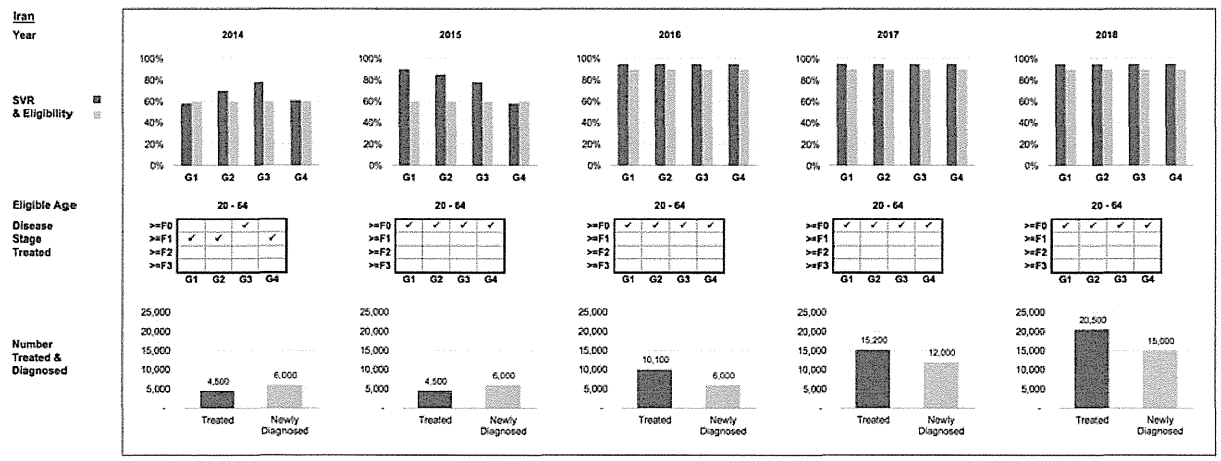

Fig. 5 Iran model inputs, by year.

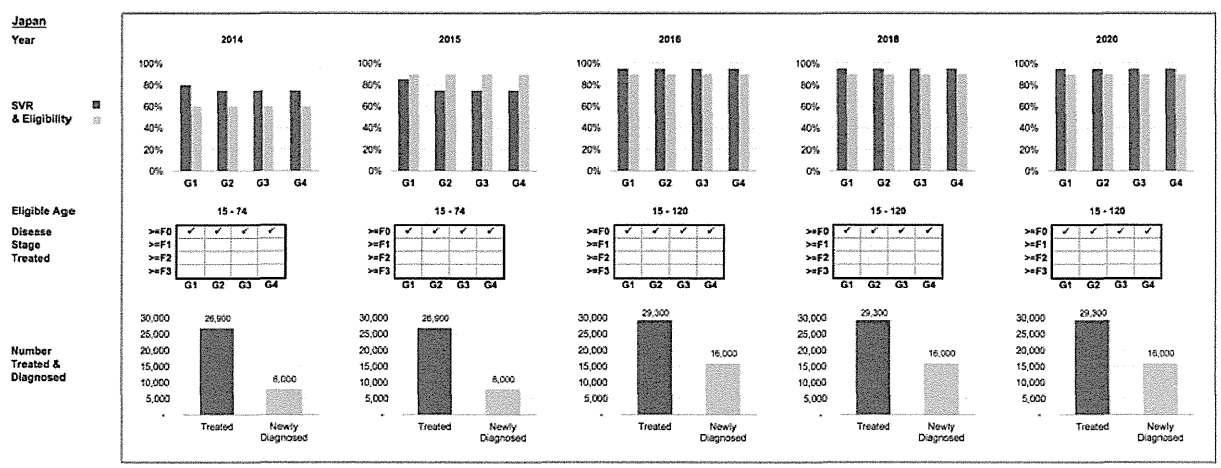

Fig. 6 Japan model inputs, by year.

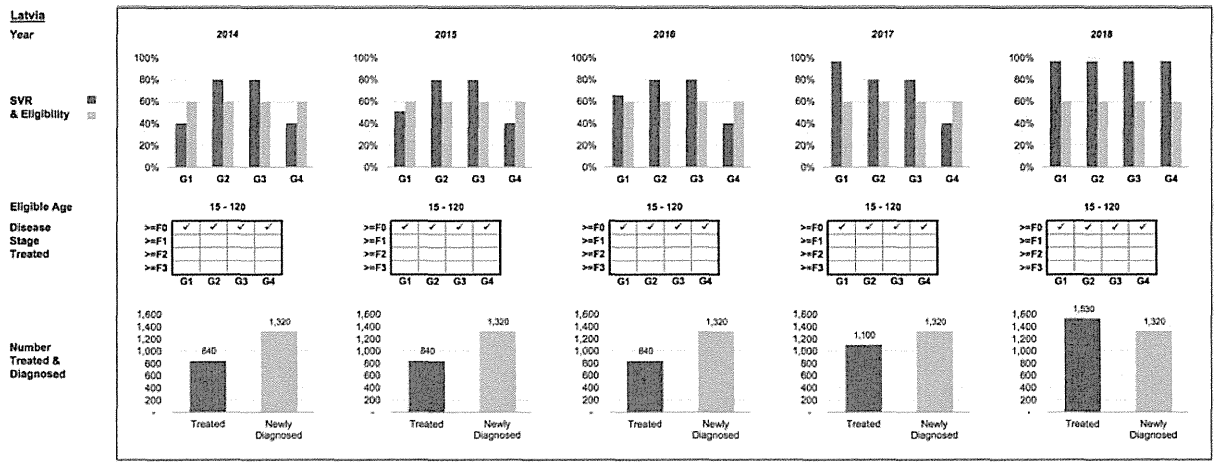

Fig. 7 Latvia model inputs, by year.

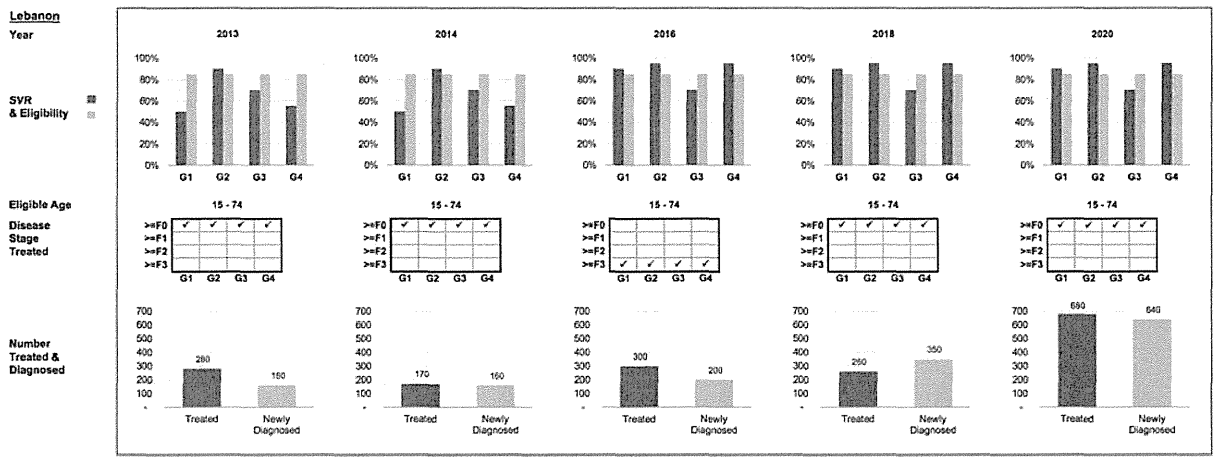

Fig. 8 Lebanon model inputs, by year.

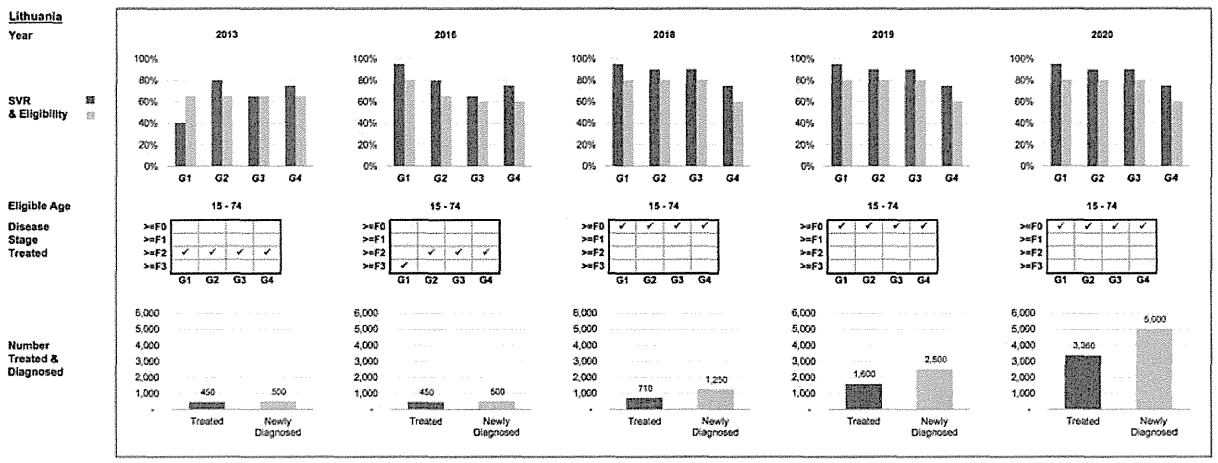

Fig. 9 Lithuania model inputs, by year.

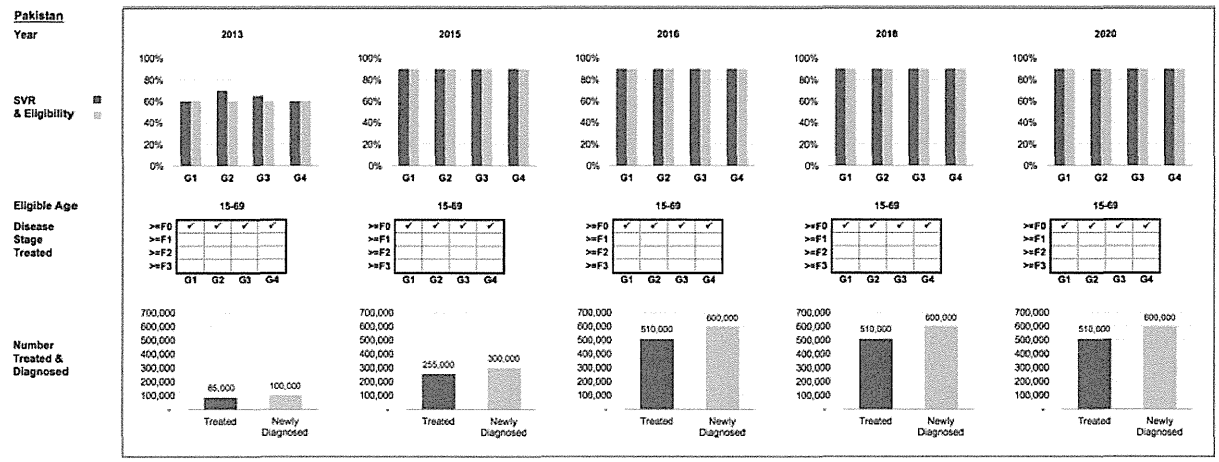

Fig. 10 Pakistan model inputs, by year.

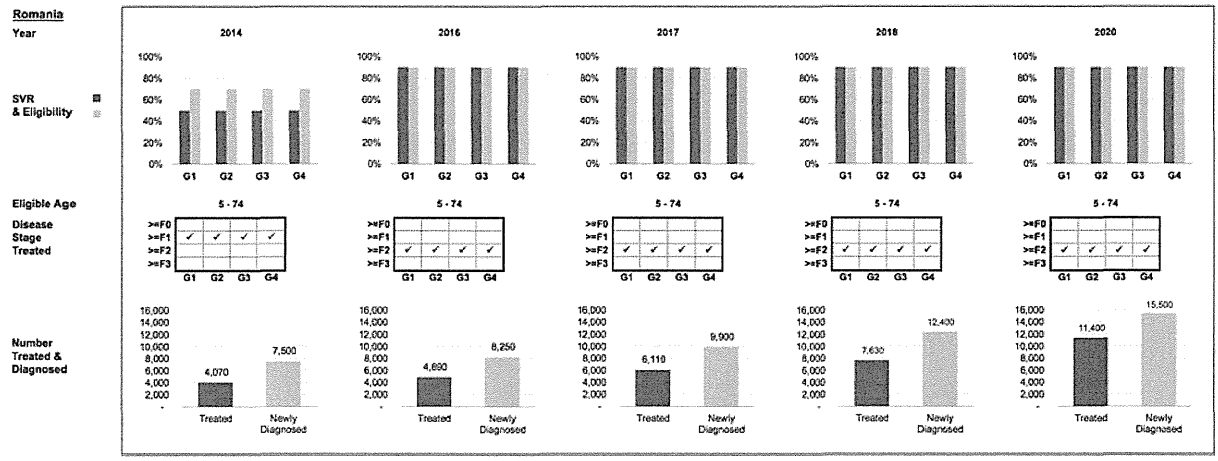

Fig. 11 Romania model inputs, by year.

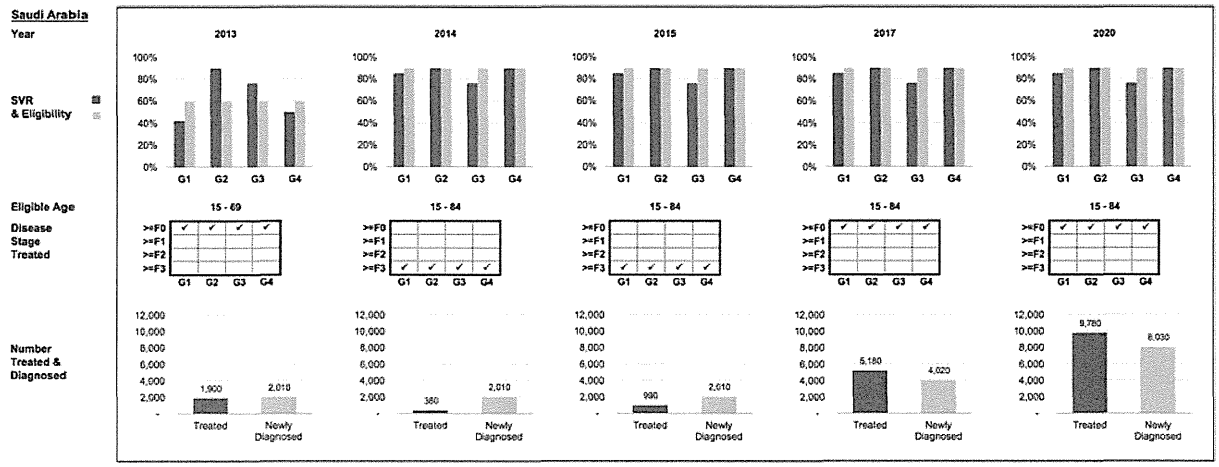

Fig. 12 Saudi Arabia model inputs, by year.

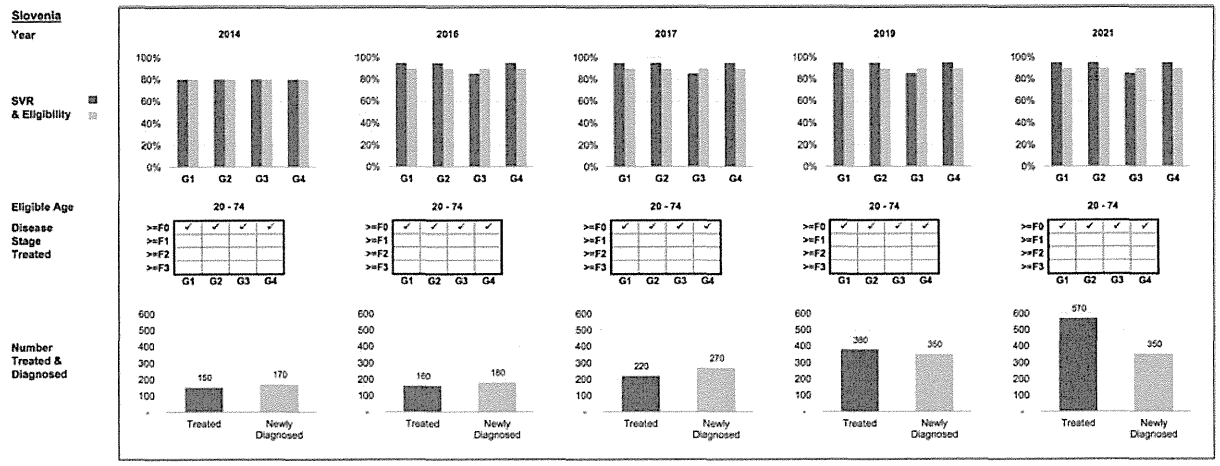

Fig. 13 Slovenia model inputs, by year.

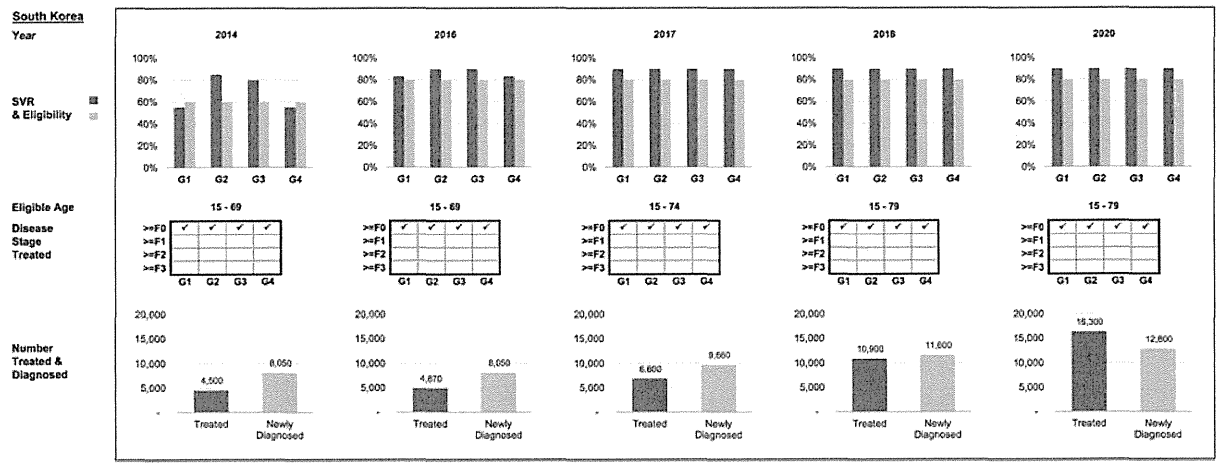

Fig. 14 South Korea model inputs, by year.

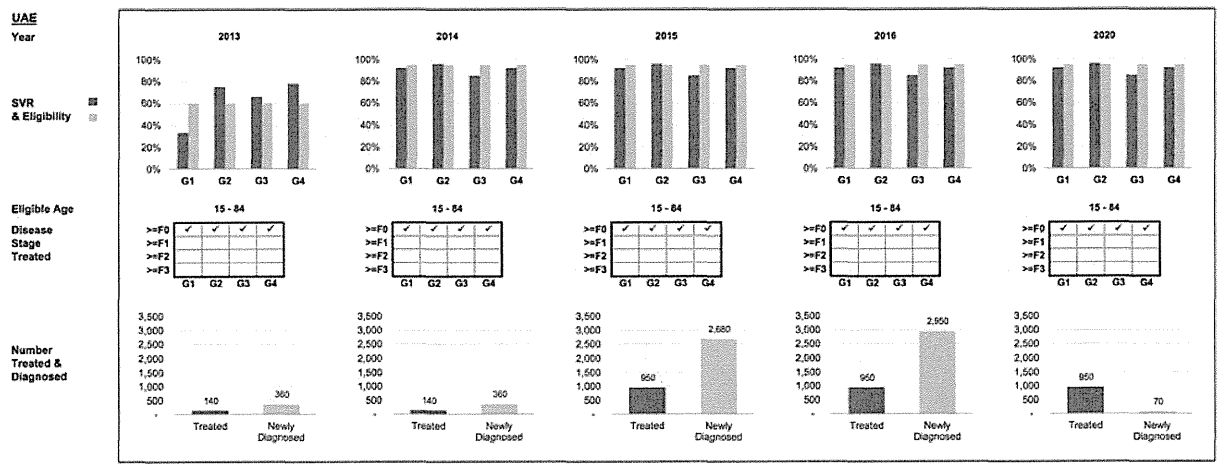

Fig. 15 UAE model inputs, by year.

by disease stage were assumed to occur among the viremic HCV population – that is, the effects of non-HCV-related liver disease were not considered in this analysis.

Birth cohort effect

The age distribution of each country was gathered from published data and reported previously [7]. The disease progression model was used to age the HCV-infected population after taking into account mortality and SVR [1]. For this analysis, the median age in each five-year age cohort was selected and converted to a birth year. A range of birth years was selected that accounted for approximately 70% (or more) of the total HCV-infected population using the 2014 HCV population distribution [1].

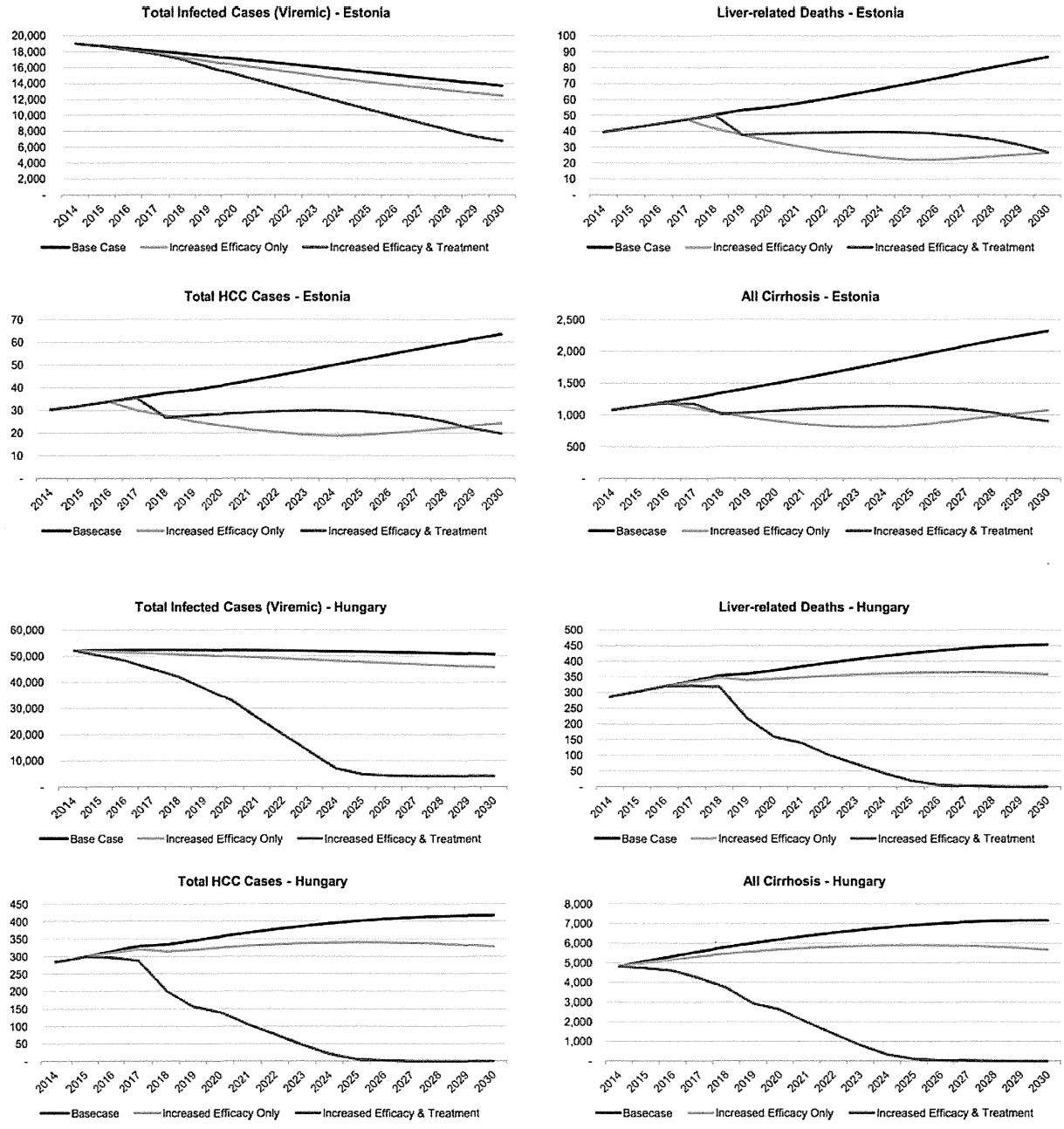

Fig. 16 Change in HCV morbidity and mortality, by scenario, 2014–2030.

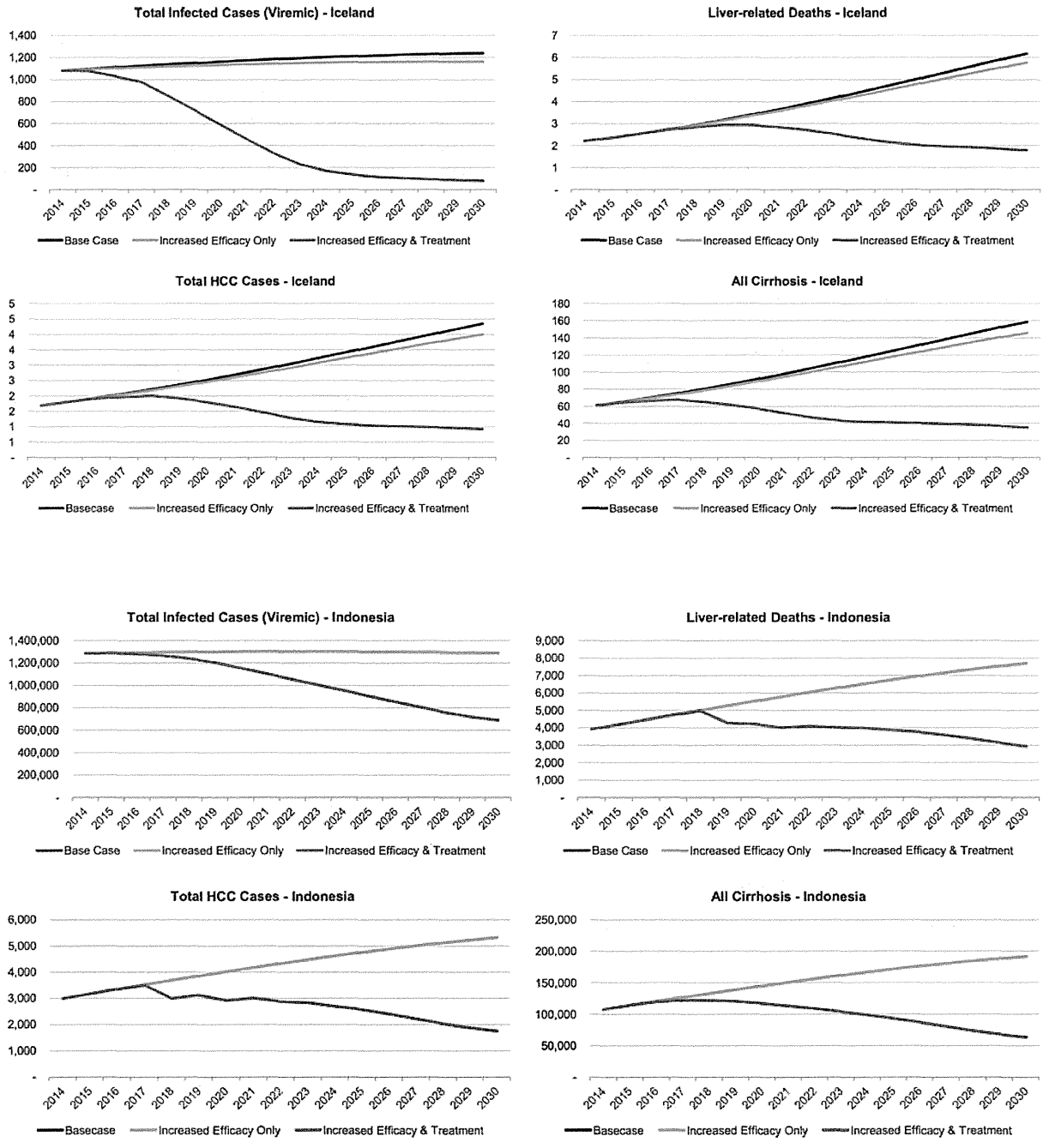

Fig. 16 continued

RESULTS

The results of the analyses are summarized in Fig. 16. The birth cohort effect in the HCV-infected population is shown in Fig. 17. Each bar represents the range of birth years, with the value on each bar showing the percentage of the total infected population who were born between the years shown. Country-specific scenario results are discussed below.

Estonia

Increased efficacy only

There would be 1200 fewer viremic individuals in 2030, a 9% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 25 cases, a 60% decrease from the base case. Similarly, the number of liver-related deaths would decrease by 70% from the base, with 25 in 2030. Decompensated and compensated cirrhosis

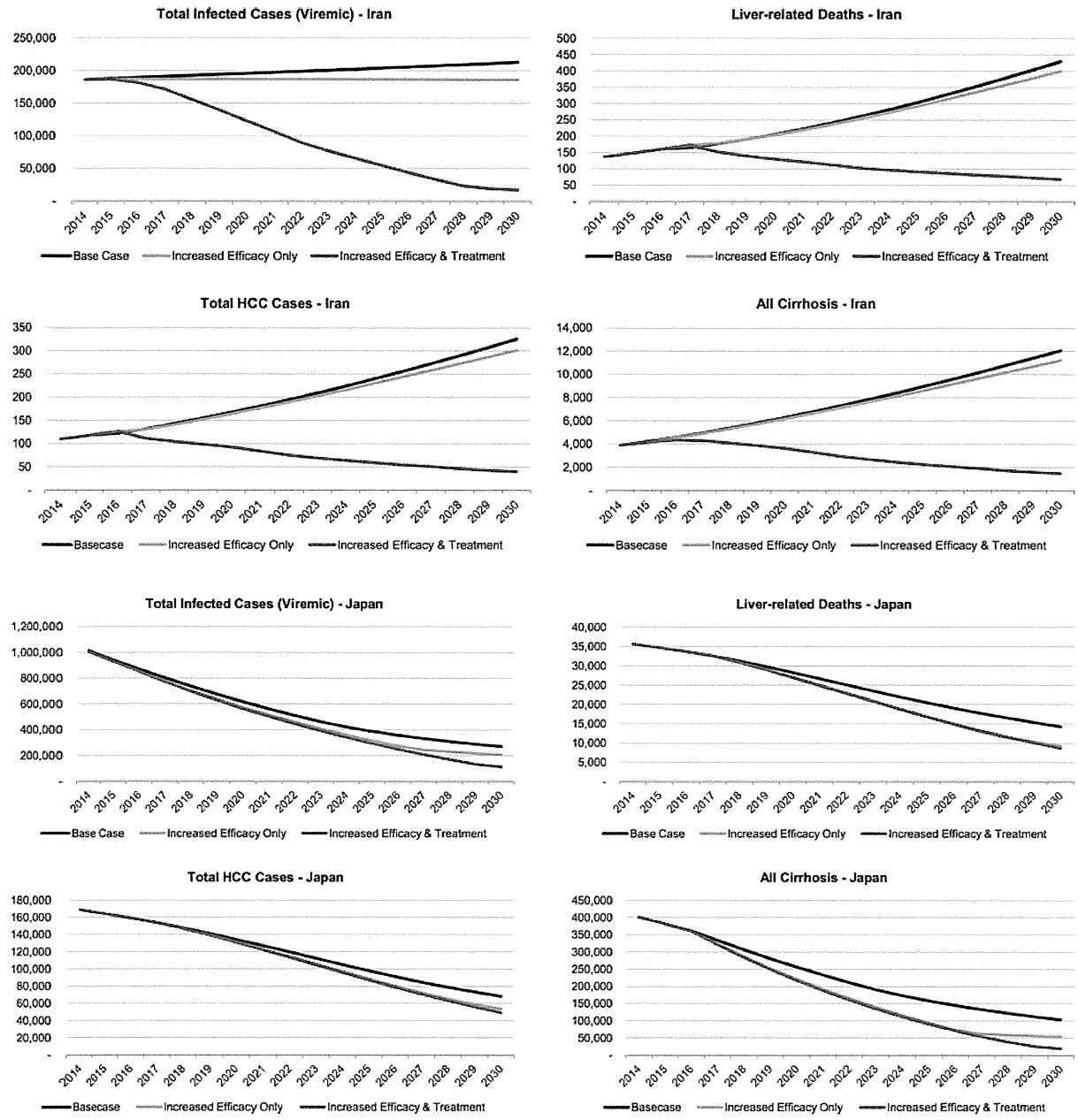

Fig. 16 continued

would decrease by 75% and 50%, respectively, from the base, with 50 and 1000 cases in 2030.

Increased efficacy & treatment uptake

There would be 6900 fewer viremic individuals in 2030, a 50% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 20 cases, a 70% decrease from the base case. Similarly, the number of liver-related deaths would decrease by 70% from the base, with 25 in 2030. Decompensated and compensated cirrhosis would decrease by 80% and 60%, respectively, from the base, with 45 and 860 cases in 2030.

Hungary

Increased efficacy only

There will be 5000 fewer viremic individuals in 2030, a 10% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 330 cases, a 20% decrease from the base case. Similarly, the number of

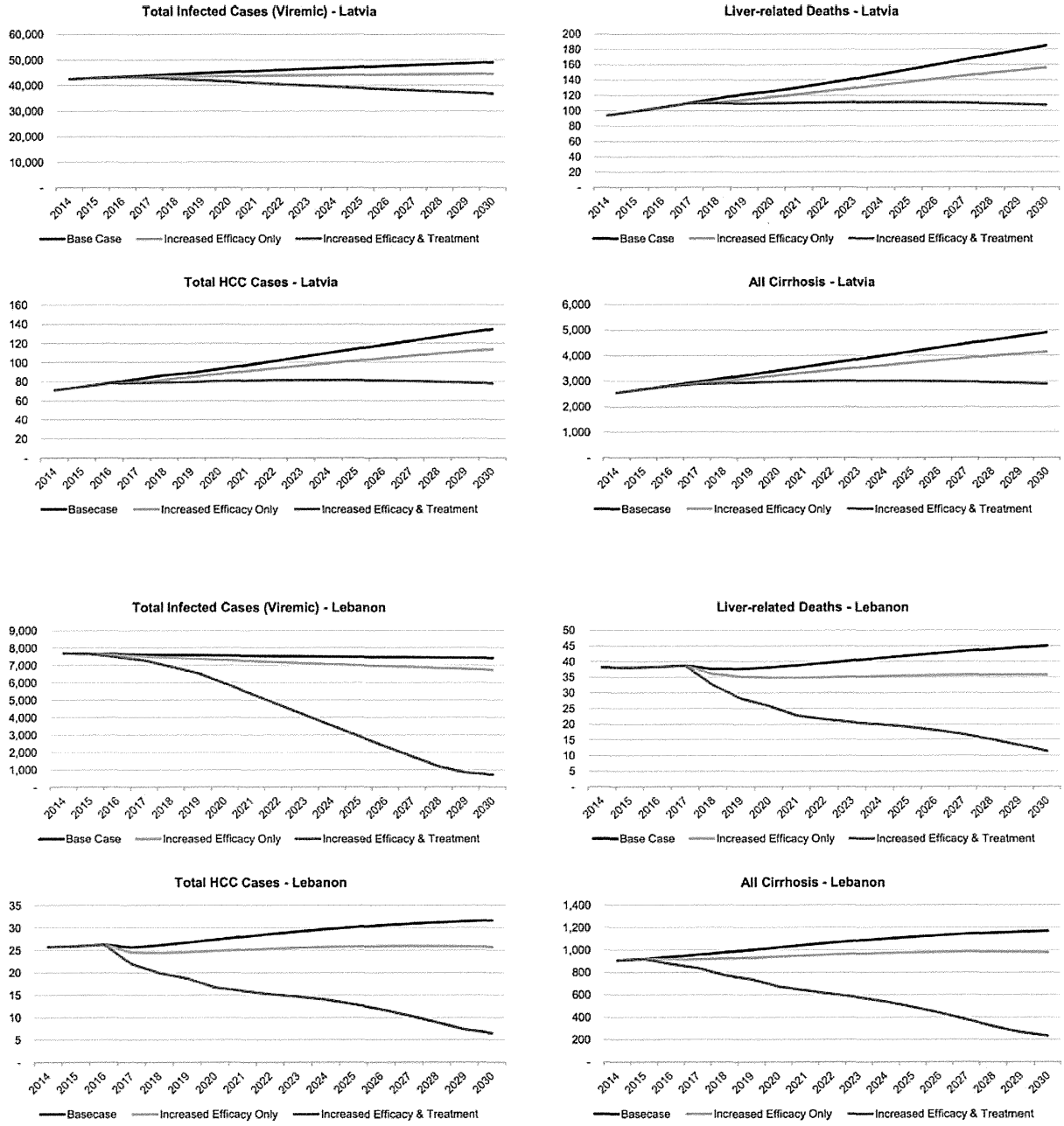

Fig. 16 *continued*

liver-related deaths will decrease by 20% from the base, with 360 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 25% and 20% from the base, with 470 and 5100 cases in 2030.

Increased efficacy & treatment uptake

With an aggressive treatment strategy, there will be 46 600 fewer viremic individuals in 2030, a 90% reduction as compared to the base case. The number of HCV-related HCC cases in 2030 was estimated at 0 cases, a 100% decrease from the base case. Similarly, the number of HCV-related liver-related deaths will decrease by 100% from the base, with 1 death in 2030. HCV-related decompensated and compensated cirrhosis will decrease by 100% from the base, with 0 and 2 cases in 2030. HCV-related liver transplants would decrease by 90% from the base, from 21 to 2 cases in 2030.

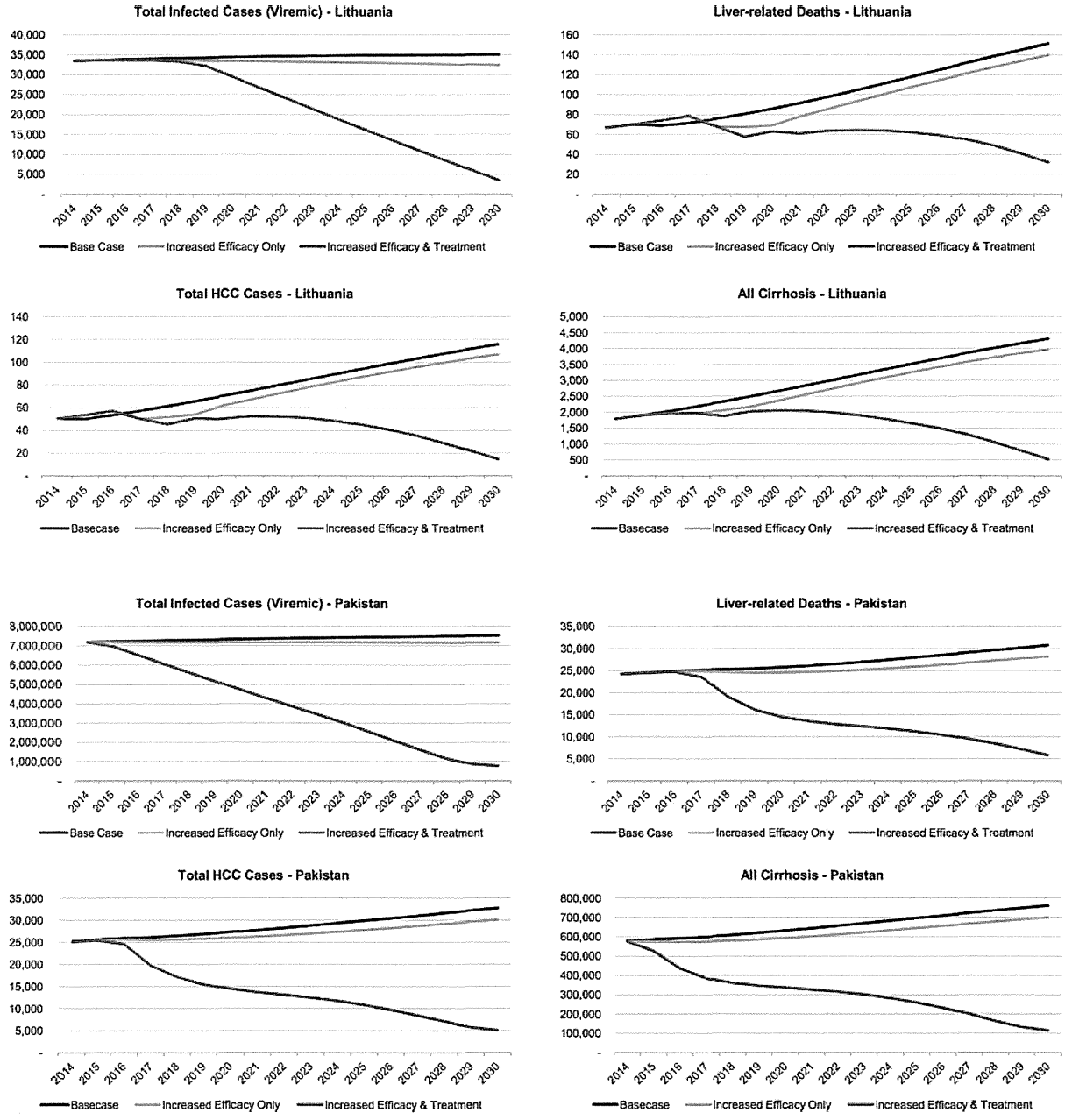

Fig. 16 continued

Iceland

Increased efficacy only

There would be 80 fewer viremic individuals in 2030, a 5% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 4 cases, an 8% decrease from the base case. The number of liver-related deaths would decrease by 7% from the base, with 6 deaths[1] in 2030. Decompensated and compensated cirrhosis would decrease by 8% from the base, with 12 and 130 prevalent cases in 2030.

Increased efficacy & treatment uptake

With an aggressive treatment and diagnosis strategy, there would be 1200 fewer viremic individuals in 2030, a 95% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 1 case, an 80% decrease from the base case. Similarly, the number of liver-related deaths would decrease by 70% from the base, with 2 deaths in 2030. Decompensated and compensated cirrhosis would decrease by 75% from the base, with 4 and 30 cases, respectively, in 2030.

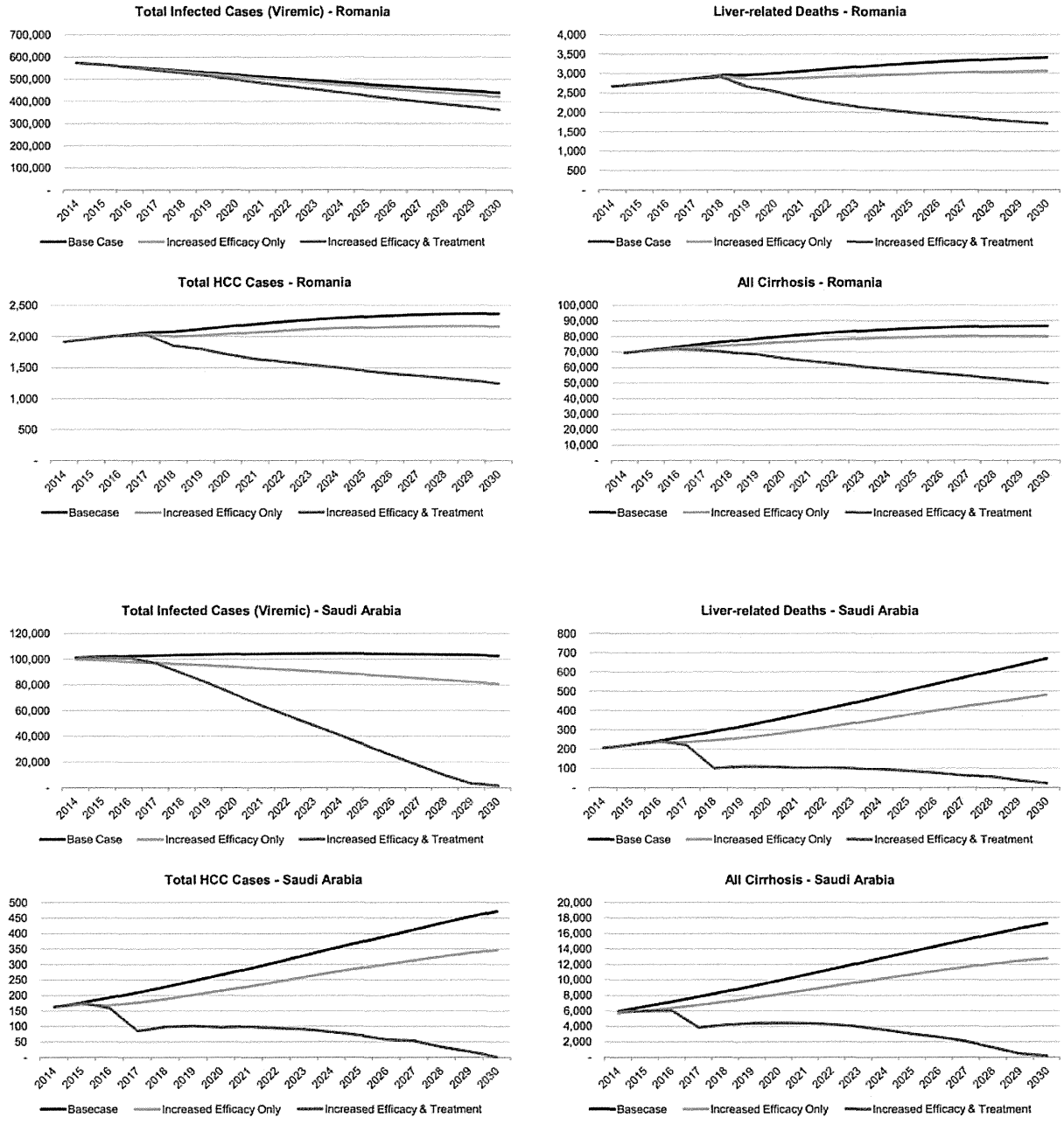

Fig. 16 continued

Indonesia

Increased efficacy only

There would be 290 fewer viremic individuals in 2030, a < 1% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 5300 cases, a < 1% decrease from the base case. Similarly, the number of liver-related deaths would decrease by <1% from the base, with 7700 in 2030. Decompensated and compensated cirrhosis would decrease by <1% from the base, with 19 400 and 172 000 cases in 2030.

Increased efficacy & treatment uptake

There would be 600 000 fewer viremic individuals in 2030, a 50% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 1800 cases, a 70% decrease from the base case. Similarly, the number of liver-related deaths would decrease by 60% from the base, with

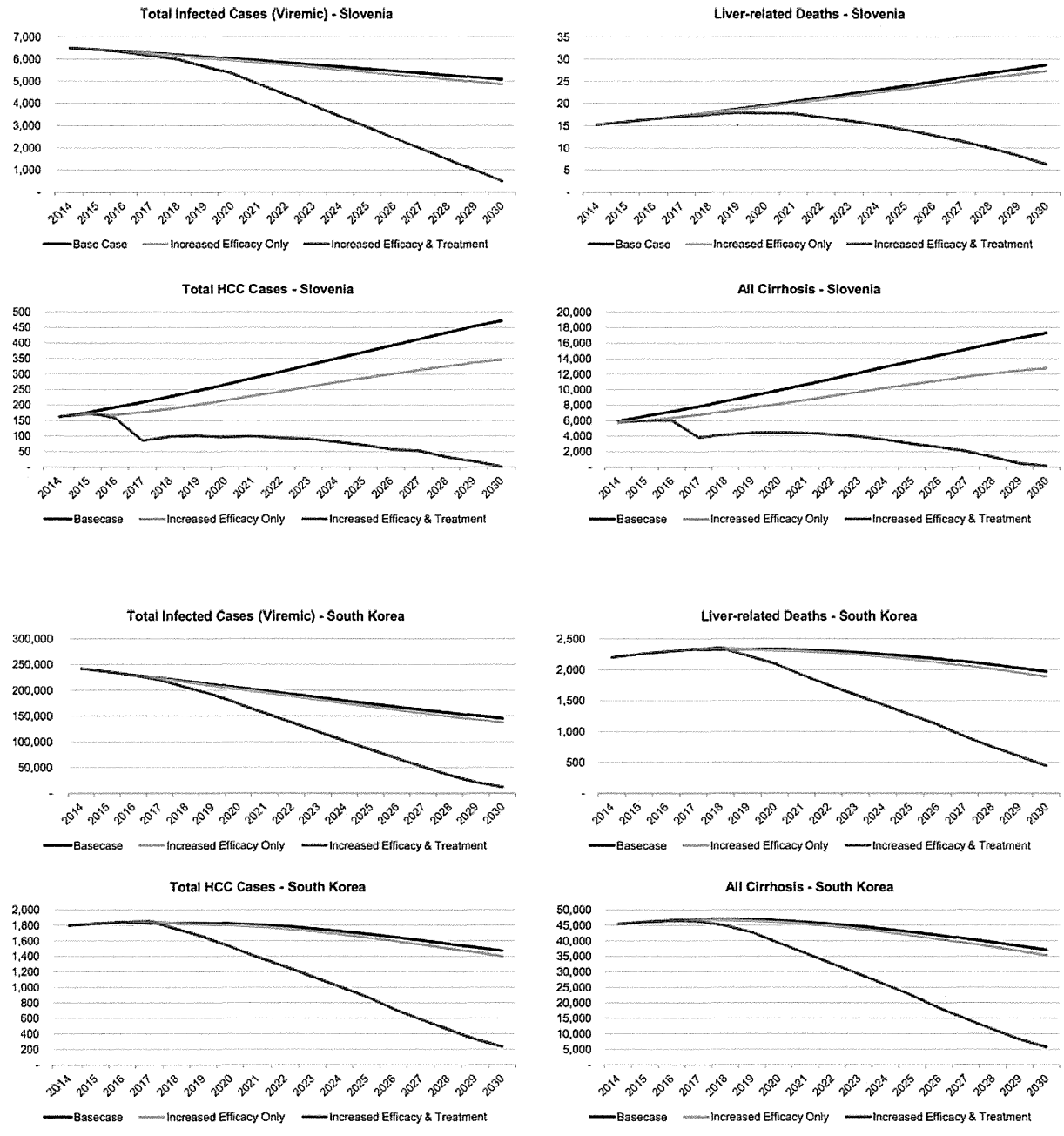

Fig. 16 continued

2900 deaths in 2030. Decompensated and compensated cirrhosis would decrease by 60% and 70%, respectively, from the base, with 7300 and 56 000 cases in 2030.

Iran

Increased efficacy only

There would be 26 700 fewer viremic individuals in 2030, a 13% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 300 cases, a 7% decrease from the base case. Similarly, the number of liver-related deaths would decrease by 7% from the base, with 400 deaths in 2030. Decompensated and compensated cirrhosis would decrease by 10% and 7% from the base, with 590 and 10 100 cases in 2030.

Increased efficacy & treatment uptake

Utilizing an aggressive treatment and diagnosis strategy, there would be a 90% reduction in the total number of viremic individuals, representing 196 000 fewer viremic

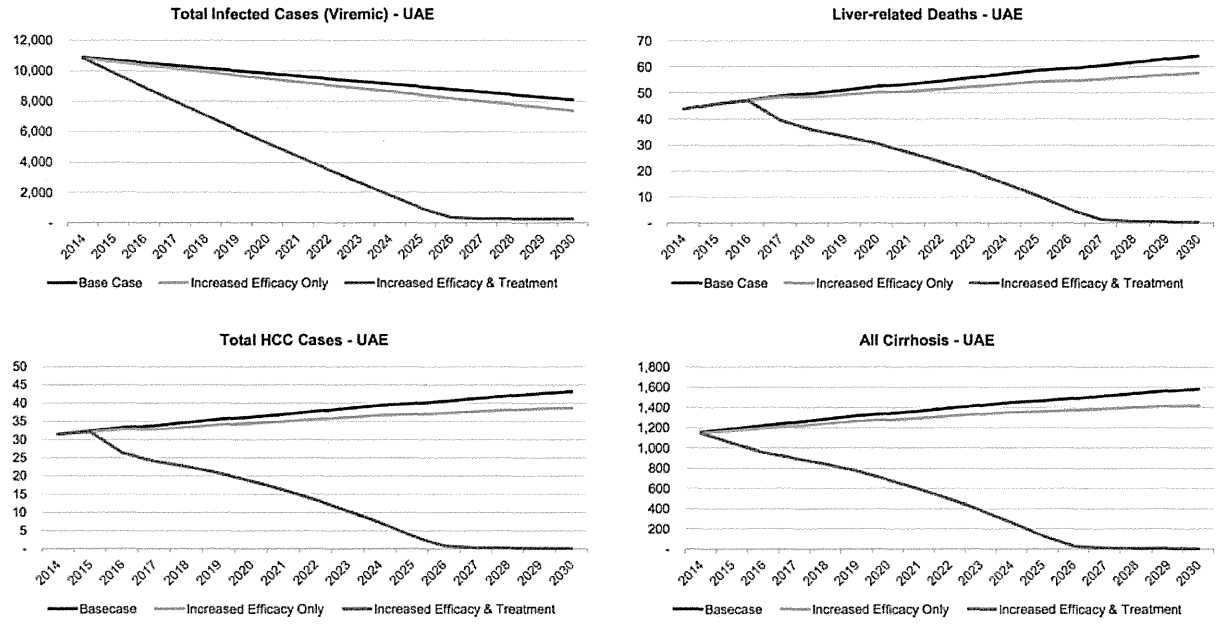

Fig. 16 continued

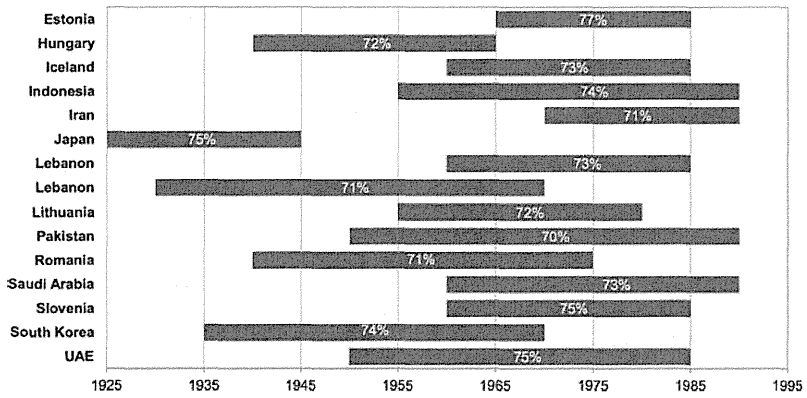

Fig. 17 Distribution of HCV-infected population by birth year cohort.

individuals in 2030, relative to the base case. The number of HCC cases in 2030 was estimated at 40 cases, a 90% decrease from the base case. Similarly, the number of liver-related deaths would decrease by 85% from the base, with 70 deaths in 2030. Decompensated and compensated cirrhosis would decrease by 80% and 90% from the base, with 140 and 1300 cases in 2030.

Japan

Increased efficacy only

There would be 64 500 fewer viremic individuals in 2030, a 25% reduction as compared to the base case. The number of prevalent HCC cases in 2030 was estimated at 53 600 cases, a 20% decrease from the base case, while the number of incident HCC cases in 2030 was estimated at 3300, a 45% decrease from the base case. The number of liver-related deaths would decrease by 35% from the base, with 9300 deaths in 2030. Decompensated and compensated cirrhosis would decrease by 85% and 40% from the base, with 2400 and 50 700 cases, respectively, in 2030.

Increased efficacy & treatment uptake

With an aggressive treatment and diagnosis strategy, there would be 159 000 fewer viremic individuals in 2030, a 60% reduction as compared to the base case. The number of prevalent HCC cases in 2030 was estimated at 49 300 cases, a 30% decrease from the base case, while the number of incident HCC cases in 2030 was estimated at 1500,

a 75% decrease from the base case. Similarly, the number of liver-related deaths would decrease by 40% from the base, with 8700 deaths in 2030. Decompensated and compensated cirrhosis would decrease by 95% and 80% from the base, with 950 and 17 700 cases, respectively, in 2030.

Latvia

Increased efficacy only

There would be 4400 fewer viremic individuals in 2030, a 9% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 110 cases, a 15% decrease from the base case. Similarly, the number of liver-related deaths would decrease by 15% from the base, with 160 deaths in 2030. Decompensated and compensated cirrhosis would decrease by 15% from the base, with 380 and 3800 cases in 2030.

Increased efficacy & treatment uptake

With treatment of 1530 patients annually beginning in 2018, there would be 12 200 fewer viremic individuals in 2030, a 25% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 80 cases, a 40% reduction from the base case. Similarly, the number of liver-related deaths would decrease by 40% from the base, with 110 deaths in 2030. Decompensated and compensated cirrhosis would decrease by 45% and 40% respectively, from the base, with 240 and 2700 cases in 2030.

Lebanon

Increased efficacy only

There would be 680 fewer viremic individuals in 2030, a 9% reduction as compared to the base case. The number of HCC cases due to HCV in 2030 was estimated at 30 cases, a 19% decrease from the base case. Similarly, the number of liver-related deaths would decrease by 20% from the base, with 40 deaths in 2030. Decompensated and compensated cirrhosis would decrease by 25% and 15%, respectively, from the base, with 80 and 900 cases in 2030.

Increased efficacy & treatment uptake

With an aggressive increase in treated patients, there would be 6700 fewer viremic individuals in 2030, a 90% reduction as compared to the base case. The number of HCC cases due to HCV in 2030 was estimated at 6 cases, an 80% decrease from the base case. Similarly, the number of liver-related deaths would decrease by 75% from the base, with 11 deaths in 2030. Decompensated and compensated cirrhosis would decrease by 75% and 80%, respectively, from the base, with 30 and 210 cases in 2030.

Lithuania

Increased efficacy only

There would be 2700 fewer viremic individuals in 2030, an 8% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 110 cases, an 8% decrease from the base case. Similarly, the number of liver-related deaths would decrease by 8% from the base, with 140 deaths in 2030. Decompensated and compensated cirrhosis would decrease by 9% and 8%, respectively, from the base, with 310 and 3600 cases in 2030.

Increased efficacy & treatment uptake

With an aggressive increase in treated patients, there would be 31 500 fewer viremic individuals in 2030, a 90% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 15 cases, an 85% decrease from the base case. Similarly, the number of liver-related deaths would decrease by 80% from the base, with 30 deaths in 2030. Decompensated and compensated cirrhosis would decrease by 85% and 90%, respectively, from the base, with 50 and 470 cases in 2030.

Pakistan

Increased efficacy only

There would be 360 000 fewer viremic individuals in 2030, a 5% reduction compared to the base case. The number of HCC cases in 2030 was estimated at 30 200 cases, an 8% decrease from the base case. Similarly, the number of liver-related deaths would decrease by 8% from the base, with 28 200 deaths in 2030. Decompensated and compensated cirrhosis would decrease by 8–9% from the base, with 89 000 and 610 000 cases, respectively, in 2030.

Increased efficacy & treatment uptake

Utilizing an aggressive treatment strategy, there would be a 90% reduction in the total number of viremic individuals, representing 6 754 000 fewer viremic individuals, in 2030, relative to the base case. The number of HCC cases in 2030 was estimated at 5100 cases, an 85% decrease from the base case. Similarly, the number of liver-related deaths would decrease by 80% from the base, with 5900 deaths in 2030. Decompensated and compensated cirrhosis would decrease by 85% from the base, with 13 500 and 102 000 cases in 2030.

Romania

Increased efficacy only

There would be 17 400 fewer viremic individuals in 2030, a 4% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 2200 cases, a 9% reduction from the base case. Similarly, the number of

liver-related deaths would decrease by 10% from the base scenario, with 3100 deaths in 2030. Decompensated and compensated cirrhosis would decrease by 12% and 7%, respectively, from the base, with 7200 and 72 600 cases in 2030.

Increased efficacy & treatment uptake

With an increased treatment and diagnosis strategy, there would be 76 000 fewer viremic individuals in 2030, a 17% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 1200 cases, a 45% decrease from the base case. Similarly, the number of liver-related deaths would decrease by 50% from the base, with 1700 deaths in 2030. Decompensated and compensated cirrhosis would decrease by 55% and 40%, respectively, from the base, with 3700 and 45 900 cases in 2030.

Saudi Arabia

Increased efficacy only

Increasing the efficacy of treatment would result in 22 100 fewer viremic cases in 2030, a 21% reduction from the base scenario. The number of HCC cases would decrease by 27% to 350 cases in 2030. Liver-related mortality would be reduced to 480 deaths in 2030, a 28% decrease. Decompensated and compensated cirrhosis would decrease by 34% and 26%, respectively, compared with the base scenario, to 850 and 11 500 cases in 2030.

Increased efficacy & treatment uptake

With an aggressive treatment strategy, viremic prevalence would be reduced to 1700 cases in 2030, an almost 100% decrease compared with the base scenario. Cases of HCC would be 100% fewer at 1 case by 2030. Liver-related mortality would drop by 95% compared with the base scenario to 20 deaths in 2030. Cases of decompensated and compensated cirrhosis would be 6 and 130 in 2030, respectively; nearly 100% reduced compared with the base scenario.

Slovenia

Increased efficacy only

There would be 210 fewer viremic individuals in 2030, a 4% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 20 cases, a 5% decrease from the base case. Similarly, the number of liver-related deaths would decrease by 5% from the base, with 25 deaths in 2030. Decompensated and compensated cirrhosis would decrease by 6% and 5% from the base, with 60 and 640 cases, respectively, in 2030.

Increased efficacy & treatment uptake

By scaling up the number of newly diagnosed and treated patients and starting higher efficacy treatments in 2016, there would be an estimated 4600 fewer viremic individuals in 2030, a 90% reduction from the base case. Liver-related deaths would decrease by 80% from the base, with 6 cases in 2030. Similarly, the number of HCC cases would decrease by 85%, with 3 cases in 2030. Decompensated and compensated cirrhosis would decrease by 85% and 90%, respectively, from the base, with 10 and 80 cases in 2030.

South Korea

Increased efficacy only

There would be 7700 fewer viremic individuals in 2030, a 5% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 1400 cases, a 5% decrease from the base case. Similarly, the number of liver-related deaths would decrease by 4% from the base, with 1900 in 2030. Decompensated and compensated cirrhosis would decrease by 4% and 5% from the base, with 3700 and 31 400 cases, respectively, in 2030.

Increased efficacy & treatment uptake

There would be 134 000 fewer viremic individuals in 2030, a 90% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 240 cases, an 85% decrease from the base case. Similarly, the number of liver-related deaths would decrease by 75% from the base, with 450 deaths in 2030. Decompensated and compensated cirrhosis would decrease by 80% and 85%, respectively, from the base, with 750 and 4900 cases in 2030.

UAE

Increased efficacy only

Increasing the efficacy of treatment to the post-2014 standard of care resulted in 720 fewer viremic cases in 2030, a 9% change from the base scenario. The number of HCC cases decreased by 10% to 40 cases in 2030. Liver-related mortality was reduced to 60 deaths in 2030, a 10% decrease. Decompensated and compensated cirrhosis decreased by 15% and 10%, respectively, compared with the base scenario, to 90 and 1300 cases in 2030.

Increased efficacy & treatment uptake

With an aggressive treatment strategy, viremic prevalence was reduced to 240 cases in 2030, a 95% decrease compared with the base scenario. Cases of HCC and liver-related mortality were eliminated by 2030. Cases of decompensated and compensated cirrhosis were <5 each in 2030, >99% decreases compared with the base scenario.

DISCUSSION

This analysis suggests that successful diagnosis and treatment of a small proportion of patients can contribute

significantly to the reduction in disease burden in the countries studied. As could be expected, 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 in this analysis, 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, HCV-related morbidity and mortality is expected to increase past 2030 in most countries, with the exception of Japan and South Korea [1]. Additionally, in nine countries, the total number of HCV-infected individuals is expected to increase or remain flat – Hungary, Iceland, Indonesia, Iran, Latvia, Lebanon, Lithuania, Pakistan and Saudi Arabia.

This analysis demonstrates that with a treatment rate of approximately 10%, it is possible to achieve elimination of HCV (>90% drop in total infections by 2030). In addition, it highlights that switching to high SVR therapies would reduce HCV-related morbidity and mortality in many countries. This impact is magnified in countries which already have higher treatment rates of >2.0% – Estonia, Hungary, Iceland, Iran, Japan, Latvia, Lebanon and Slovenia.

As part of this analysis, two broad categories of strategies were generally investigated: disease control and HCV elimination. In the former case, the future SVR, as well as eligible, treated and diagnosed populations, was modified to keep HCV morbidity and mortality at the same level as 2014. In the latter case, the same variables were modified to get the total number of infections below 10% of 2014 values. In a few countries, achieving a specific goal was of greater interest, or was deemed to be more realistic than an elimination or mortality prevention strategy, given the current situation in the country. For example, in Romania, an 18% reduction in viremic cases was deemed an achievable goal.

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. However, treatment of F0–F1 patients was necessary if the goal of the strategy was to eliminate HCV. In fact, the most effective strategy identified was to increase treatment in >F2 patients until that patient pool was depleted, and then to expand treatment to all. However, this strategy did have a major drawback. The HCV infected population is ageing, and waiting to treat early-stage patients meant that some would be too old to be treated. The age of the infected population is one of the key variables for not being able to feasibly achieve zero infections in a country. Another factor that would likely prevent reaching complete eradication is immigration in today's mobile society. The models 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.

Estonia

Under the current treatment structure, the prevalence of chronic HCV was projected to decrease by 30%, which is substantial compared with some of the other countries presented here. A moderate treatment rate (2.6%) and infection rate (15.6 per 100 000) are likely contributors to the projected decline. In this analysis, it was found that the adoption of higher SVR therapies among patients with advanced fibrosis (≥F3) would have a substantial impact on the burden of advanced disease (60–75%), even without increasing treatment rates. Combined with an increased treatment rate up to 4.8%, there was an additional benefit of a 50% reduction in total viremic infections.

Treatment in Estonia is provided at two large regional hospitals as well as four city hospitals; however, treatment must be prescribed by an infectious disease specialist or a gastroenterologist. Long wait lists for consultations with these specialists may provide a barrier to increasing the number of patients treated in the future.

Hungary

Under the current treatment structure, the prevalence of chronic HCV was projected to decrease by 3%. However, cases of advanced liver disease and liver-related deaths are projected to continue to rise (50–60%). In this analysis, it was found that the adoption of higher SVR therapies would have a moderate impact on the burden of advanced disease (20–25%), even without increasing treatment rates. Under the second scenario, average SVR was increased from 55% in 2014 to 90% in 2015 (among those with a fibrosis score ≥F0 or ≥F1). Treatment was expanded to a fibrosis score ≥F0 for all genotypes in 2019. The number of treated patients was increased from 1200 in 2014 to 8850 by 2021, while the number of newly diagnosed cases had to be increased from 2090 in 2014 to 6880 cases by 2021 to provide a sufficient pool of diagnosed patients to treat. A combination of increased treatment, SVR and diagnosis would have a substantial impact on the burden of advanced disease (90–100%). The projected impact of these scenarios will facilitate disease forecasting, resource planning and rational strategies for HCV management in Hungary.

Iceland

There are few studies exploring the prevalence of HCV among the Icelandic population, but data suggest that HCV infection rates are relatively low. However, chronic HCV infection is a major contributor towards advanced liver disease in Iceland; a study of 99 cirrhotic patients

found that 24% were HCV positive [8]. With current treatment levels, prevalence is projected to increase through 2030. A scenario focused on increased treatment efficacy alone had relatively little impact on overall disease burden. To reduce HCV-related morbidity and mortality, increases in the annual number of treated patients are necessary. By increasing treatment to a maximum of 160 cases annually, viremic prevalence decreased to <0.1% by 2030.

Indonesia

Under the current treatment structure, the number of individuals infected with chronic HCV was projected to remain relatively stable through 2030. Currently, only 230 patients (<0.01%) are estimated to be treated annually in Indonesia. Although some patients travel abroad to receive treatment and liver transplantation, they have not been considered here. Increasing SVR in the absence of an increased number of treated patients would have a negligible impact on viremic cases or advanced disease progression. Increasing the treatment rate to 3.8% by 2020 would have a large impact on the number of viremic individuals by 2030 (45% reduction), with an even greater impact on the number of liver-related deaths (60% reduction) as compared with the base case. To achieve such reductions, a substantial increase in the annual number of diagnosed patients would be necessary (145 680 new cases diagnosed annually by 2019).

Within the last year, the Indonesian Ministry of Health has developed a road map to address the increasing burden of HCV. One primary goal of this plan is to improve the lives of 30% of patients by 2019, through services including diagnosis and treatment. It is estimated that at most 10% of the HCV-infected Indonesian population is aware of their infection, so strategies involving an increase in the number of treated patients would likely require increased screening and diagnosis.

Iran

Iran has one of the lowest rates of HCV prevalence in the Middle East. Under the current treatment paradigm, HCV infections will increase in Iran. Much more problematic are the expected large increases in the disease burden that will occur due to the ageing of the currently young infected population. This provides Iran with a unique opportunity to halt the growing disease burden before it becomes overwhelming. Complementary to this is the fact that young infected individuals have both higher eligibility as well as SVR rates.

While increasing efficacy has moderate declines in all HCV-related indicators, an aggressive treatment strategy would eliminate HCV in Iran, bringing the viremic prevalence to approximately 0.02% by 2030. This can be achieved through a national strategy that would increase treatment by 5000 individuals every year starting in 2016 until reaching a maximum treatment of 20 500 in 2018. By treating over 20 000 individuals annually for 5 years, the treatment could then decrease to below current levels by 2030. Due to the large numbers of individuals being treated, there would need to be an increase in diagnosis rate to keep pace with the treatment rate. Utilizing a birth cohort with the young infected population could make diagnosis, treatment and thus elimination, a real possibility in Iran.

Japan

Given high HCV prevalence among the older adults in Japan [9], the HCV-infected population is rapidly ageing, and the infected population will decline in future years. The occurrence of substantial numbers of incident HCV-attributable HCC cases began decades earlier in Japan as compared with the USA [10], and the burden of HCV-attributable advanced liver disease is now declining in Japan. However, the burden of disease is still notable, with over half of HCC cases in Japan occurring among HCV-infected individuals [11]. A scenario focused on increased treatment efficacy alone had a relatively large impact on HCC incidence by 2030. By increasing the annual treated population by a relatively small number, a 75% reduction in HCC incidence would be possible by 2030.

Latvia

Under the current treatment structure, the prevalence of chronic HCV is projected to increase through 2030. Despite a treatment rate of approximately 2.0%, the rate of new infections (97 per 100 k) due to continued transmission through injection drug use (IDU) and in the general community and medical settings may hinder efforts to mitigate the burden of HCV in Latvia. In this analysis, it was found that the adoption of higher SVR therapies would have a small impact on the burden of advanced disease (15%) and overall viremic cases (10%). Combined with an increase in treatment rate (up to 2.7%), the burden of advanced disease was reduced by 40–45% and overall viremic infections by 25%.

Lebanon

Under the current treatment paradigm, the prevalence of chronic HCV is projected to fall slightly by 2030, with a 4% decrease, but cases of advanced stage liver disease are projected to increase by 18–30%. Adoption of higher efficacy treatments alone would lead to a reduction in cases of advanced stage liver disease, but would not result in large differences in viremic prevalence from the current treatment paradigm. Eradication could be possible with

increased efficacy and treatment; however, awareness campaigns and a national screening programme are needed to increase diagnosis before major increases in treatment rates can occur.

Lithuania

Under the current treatment structure, the prevalence of chronic HCV was projected to remain relatively flat, with a 5% increase by 2030. A modest treatment rate (1.4%) and high incidence rate (35 cases per 100 000 persons) may contribute to this sustained prevalence. In this analysis, it was found that the adoption of higher SVR therapies, in the absence of an increased number of patients treated, would have a minimal impact on viremic cases and advanced disease (8–9% reduction). Increasing the treatment rate to 14.9% by 2020 would have a substantial impact on the number of viremic individuals and advanced outcomes by 2030 (80–90% reduction) as compared with the base case.

Pakistan

Although Pakistan has one of the largest numbers of infected individuals in the world, with an estimated 231 100 new cases each year, the total number of infected is increasing under the current treatment paradigm. The HCV-infected population in Pakistan is older, with greater occurrence of advanced disease sequelae and a relatively low treatment rate. These factors contribute to the fact that increasing SVR will have a minimal effect, a 5% decrease from the base case, on the infected population.

To truly mitigate the HCV disease burden in Pakistan, one needs to address the trinity of prevention, treatment and diagnosis. A major step in prevention would be a nationwide transition to the use of syringes with reuse prevention features, as nosocomial transmission is the major mode of transmission in Pakistan. With such a large infected population, it is imperative to increase treatment. By increasing treatment to 510 000 individuals for 13 years, there would be an estimated 90% reduction in the total number of viremic individuals. The increase in diagnosis is only required to keep pace with the increase in the number of individuals treated. By addressing these three areas, Pakistan provides evidence that even in a highly endemic and low income country, HCV can be eliminated via a cohesive national strategy.

Romania

The number of viremic infections is expected to decrease 25% by 2030, despite low treatment rates and efficacy under the current treatment paradigm, due to an ageing infected population. HCV prevalence in individuals aged 60–69 years is almost double that of individuals aged 50–59 years [12]. Large increases in the annual diagnosed and treated population are necessary to reduce the number of viremic individuals in Romania, but increasing treatment efficacy and gradually increasing treatment rates to three times the current rate would reduce rates of HCC and decompensated cirrhosis by 50–55% by 2030. Modelling an increased efficacy and treatment scenario required an increase in diagnosis by 10–25% each year that treatment was increased. Under the base case, <20% of the prevalent population was living with a diagnosis in 2014.

Saudi Arabia

Under the current treatment strategy, the number of viremic cases of HCV is expected to remain stable through 2030. While the incidence rate is moderate (11 cases per 100 000 persons), this is likely only partially offset by a low treatment rate (2%). However, modelling the use of advanced SVR therapies showed a 50–70% reduction in advanced stage HCV and liver-related mortality. Modelling increased SVR therapies and an increase in treatment from 380 to 5180 patients in 2017 and 9780 patients in 2020 would result in an almost 100% reduction in prevalence and >95% reduction in advanced stage HCV. Such a scenario requires that the number of patients diagnosed increases significantly along with the number treated. A national strategy to achieve these outcomes would likely require an aggressive screening programme.

Slovenia

In Slovenia, the national strategy for the control of HCV infection was set up in 1997, together with the National Viral Hepatitis Expert Group, for the management of HCV regarding diagnosing, treatment and prevention. Incidence of HCV in Slovenia is declining due to awareness campaigns, introduction of free-of-charge anonymous HCV testing and routine testing and counselling in the national healthcare network of 18 centres for the prevention and treatment of drug addiction that are integrated to five specialized clinics for HCV treatment [13]. Treated patients under the current treatment paradigm have, on average, an 80% SVR due to treatment optimization efforts, rigorous follow-up and adherence to treatment. As a result, viremic prevalence is projected to decrease by 20% by 2030. For this reason, increasing SVR only has little effect on the projected number of viremic cases compared with some of the other countries presented here, which often have lower base efficacy rates. In Slovenia, viremic patients are treated without restrictions, yet the detection rate, including in those with advanced liver disease, is relatively low. An increase in detection of HCV-infected patients with advanced liver disease and, if necessary, restricting available treatment regimens to more advanced cases would

cause a greater reduction in HCC, compensated cirrhosis and decompensated cirrhosis.

By incrementally increasing the number of annually treated patients to 590 in 2026 from a base of 150, Slovenia could achieve a 90% reduction in prevalence by 2030. Increasing treatment rates starting in 2016 would require the annual diagnosis rate to increase to 350 patients by 2019. Approximately half of the viremic cases in Slovenia have already been diagnosed.

South Korea

The burden of HCV in South Korea is largely concentrated in the older adult population, with relatively few new infections occurring annually (7.8 cases per 100 000 persons). As the population ages, the number of advanced stage patients will peak around 2020, before decreasing to 10–20% below 2014 values in 2030. Currently, 1.9% of viremic patients are treated annually, with an average SVR of 74%. Increasing SVR in the absence of an increased number of treated patients would have a minimal impact on viremic cases and advanced disease progression by 2030 (5% reduction). A 90% reduction in viremic cases would require an incremental increase in the number of treated patients, from 4500 annually in 2014 to 16 300 annually in 2020, with a simultaneous increase in the number of diagnosed cases (from 8050 annually in 2014 to 12 800 annually in 2030). Additionally, due to the ageing older population, treatment of adults up to 74 years of age would be necessary beginning in 2017 with treatment of adults up to 84 years of age by 2025.

UAE

Under the pre-DAA treatment strategy, the number of viremic cases of HCV would be expected to decrease steadily by 26% from 2014 to 2030. While the incidence rate is low (7.5 cases per 100 000 persons), this is likely only partially offset by a low treatment rate (1.3%). However, modelling the use of advanced SVR therapies, which were indeed introduced to the UAE in 2014, showed a 10–15% reduction in advanced stage HCV and liver-related mortality. Modelling increased SVR therapies and an increase in treatment from 140 to 950 patients per year in years 2015–2025 would result in a 95% decrease in prevalence and >99% reduction in advanced stage HCV. Such a scenario requires that the number of patients diagnosed increases significantly along with the number treated. A national strategy in this scenario would likely require an aggressive screening programme. Although the implementation of more effective therapies in the UAE will help to reduce the burden of HCV, a scenario in which treatment was expanded would have a significantly greater impact.

Utility of HCV Screening

As shown previously [1,7], diagnosis remains low in many countries. In some countries, the diagnosis rate was modelled to increase to provide a sufficient patient pool to achieve the desired strategy. However, it is not clear whether the number of newly diagnosed patients can realistically be increased without a focused screening strategy.

In the United States, the Centers for Disease Control and Prevention have recommended screening the birth cohorts with a higher prevalence rate to allow for a more efficient use of resources [14–16]. A birth cohort analysis was conducted for the studied countries, and the results are shown in Fig. 17. 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 analysed, was from 20 to 40 years, likely due to variations in risk factors. The range was wider when nosocomial infection was identified as a risk factor (e.g., blood transfusions prior to blood screening). In countries where IDU was identified as a key risk factor, the birth cohort range often included individuals born between 1980 and 1990. The birth year cohorts provide an efficient source for identifying new patients as part of a national screening strategy.

There were a number of limitations with this study. SVR rates for current treatment protocols were based on clinical data from centres experienced in treating patients and managing adverse events. SVR rates observed in other treatment venues could be substantially lower [17] than what is stated here, resulting in a larger difference between the base case and each of the scenarios. In addition, there is variance in HCV prevalence estimates [7]. Therefore, the relative impact of each scenario may be more or less pronounced if true prevalence is higher or lower than the estimated values used in this analysis.

Another limitation was that modelled increases in treatment rate, diagnosis rate, eligibility and SVR were assumed to take effect immediately. In reality, the successful adoption of new therapies and implementation of infection control strategies at the national level would take several years to accomplish. However, analyses examining the impact of accelerating or delaying increases in SVR or treatment consistently demonstrated that desired outcomes were more likely to be achieved when the strategies were implemented earlier.

A final limitation of this analysis is that disease progression was considered to halt once patients were cured. However, it has been shown that the risks of advanced liver disease and related mortality can remain among cured patients, but at markedly lower rates [18]. Therefore, the model could overestimate the impact of curing patients on overall HCV liver-related morbidity and mortality. Any underestimation is likely to be minimal, as most reduction

in HCV morbidity and mortality came from prevention of HCV progression in earlier disease stages where progression to more advanced liver disease is unlikely.

This analysis demonstrated that the total number of HCV infections is expected to decline or remain flat in most countries. However, HCV-related morbidity and mortality are expected to increase in almost all countries. Reducing HCV disease burden is possible with a two-pronged effort, where active screening programmes find and identify HCV-infected individuals and where active management with antiviral therapy is maintained.

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Note

[1]Due to rounding, changes relative to base case are equivalent to <1 case.

REFERENCES

1 Sibley A, Han KH, Abourached A *et al.* The present and future disease burden of hepatitis C virus (HCV) infections with today's treatment paradigm - volume 3. *J Viral Hepat* 2015; 22(Suppl 4): 21–41.

2 Hatzakis A, Chulanov V, Gadano AC *et al.* The present and future disease burden of hepatitis C virus (HCV) infections with today's treatment paradigm - volume 2. *J Viral Hepat* 2015; 22(Suppl 1): 26–45.

3 Razavi H, Waked I, Sarrazin C *et al.* The present and future disease burden of hepatitis C virus (HCV) infection with today's treatment paradigm. *J Viral Hepat* 2014; 21 (Suppl 1): 34–59.

4 Evon DM, Verma A, Dougherty KA *et al.* High deferral rates and poorer treatment outcomes for HCV patients with psychiatric and substance use comorbidities. *Dig Dis Sci* 2007; 52(11): 3251–3258.
5 Morrill JA, Shrestha M, Grant RW. Barriers to the treatment of hepatitis C. Patient, provider, and system factors. *J Gen Intern Med* 2005; 20(8): 754–758.
6 North CS, Hong BA, Adewuyi SA *et al.* Hepatitis C treatment and SVR: the gap between clinical trials and real-world treatment aspirations. *Gen Hosp Psychiatry* 2013; 35 (2): 122–128.
7 Liakina V, Hamid S, Tanaka J *et al.* Historical epidemiology of hepatitis C virus (HCV) in select countries-volume 3. *J Viral Hepat* 2015; 22 (Suppl 4): 4–20.
8 Olafsson S, Bergmann O, Jonasson J, Ormarsdottir S. Major increase in the incidence of cirrhosis in Iceland - results of a nationwide population based study. *Hepatology* 2011; 54 (S1): 587A–588A.
9 Tanaka J, Koyama T, Mizui M *et al.* Total numbers of undiagnosed carriers of hepatitis C and B viruses in Japan estimated by age- and area-specific prevalence on the national scale. *Intervirology* 2011; 54(4): 185–195.
10 Tanaka Y, Hanada K, Mizokami M *et al.* A comparison of the molecular clock of hepatitis C virus in the United States and Japan predicts that hepatocellular carcinoma incidence in the United States will increase over the next two decades. *Proc Natl Acad Sci U S A* 2002; 99 (24): 15584–15589.
11 Umemura T, Ichijo T, Yoshizawa K, Tanaka E, Kiyosawa K. Epidemiology of hepatocellular carcinoma in Japan. *J Gastroenterol* 2009; 44 (Suppl 19): 102–107.
12 Gheorghe L, Csiki IE, Iacob S, Gheorghe C, Smira G, Regep L. The prevalence and risk factors of hepatitis C virus infection in adult population in Romania: a nationwide survey 2006–2008. *J Gastrointestin Liver Dis* 2010; 19(4): 373–379.
13 Matičič M. A national multidisciplinary healthcare network for treatment of hepatitis C in people who inject drugs in Slovenia. *BMC Infect Dis* 2014; 14(Suppl 6): S6.
14 Ward JW. The hidden epidemic of hepatitis C virus infection in the United States: occult transmission and burden of disease. *Top Antivir Med* 2013; 21(1): 15–19.
15 Smith BD, Morgan RL, Beckett GA *et al.* Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945–1965. *MMWR Recomm Rep* 2012; 4: 1–32.
16 Rein DB, Smith BD, Wittenborn JS *et al.* The cost-effectiveness of birth-cohort screening for hepatitis C antibody in U.S. primary care settings. *Ann Intern Med* 2012; 156(4): 263–270.
17 Backus LI, Boothroyd DB, Phillips BR, Mole LA. Predictors of response of US veterans to treatment for the hepatitis C virus. *Hepatology* 2007; 46(1): 37–47.
18 Aleman S, Rahbin N, Weiland O *et al.* A risk for hepatocellular carcinoma persists long-term after sustained virologic response in patients with hepatitis C-associated liver cirrhosis. *Clin Infect Dis* 2013; 57(2): 230–236.