

Strategies to manage hepatitis C virus (HCV) infection disease burden – volume 2

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O. Dalgard has no conflicts of interest.

I. Shestakova has no conflicts of interest.

P. Nymadawa has no conflicts of interest.

S. Blach, C. Estes, E. Gower, H. Razavi and K. Razavi-Shearer have no conflicts of interest. They are employees of The Center for Disease Analysis and are barred from accepting any personal consulting or any other outside funding. The Center for Disease Analysis has received research funding from public and private sources (Gilead Sciences, Boehringer Ingelheim and AbbVie), but its projects are limited to basic epidemiology and modeling research.

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ABSTRACT

The hepatitis C virus (HCV) epidemic was forecasted through 2030 for 15 countries, and the relative impact of two scenarios was considered: (1) increased treatment efficacy while holding the treated population constant and (2) increased treatment efficacy and increased annual treated population. Increasing levels of diagnosis and treatment, in combination with improved treatment efficacy, were critical for achieving substantial reductions in disease burden. In most countries, the annual treated population had to increase several fold in order to achieve the largest reductions in HCV-related morbidity and mortality. This suggests that increased capacity for screening and treatment will be critical in many countries. Birth cohort screening is a helpful tool for maximizing resources. In most of the studied countries, the majority of patients were born between 1945 and 1985.

ABBREVIATIONS

DAA, direct acting antiviral agent; HCC, hepatocellular carcinoma; G, Genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug use; MSM, men who have sex with men; Peg-IFN, Pegylated interferon; PI, protease inhibitor; RBV, ribavirin; SVR, sustained viral response;

INTRODUCTION

The previous publication in this supplement showed the forecasted increase in hepatitis C virus (HCV) related mortality and morbidity, although the total number of infections is declining in many countries (1). Both trends are driven by the aging population. This leads to an increase in all-cause mortality, resulting in a decline in the total number of infections. The aging population also leads to an increase in liver related deaths as the HCV infected population advances to late-stage liver disease. The previous publication focused on the analysis of disease burden if the current treatment paradigm continues.

In reality, the treatment paradigm is likely to change in the future with the introduction of new all-oral therapies with a higher cure rate, fewer side effects, less on-treatment monitoring and shorter duration of treatment. However, how these new therapies will change clinical practice is more difficult to forecast. There is no doubt that better tolerated, less complex regimens should

remove current real and perceived barriers to treatment uptake, whilst improving access in the community. The change in future treatment of HCV will depend on the approval of new therapies, their cost, the healthcare budget allocated to HCV, physicians' experience with the new therapies outside of a clinical setting and the size of the diagnosed population with access to care. There is an ongoing debate regarding the cost of the new therapies, and there are numerous groups and government agencies who are conducting cost effectiveness studies. In addition, significant inter-regional differences in disease prevalence, access to specialist care and reimbursement policies are likely to create global inequalities for access to new therapies.

The impact of treatment cost was not considered here. The aim of this analysis was to show the impact of conservative and aggressive intervention strategies on the future disease burden. Extreme strategies were considered to illustrate the potential range of outcomes. The reality may fall within one of these strategies. The focus of this analysis was not prescriptive, stating what should be done to reduce HCV disease burden. Instead, the focus was descriptive, showing the impact on disease burden if certain assumptions became true.

METHODOLOGY

The details of the model used to forecast HCV disease burden was described previously (1;2). The model interface allowed for changing assumptions for the number of patients treated, the proportion of cases eligible for treatment, the reduction in treatment restrictions, the average sustained viral response (SVR) by genotype, the number of newly diagnosed individuals and the number of new infections at five different points in time. The year in which these changes took effect was also an input field. 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. 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) number diagnosed, (ii) number eligible and (iii) unrestricted cases. The latter related to implicit (defined by physician's practice) and/or explicit (defined by treatment guidelines) restrictions. These restrictions could be modified by changing the upper and lower end of patient's age and their stage of fibrosis ($\geq F4$, $\geq F3$, $\geq F2$, $\geq F1$

or $\geq F0$). Review of treatment guidelines and interviews with expert panels were used to identify both. 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 Figures 1-15. When the number of treated patients was more than those diagnosed, eligible and unrestricted, the number of newly diagnosed cases was increased or the treatment restrictions were relaxed. 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 (3-5). The definition of eligibility included lack of contraindications to the drugs (e.g., psychiatric conditions) as well as patients' 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 increased. 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.

In this analysis, three strategies were considered – base, increased efficacy only and increased efficacy and treatment. The base strategy 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. This was assumed to be the most conservative scenario that is feasible. Even more conservative scenarios are possible (e.g., stop treating HCV patients completely), but those were deemed to be unlikely. The base scenario for each country was described in detail previously (1). In the second strategy, the impact of increasing the SVR of therapies was considered. The number of treated patients was kept constant as in the base strategy. In a few countries, treatment restrictions were relaxed if we ran out of patients to treat in the future. However, all other assumptions remained consistent with the base strategy.

The third scenario included an increase in SVR and treatment. The assumptions for the number of treated patients in the future were often driven by a desire to achieve a certain goal (i.e., control HCV disease burden) and were developed in discussion with expert panels. In order to

achieve some of these strategies, expanding access to patients with early stages of fibrosis (F0-F2) was considered. In most instances, the number of newly diagnosed cases also had to be increased to keep up with the depletion of the diagnosed eligible patient pool.

Scenario inputs, including SVR, fibrosis stage and medical eligibility are provided, by genotype and year, in Figures 1-15. The numbers of treated and diagnosed patients necessary to achieve the desired scenario outputs are also provided.

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 incidence was used for new HCV infections and not newly diagnosed. Hepatocellular carcinoma (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.

Birth Cohort Effect – The age distribution of each country was gathered from published data and reported previously (6). 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 75% (or more) of the total HCV infected population using the 2013 HCV population distribution (1).

RESULTS

The results of the analyses are summarized in Figure 16. The birth cohort effect in the HCV infected population is shown in Figure 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.

Argentina

Increased Efficacy Only: There will be 710 fewer viremic individuals in 2030, a 0.3% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 3510 cases, a 0.2% decrease from the base case. Similarly, the number of liver related deaths will decrease by

0.2% from the base, with 3050 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 0.2% and 0.3% from the base, with 8450 and 62 470 cases in 2030.

Increased Efficacy & Treatment: With an aggressive treatment and diagnosis strategy, there will be 112 400 fewer viremic individuals in 2030, a 45% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 1830 cases, a 50% decrease from the base case. Similarly, the number of liver related deaths will decrease by 50% from the base, with 1560 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 60% from the base, with 3280 and 25 100 cases respectively in 2030.

Finland

Increased Efficacy Only: There will be 800 fewer viremic individuals in 2030, a 5% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 90 cases, a 10% decrease from the base case. Similarly, the number of liver related deaths will decrease by 10% from the base, with 70 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 10% from the base, with 180 and 1670 cases in 2030.

Increased Efficacy & Treatment: With an aggressive treatment strategy, there will be 10 800 fewer viremic individuals in 2030, a 50% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 50 cases, a 50% decrease from the base case. Similarly, the number of liver related deaths will decrease by 50% from the base, with 40 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 65% and 60% from the base, with 80 and 720 cases respectively in 2030.

Greece

Increased Efficacy Only: There will be 4340 fewer viremic individuals in 2030, a 5% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 930 cases, a 25% decrease from the base case. Similarly, the number of liver related deaths will decrease by 25% from the base, with 770 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 30% from the base, with 1930 and 13 980 cases in 2030.

Increased Efficacy & Treatment: With an aggressive treatment strategy, there will be 64 800 fewer viremic individuals in 2030, a 60% reduction as compared to the base case. The number of

HCC cases in 2030 was estimated at 410 cases, a 65% decrease from the base case. Similarly, the number of liver related deaths will decrease by 65% from the base, with 370 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 70% from the base, with 820 and 5880 cases in 2030.

India

Increased Efficacy Only: There will be 39 000 fewer viremic individuals in 2030, a 0.5% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 55 200 cases, a 3% decrease from the base case. Similarly, the number of liver related deaths will decrease by 3% from the base, with 51 900 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 4% and 3% from the base, with 159 000 and 1 164 000 cases, respectively, in 2030.

Increased Efficacy & Treatment: With an aggressive treatment and diagnosis strategy, there will be 1 960 000 fewer viremic individuals in 2030, a 25% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 25 300 cases, a 55% decrease from the base case. Similarly, the number of liver related deaths will decrease by 50% from the base, with 26 100 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 60% and 55% from the base, with 69 900 and 523 000 cases respectively in 2030.

Ireland

Increased Efficacy Only: There will be 680 fewer viremic individuals in 2030, a 2% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 160 cases, a 5% decrease from the base case. Similarly, the number of liver related deaths will decrease by 5% from the base, with 140 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 5% from the base, with 175 and 3210 cases in 2030.

Increased Efficacy & Treatment: With an aggressive treatment and diagnosis strategy, there will be 28 600 fewer viremic individuals in 2030, a 95% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 10 cases, a 95% decrease from the base case. Similarly, the number of liver related deaths will decrease by 95% from the base, with 10 deaths

in 2030. Decompensated and compensated cirrhosis will decrease by 95% from the base, with 5 and 105 cases respectively in 2030.

Israel

Increased Efficacy Only: There will be 2610 fewer viremic individuals in 2030, a 5% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 850 cases, a 5% decrease from the base case. Similarly, the number of liver related deaths will decrease by 5% from the base, with 760 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 5% from the base, with 2250 and 15290 cases in 2030.

Increased Efficacy & Treatment: With an aggressive treatment and diagnosis strategy, there will be 33 400 fewer viremic individuals in 2030, a 50% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 590 cases, a 35% decrease from the base case. Similarly, the number of liver related deaths will decrease by 40% from the base, with 490 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 50% and 45% from the base, with 1230 and 8850 cases in 2030.

Luxembourg

Increased Efficacy Only: There will be 303 fewer viremic individuals in 2030, a 10% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 4 cases, a 35% decrease from the base case. Similarly, the number of liver related deaths will decrease by 40% from the base, with 3 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 50% and 45% from the base, with 5 and 60 cases in 2030.

Increased Efficacy & Treatment: With an aggressive treatment strategy, there will be 2400 fewer viremic individuals in 2030, an 85% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 4 cases, a 40% decrease from the base case. Similarly, the number of liver related deaths will decrease by 35% from the base, with 3 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 50% and 55% from the base, with 5 and 55 cases in 2030.

Mexico

Increased Efficacy Only: There will be 28 800 fewer viremic individuals in 2030, a 5% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 3780 cases, a 10% decrease from the base case. Similarly, the number of liver related deaths will decrease by 10% from the base, with 3290 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 10% from the base, with 9330 and 68 100 cases in 2030.

Increased Efficacy & Treatment: With an increase in treatment rate, there will be 51 400 fewer viremic individuals in 2030, a 10% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 3310 cases, a 20% decrease from the base case. Similarly, the number of liver related deaths will decrease by 20% from the base, with 2870 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 25% from the base, with 7820 and 57 800 cases in 2030.

Mongolia

Increased Efficacy Only: There will be 710 fewer viremic individuals in 2030, a 0.3% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 1510 cases, a 1.0% decrease from the base case. Similarly, the number of liver related deaths will decrease by 1.1% from the base, with 1390 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 1.2% and 1.3% from the base, with 4280 and 27 180 cases in 2030.

Increased Efficacy & Treatment: With an aggressive treatment and diagnosis strategy, there will be 16 200 fewer viremic individuals in 2030, a 90% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 250 cases, an 85% decrease from the base case. Similarly, the number of liver related deaths will decrease by 85% from the base, with 210 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 90% from the base, with 470 and 2870 cases respectively in 2030.

Netherlands

Increased Efficacy Only: There will be 2560 fewer viremic individuals in 2030, a 25% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 70 cases, a

30% decrease from the base case. Similarly, the number of liver related deaths will decrease by 30% from the base, with 60 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 40% and 35% from the base, with 90 and 870 cases respectively in 2030.

Increased Efficacy & Treatment: With an aggressive treatment and diagnosis strategy, there will be 9080 fewer viremic individuals in 2030, an 85% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 30 cases, a 70% decrease from the base case. Similarly, the number of liver related deaths will decrease by 70% from the base, with 20 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 75% from the base, with 40 and 330 cases respectively in 2030.

New Zealand

Increased Efficacy Only: There will be 3250 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 10% decrease from the base case. Similarly, the number of liver related deaths will decrease by 15% from the base, with 290 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 15% and 10% from the base, with 810 and 6680 cases in 2030.

Increased Efficacy & Treatment: With an aggressive treatment strategy, there will be 35 520 fewer viremic individuals in 2030, a 90% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 95 cases, a 75% decrease from the base case. Similarly, the number of liver related deaths will decrease by 70% from the base, with 110 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 80% from the base, with 170 and 1330 cases respectively in 2030.

Norway

Increased Efficacy Only: There will be 2440 fewer viremic individuals in 2030, a 10% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 79 cases, a 25% decrease from the base case. Similarly, the number of liver related deaths will decrease by 25% from the base, with 60 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 35% and 30% from the base, with 60 and 1300 cases in 2030.

Increased Efficacy & Treatment: With an aggressive treatment and diagnosis strategy, there will be 17 800 fewer viremic individuals in 2030, an 85% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 40 cases, a 60% decrease from the base case. Similarly, the number of liver related deaths will decrease by 55% from the base, with 40 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 70% from the base, with 30 and 560 cases in 2030.

Poland

Increased Efficacy Only: There will be 24 700 fewer viremic individuals in 2030, a 15% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 1020 cases, a 15% decrease from the base case. Similarly, the number of liver related deaths will decrease by 15% from the base, with 880 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 15% from the base, with 1910 and 18 400 cases in 2030.

Increased Efficacy & Treatment: With an aggressive treatment and diagnosis strategy, there will be 168 000 fewer viremic individuals in 2030, a 90% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 200 cases, an 80% decrease from the base case. Similarly, the number of liver related deaths will decrease by 80% from the base, with 200 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 85% from the base, with 300 and 2810 cases in 2030.

Russia

Increased Efficacy Only: There will be 24 600 fewer viremic individuals in 2030, a 1% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 16 400 cases, a 1% decrease from the base case. Similarly, the number of liver related deaths will decrease by 1% from the base, with 16 000 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 1% from the base, with 51 600 and 396 000 cases respectively in 2030.

Increased Efficacy & Treatment: With an aggressive treatment strategy, there will be 2 480 000 fewer viremic individuals in 2030, a 40% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 4740 cases, a 70% decrease from the base case. Similarly, the number of liver related deaths will decrease by 75% from the base, with 4270 deaths in 2030.

Decompensated and compensated cirrhosis will decrease by 80% from the base, with 9190 and 85 600 cases respectively in 2030.

Slovak Republic

Increased Efficacy Only: There will be 1540 fewer viremic individuals in 2030, a 5% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 180 cases, a 10% decrease from the base case. Similarly, the number of liver related deaths will decrease by 10% from the base, with 160 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 10% from the base, with 450 and 3400 cases in 2030.

Increased Efficacy & Treatment: With an aggressive treatment and diagnosis strategy, there will be 26 400 fewer viremic individuals in 2030, a 90% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 30 cases, an 80% decrease from the base case. Similarly, the number of liver related deaths will decrease by 80% from the base, with 40 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 80% and 85% from the base, with 60 and 460 cases respectively in 2030.

South Africa

Increased Efficacy Only: A strategy was created to assess the impact of increased SVR on disease burden. However, due to a low treatment rate, there was no impact on disease burden at the national level.

Increased Efficacy & Treatment: With an increased treatment strategy, there will be 23 300 fewer viremic individuals in 2030, a 10% reduction as compared to the base case. The number of HCC cases in 2030 was estimated at 1670 cases, a 20% decrease from the base case. Similarly, the number of liver related deaths will decrease by 20% from the base, with 1630 deaths in 2030. Decompensated and compensated cirrhosis will decrease by 25% from the base, with 4330 and 30 800 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 drop in Argentina, Greece, Luxembourg, Mexico, the Netherlands, New Zealand, Poland, Slovak Republic and South Africa and remain relatively flat or increase in Finland, India, Norway and Russia. However, HCV related mortality and morbidity is expected to increase in all countries with the exception of the Netherlands, which has a high treatment rate (1). This analysis demonstrated 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 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 2.8-4.5% – the Netherlands, Luxembourg and Norway.

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.

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 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 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.

Argentina –

There are few studies exploring the prevalence of HCV among the general population in Argentina, as many studies have been limited to regional or high-risk populations. Among blood donors, there were significant declines in HCV prevalence between 2004 and 2011 in most regions (7). The Statement of the Argentinian Consensus on Hepatitis C 2007 (8) estimated HCV prevalence of 2.0%, but this rate has likely decreased and is largely based upon studies in adults.

With current treatment levels, prevalence is projected to decline over 30% by 2030 to 0.5%. Most of this decrease is due to mortality among the infected population, as treatment levels are low, and the average age of the infected population is increasing. A scenario focused on increased treatment efficacy alone had little impact on overall disease burden. In order to reduce HCV-related morbidity and mortality, large increases in the annual diagnosed and treated population are necessary.

Finland –

Finland has an active infectious disease registry system managed by the National Institute for Health and Welfare that has captured HCV diagnosis data since 1995, providing a well characterized diagnosed population pool. However, treatment of chronic HCV has remained more limited with an estimated treatment rate of 1.4%. Increasing treatment efficacy resulted in a small decrease (10%) in HCV-related mortality without growing the diagnosed or treated population. With ongoing transmission through IDU and a projected steady-state of new infections, a strategy was developed to assess the required number of treated individuals to achieve a reduction in prevalence of 50% by 2030. By increasing the treatment rate from 300 to 1130 individuals annually by 2020 with no change in diagnosis, total infections were reduced by 50%. Further, because chronic infection is most prevalent among younger individuals (24-29 years of age) (9), treatment benefits may extend past the scope of this analysis (2030). With that, this strategy assumes that individuals chronically infected are eligible for treatment. However, active injection drug use (IDU) is the most common reported transmission route in Finland (9),

and to be eligible for treatment, individuals must be clean from use for two years. In addition, they must receive a referral to a provider.

Greece –

The prevalence rate of chronic HCV infection in Greece is among the highest in Western Europe, and the burden of infection is increasing (10). However, approximately 80% of individuals have never been tested for HCV and among those diagnosed, 40% have not received treatment (10). With an older infected population, treatment with new therapies showed a modest decrease (25%) on HCV-related mortality with no change in treatment structure. There was minimal change (5%) in total HCV infections, likely attributed to the assumption of continued transmission through IDU. To assess the steps necessary to reduce morbidity and mortality by two-thirds, treatment and diagnosis were increased stepwise over the study period to 8260 and 10 800 individuals annually. Total infections declined 60% to less than 42 000 infected individuals.

There are known barriers to treatment among currently diagnosed patients, including but not limited to: active IDU, lack of health insurance, fear of side-effects and stigma (10). In addition, there remains a large undiagnosed population. This analysis demonstrates that favorable improvements in disease burden are realistic with policy change; however, this will require a coordinated national strategy.

India –

Although a variety of studies have been published estimating the HCV prevalence in India, choosing a study representative of the general population is difficult due to the country's large and diverse population. With a population of 1.2 billion, even a 0.01% change in prevalence has an impact of more than 100 000. In the absence of intervention, the viremic prevalence was estimated to remain relatively stable, increasing slightly until 2019 and then decreasing to 3% below 2013 estimates. Continued unsafe medical injection practices are thought to contribute to the slow reduction in cases.

Additionally, the treatment rate in India is low (0.2%) and treatment is self-funded. This makes generalizing the treated population and predicting future treatment uptake difficult. The expert panel agreed that strategies examining the impact of a coordinated government approach would be most meaningful. During these modeling efforts, it was found that targeted treatment (by age

and disease segment) could half liver related mortality by 2030, but would require a treatment rate of 2.6%. In the absence of increasing treatment, prevention efforts aimed at promoting safe medical injection practices and increasing awareness may reduce the incidence of HCV in India.

Ireland –

Screening for HCV began in 1989, and approximately 95% of diagnosed cases have been captured through the National Virus Reference Laboratory (11). Nosocomial transmission contributed to the epidemic in earlier years, including a notable number of individuals infected through contaminated anti-D immune globulin. However, the majority of infected individuals in recent years report IDU (11). There is also evidence of transmission among human immunodeficiency virus (HIV)-positive men who have sex with men (MSM) (12).

Given the large role of IDU in HCV transmission in recent years, the age of infected individuals is relatively young, and much of the burden of HCV-related morbidity and mortality will occur after 2030 in the base case scenario. With current treatment levels, prevalence is projected to decrease by fewer than 1000 cases between 2013 and 2030. Increases in the treatment efficacy and the annual treated population have the potential to greatly impact the burden of liver disease in Ireland. Compared to other countries, relatively few infected individuals have progressed to cirrhosis or advanced liver disease. However, there is evidence of increasing incidence of HCV-related advanced liver disease. Surveillance data for a cohort of individuals infected through blood products indicate growing rates of cirrhosis and HCC (13).

Israel –

HCV infection in Israel has been largely influenced by the influx of immigrants in two waves (1960s and 1990s). Analysis suggests that more than 550 viremic cases entered the country annually during the 1960s, with more than 900 viremic cases annually during the 1990s. Since the 1990s, however, the number of cases due to immigration has steadily decreased. On average, it was estimated that these cases entered the country with a METAVIR stage F2, due to the demographic profile of the individuals immigrating. As a result of the more advanced stage population, HCC and liver related mortality were expected to increase 80-90% by 2030.

The treatment rate in Israel was approximately 1%, and the impact of increasing SVR without increasing treatment was relatively small (approximately 5% reduction in viremic infections,

HCC and liver related deaths). It is important to note that higher SVR therapies were modeled solely for G1 patients, so the impact of new DAAs on other genotypes was not considered. Combining the G1 SVR increase with an increased treatment rate for all genotypes (to 3.9% annually), and a subsequent increase in annual diagnosis (from 2200 to 5470 viremic diagnoses) resulted in a 50% reduction in viremic infections and decompensated cirrhosis. In 2013, it was estimated that only 24% of the viremic infections in Israel were diagnosed, suggesting that strategies to increase treatment should also consider increasing screening and diagnosis.

Luxembourg –

Under the current treatment structure, the prevalence of chronic HCV was projected to decrease by 10%, which is moderate compared to some of the other countries presented here. Despite a high treatment rate (3.2%), the rate of new infections (21 per 100k) due to IDU may hinder efforts to mitigate the burden of HCV in Luxembourg. In this analysis, it was found that the adoption of higher SVR therapies would have a substantial impact on the burden of advanced disease (37-40%), even without increasing treatment rates. Combined with an increased treatment rate up to 7.7%, there was an additional benefit of an 86% reduction in total viremic infections.

The strategies modeled here did not require increases in the diagnosed population, as it was estimated that 84% of the viremic infected population was living with a diagnosis. This input has some uncertainty, however, as it was estimated through the combination of two databases that may overlap, although the degree of overlap is uncertain. The current diagnosis rate is in line with countries such as Australia and Sweden, and reducing the diagnosis rate to 70% (assuming 15% database overlap) would still place Luxembourg in line with France and Canada (14).

Mexico –

Mexican physicians have been active in the analysis and quantification of the burden of HCV disease. The majority of infections in Mexico are due to previous transfusion, and it is well known that disease, mortality and cost related to chronic HCV infection is increasing as the population ages (15-17). In a study of the etiology of liver cirrhosis, HCV was attributed in 37% of cases (18). Further, HCV has been attributed in 21% to 48% of liver transplants, with variations between transplant centers (19-22). With this in mind, it was important to develop realistic scenarios to curb the epidemic.

With a treatment rate of 0.6% in 2013, small improvements (10%) in HCV infection and HCV-related mortality were projected. A second strategy was developed to assess the impact of an increase in treatment from 3110 individuals annually to 5140 (treatment rate of 1.0%) individuals annually by 2016 with no change in diagnosis. This strategy was believed to be achievable and resulted in a decrease of HCV-related mortality of 20% by 2030. An increase in treatment rate to 2.0% (10000 individuals treated annually in F3) in the same timeframe showed decreases in HCV-related mortality of 50% (results not shown).

Mongolia –

There are few studies exploring the prevalence of HCV among Mongolian population, but data suggest that HCV infection rates are among the highest in the world. Likewise, Mongolia has one of the highest rates of liver cancer worldwide, and chronic HCV infection is a major contributor (23). With current treatment levels, prevalence is projected to decline by 2030. Most of this decrease is due to mortality among the infected population, as treatment levels are low, and the average age of the infected population is increasing. A scenario focused on increased treatment efficacy alone had little impact on overall disease burden. In order to reduce HCV-related morbidity and mortality, large increases in the annual diagnosed and treated population are necessary.

Netherlands –

Under the current treatment structure, the prevalence of chronic HCV infection was projected to decrease 45% over the next 15 years. This sharp decline is likely attributed to reductions in IDU and mortality among the aging population. However, the number progressing to end-stage liver disease was projected to increase, and there remains low awareness among the general population, as well as general practitioners, regarding the necessity of screening and treatment for chronic HCV infection.

Increasing treatment efficacy resulted in a reduction in HCV-related mortality of 30% without changes in treatment structure. In this strategy, treatment through 2015 was restricted to patients with a fibrosis stage \geq F3 before access was opened to F2 patients (2017) and F1 patients (2020). It is important to note that diagnosis of fibrosis is assessed using fibroscan technology, and distinguishing between different stages of liver disease may not always be reliably diagnosed;

thus, in practice, targeting treatment toward patients based on fibrosis may be more difficult. This analysis also demonstrated that by increasing treatment to 1700 individuals annually, and allowing treatment access to individuals regardless of fibrosis stage, the number of HCV infections in the Netherlands may be reduced by 95% to 1460 prevalent HCV infections by 2030. On average, there have been 1000 (Range: 880-1130) treatments with ribavirin annually from 2008-2013 (24;25). Assuming that this number is representative of the number of treatments for HCV, an increase to 1700 treatments annually may be feasible in the Netherlands as new therapies boast shorter duration of treatment as well as reduced side-effects. However, achievement of this strategy is dependent upon the detection of HCV infection, thus reinforcing the need for increased awareness among individuals and professionals.

Unfortunately, there is no national hepatitis plan in the Netherlands. While initiatives are underway, there is little concerted action. Necessary actions, albeit each with individual organizational and financial challenges, include active screening and treatment in risk groups such as: drug users enrolled in methadone treatment, HIV-infected MSM currently in care and migrants born in countries where HCV infection is endemic. In addition, there needs to be more attention to follow-up for individuals confirmed to be RNA-positive following blood donation. A coordinated national plan should be high on the political agenda.

New Zealand –

Earlier estimates of HCV prevalence in New Zealand were lower than the most recent estimate of 50 000 chronically infected individuals (26;27). In recent years, over 80% of infected individuals have reported a history of IDU (28). However, many cases occurred decades earlier, through both IDU and nosocomial transmission.

With current treatment levels, the population of infected individuals was projected to decline 20% between 2013 and 2030. Under a scenario with both greater treatment efficacy and substantial increases in the annual treated population, the prevalence dropped to below 5000 infected individuals by 2030, equivalent to a prevalence rate of 0.1%. This scenario also included notable increases in the annual diagnosed population. Currently, less than half of infected individuals are likely to be previously diagnosed. Screening and diagnosis of individuals at high risk for infection will be necessary to substantially reduce disease burden.

Norway –

Under the current treatment strategy, the number of viremic infections is expected to remain stable, decreasing only 3% by 2030. This is likely a result of a moderate incidence rate (15 per 100k) that is only partially offset by a moderate-high treatment rate (2.8%). Modeling the use of increased SVR therapies, however, showed a 25-35% reduction in advanced stage HCV and liver-related mortality. Increasing the treatment rate to 9.0% and treating all patients beginning in 2017 allowed for an 85% reduction in prevalence in addition to 55-65% reductions in advanced stage disease. With a 57% previously diagnosed rate and 5.0% annual diagnosis rate, modeling efforts were possible without increasing diagnosis. In reality, however, it is important to note that a diagnosed infection does not guarantee that the infected individual is necessarily aware of their diagnosis. A recent study suggests that only 40% of Norwegians were aware of their infection.

Poland –

Under a current treatment rate of approximately 2.0%, increasing treatment efficacy without an increase in treatment rate had a small impact (10%) on total HCV infections and HCV-related mortality. Under an aggressive treatment strategy where up to 15 000 individuals were treated and diagnosed annually, elimination of HCV by 2030 was modeled. It is understood that elimination of HCV by 2030 in Poland is unlikely; however, this analysis suggests that elimination could be achieved if appropriate increases in treatment and diagnosis were feasible. It is interesting to note that, with a 75% increase in treatment to 6300 patients annually by 2015, a reduction in HCV infections and HCV-related mortality of 35% was demonstrated (results not shown).

Russia –

Unlike many European countries where hepatitis C virus infection has been declining, surveillance data suggests that infection has been steadily increasing in Russia with an incidence of 12.9/100 000 individuals in 1999 and 39.1/100 000 individuals in 2012 (29). Increases have been driven by an increase in IDU since the 1990s. In spite of an increase in infections and an increase in disease burden (chronic HCV was attributed to 26% of liver cirrhosis in Moscow and 32% of liver transplants nationally), treatment remains low, with 5500 individuals treated in 2011, a 0.1% treatment rate.

In this analysis, the impact of increased treatment efficacy, with no change in treatment rate, resulted in negligible improvement at the national level. A strategy was run to consider the steps required to control disease burden in Russia by 2030. An increase in treatment to 124 000 individuals by 2019 (treatment rate of 2.6%) resulted in a 75% reduction in HCV-related mortality. This strategy focused on patients with fibrosis score of F2 or greater and required an increase in diagnosis to 300 000 individually annually to keep up with the increased treatment rate. While infeasible from an infrastructure standpoint, a 90% reduction in HCV cases was achieved when treatment was increased to 413 000 individuals (results not shown). These strategies highlight a need to develop and implement strategies early, through regional coordination and the implementation government guidelines, before patients progress to liver failure or HCC.

Slovak Republic –

Chronic HCV in the Slovak Republic is characterized by two peaks of infection: younger individuals predominantly infected through IDU and older adults, predominantly infected through unsafe transfusions or procedures. While there has been evidence of a slight decrease in the number of new infections, this analysis shows an increase in disease burden through 2030 as older adults progress to end-stage disease. Without change in treatment structure, burden will continue to increase as younger patients progress.

Increasing treatment rate without a current increase in treatment or diagnosis had only a small impact (5-10% reduction) in HCV infections and HCV-related mortality. This was primarily attributable to the low treatment rate (1.0%). A reduction of HCV infection by 90% and HCV mortality by 80% was achievable through an increase in treatment to 2880 individuals annually until the patient pool was depleted. Diagnosis of 2970 individuals annually was required to achieve this goal.

South Africa –

Infection with chronic hepatitis C virus remains a hidden epidemic in South Africa. There is momentum to increase awareness and treatment of HCV infection. In addition, efforts are in progress to update and expand the current epidemiology; however, at the time of this analysis, there were limitations due to data gaps. Most notably, the prevalence of chronic HCV infection and the transmission of infection are not well quantified. It is believed that transmission through

blood donation is low. Screening with ELISA testing began in 1990 and was expanded to include nucleic acid testing in 2005 and while HCV prevalence among IDU is high, the total number of IDU remains low (although IDU appears to be increasing and may represent a potential source of increased transmission in the future). HCV infection rates may also be influenced in South Africa due to continued migration from HCV endemic countries; however, this population does not receive routine healthcare screening, and data on the epidemiology of HCV infection in these cohorts is limited.

This analysis highlights the need to increase the number of patients to be treated in South Africa. Under an increased SVR scenario, the impact at the population level was negligible. When treatment was increased to 3000 patients annually, improvements in HCV-related mortality and end-stage liver disease were shown. Currently, treatment is not restricted based only on fibrosis stage. Patients with favorable pre-therapeutic screening are eligible for treatment. However, with potential therapeutic limitations in mind (e.g., access, cost, etc.), a scenario was run where treatment with new therapies was initially restricted to patients with more advanced disease ($\geq F3$), and patients $\geq F2$ were eligible in 2023. Under these conditions, HCV-related mortality decreased by 20% by 2030. It is not known if treatment of 3000 individuals annually will be feasible due to costs associated with new therapies. In addition, it is unknown if treatment based on fibrosis stage will become common practice in South Africa, as large increases in treatment would likely require treatment by more physicians, such as general practitioners and scale-up of laboratory support. Because treatment based on fibrosis would require an invasive biopsy or specialized devices for non-invasive scans, the infrastructure may not be in place to restrict treatment by fibrosis. Moreover, the ethical argument of restricting treatment with effective therapies to any patient remains. The same scenario was run for individuals with $>F1$ fibrosis staging, and HCV-related mortality decreased 12% by 2030.

Utility of HCV Screening – As shown previously (1;6), diagnosis remains low in many countries. For strategies in some countries, 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 focused screening strategy.

In the United States, the Centers for Disease Control and Prevention have recommended screening birth cohorts that have a higher prevalence rate to allow for an efficient use of

resources (30-32). A birth cohort analysis was conducted for the studied countries, and the results are shown in Figure 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 analyzed, was from 25 to 35 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 Argentina (33), Greece (34), Mexico (35), Poland (36) and South Africa. In countries where IDU was identified as a key risk factor, the birth cohort range often included individuals born between 1980 and 1990. The HCV epidemic is relatively young in Finland, Ireland, New Zealand and Russia, with the majority of the infected population born after 1960. Israel has a wide age distribution due to the wave of immigrations from high endemic countries. 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 centers experienced in treating patients and managing adverse events. SVR rates observed in other treatment venues could be substantially lower (37) 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 (6); the relative impact of each scenario may be more or less pronounced if true prevalence is higher or lower than the estimated values.

Another limitation was that modeled increases in treatment rate, diagnosis rate, eligibility and SVR were assumed to take effect immediately. Adoption of new therapies and strategies at the national level takes several years as new guidelines are developed. 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 is that disease progression was no longer followed when patients were cured. Among cured patients, risks for advanced liver disease and related mortality can remain, but at markedly lower rates (38). Therefore, the model could overestimate the impact of curing the patients on 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 programs find and identify HCV infected individuals and where active management with antiviral therapy is maintained.

ACKNOWLEDGEMENT

This work represents the collaboration of many experts across numerous countries, and we are indebted to them all. We would like to thank JE van Steenbergen and Anna Krabbe-Lugnér of the National Institute of Public Health and Environment for all their contributions, review of the data and discussion of the Netherlands' analyses. We are grateful to Lelia Thornton (Health Protection Surveillance Center), Cathal Walsh and Jennifer Kieran of Trinity College in Dublin for providing data and validating our assumptions in Ireland. We are also thankful for the contributions of Markku Kuusi, Henriikki Brummer-Korvenkontio, Elisa Huovinen, Salla Toikkanen, Mikko Virtanen and Maarit Sillanpää of THL, and, Martti Färkkilä of Finland. They provided data and were involved in the discussion of national data that were used in this analysis.

This project was supported by Gilead Sciences.

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Figure 1. Argentina model inputs, by Year

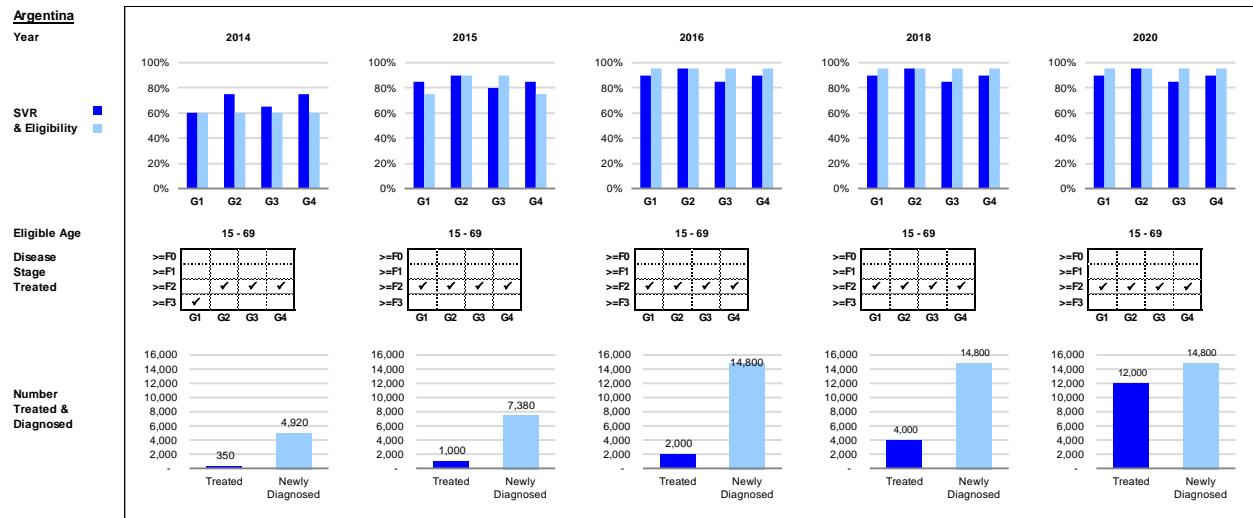


Figure 2. Finland model inputs, by year

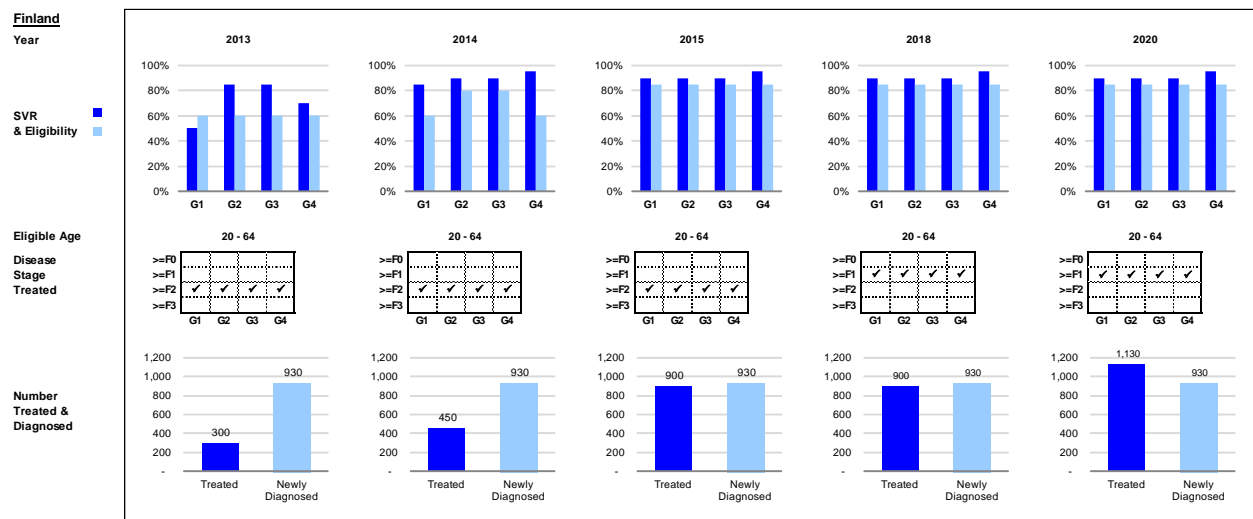


Figure 3. Greece model inputs, by year

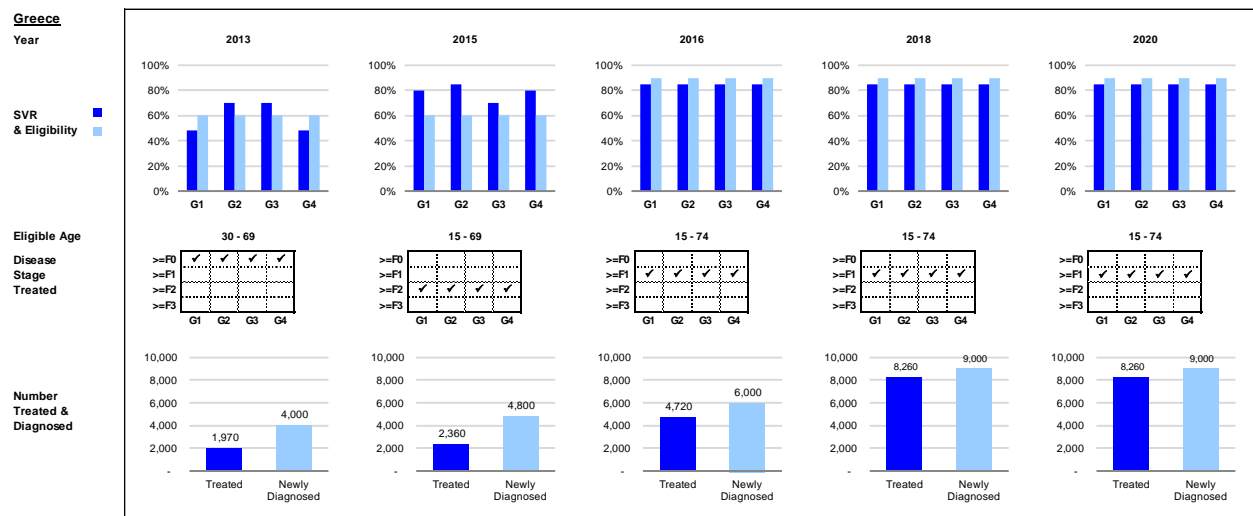


Figure 4. India model inputs, by year



Figure 5. Ireland model inputs, by year



Figure 6. Israel model inputs, by year



Figure 7. Luxembourg model inputs, by year



Figure 8. Mexico model inputs, by year

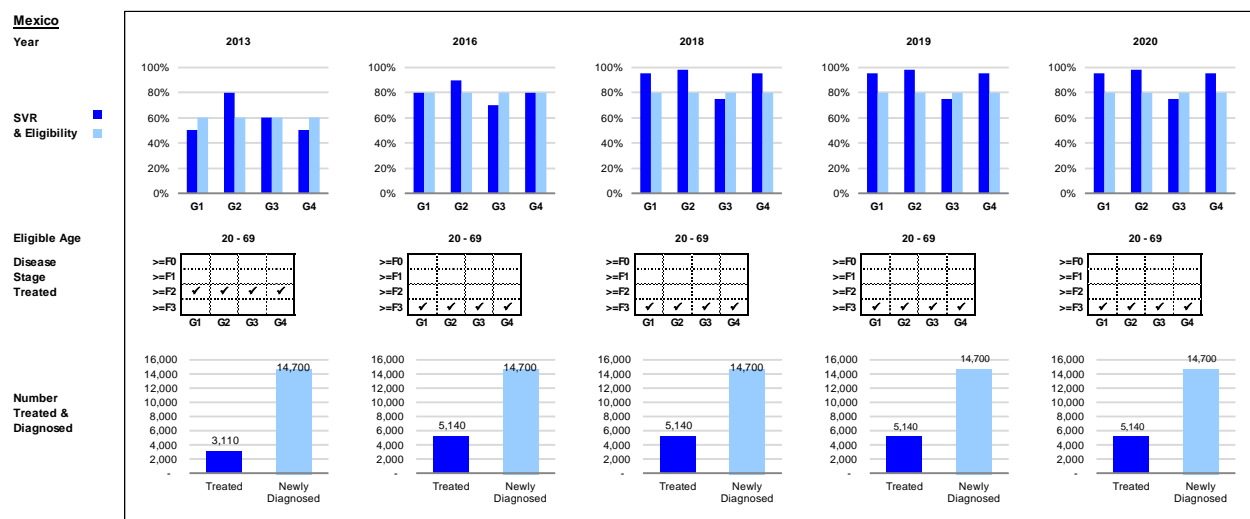


Figure 9. Mongolia model inputs, by year

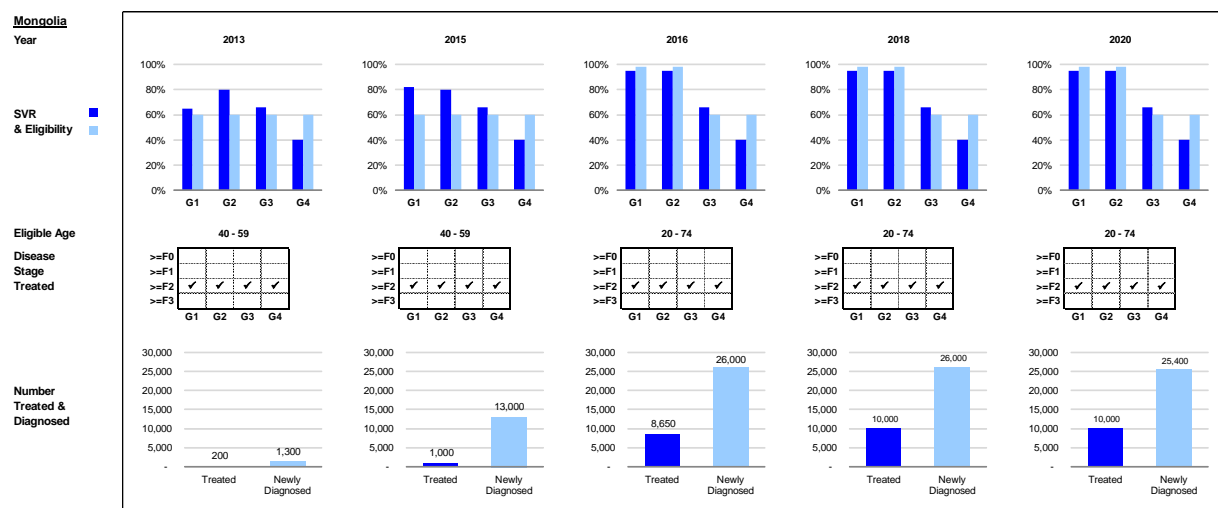


Figure 10. Netherlands model inputs, by year

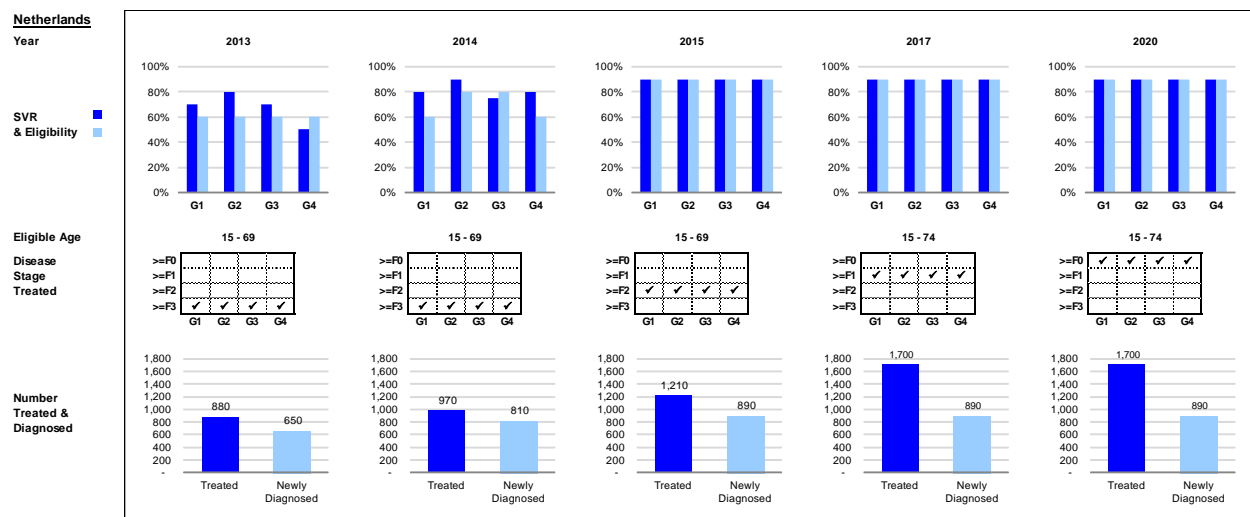


Figure 9. New Zealand model inputs, by year

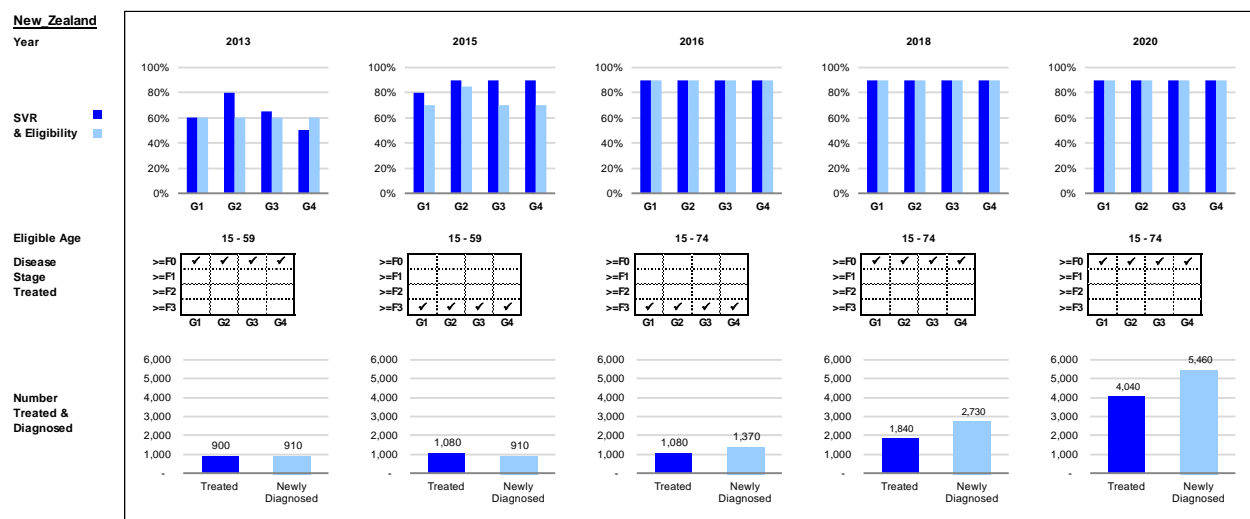


Figure 10. Norway model inputs, by year

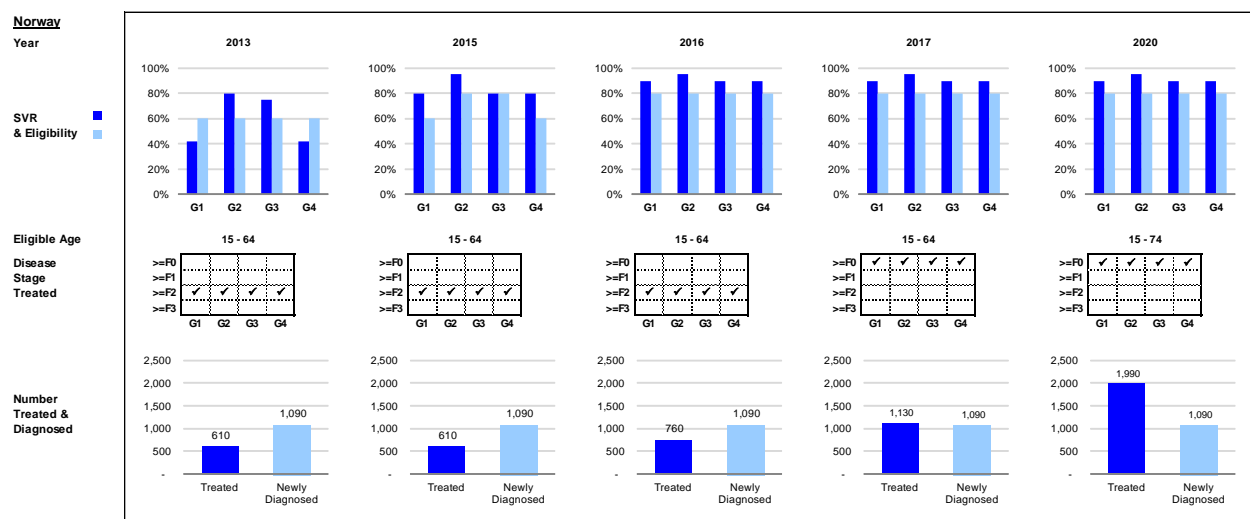


Figure 13. Poland model inputs, by year

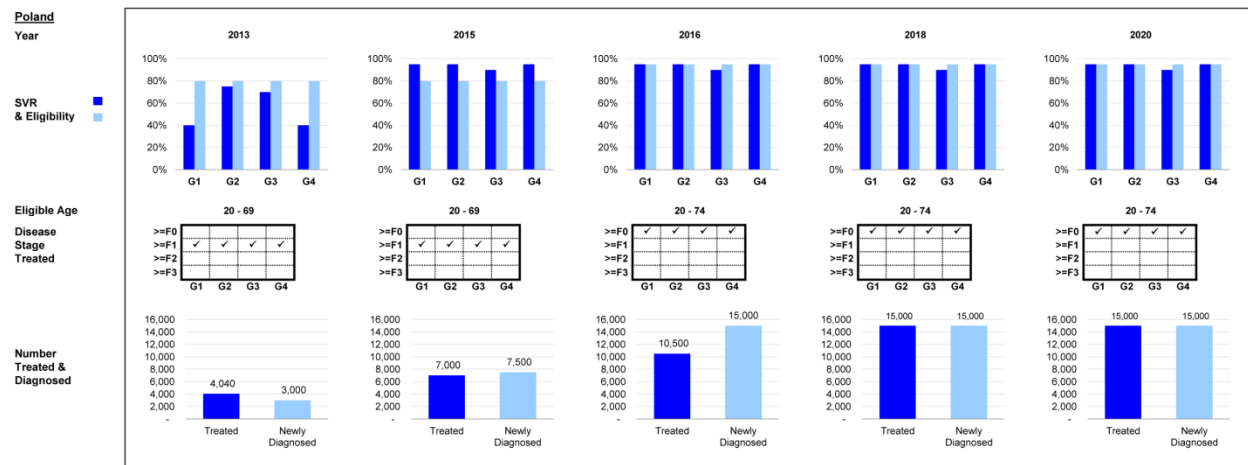


Figure 14. Russia model inputs, by year

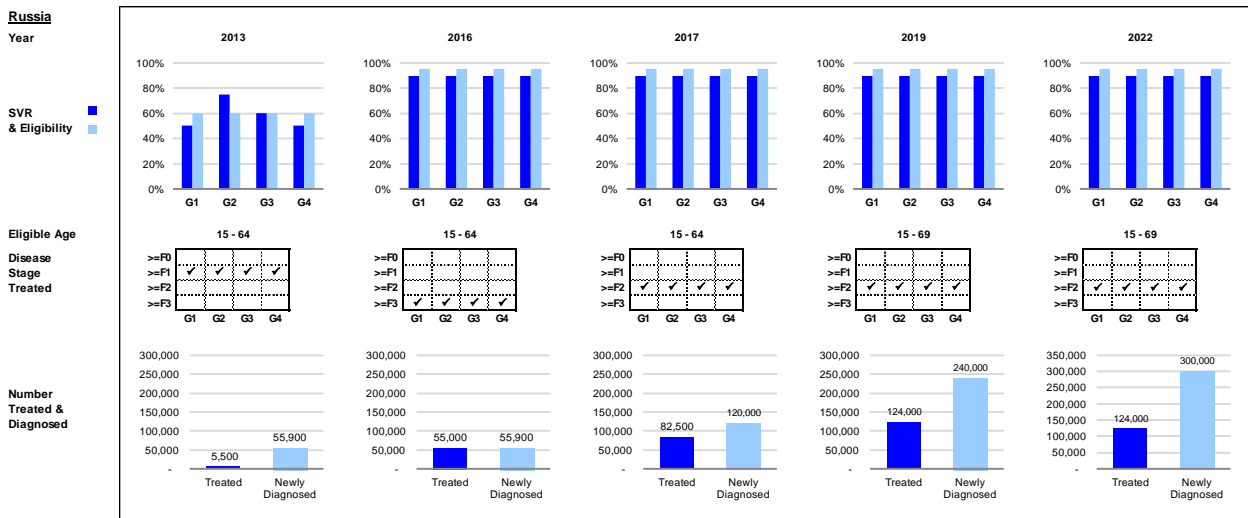


Figure 15. Slovak Republic model inputs, by year

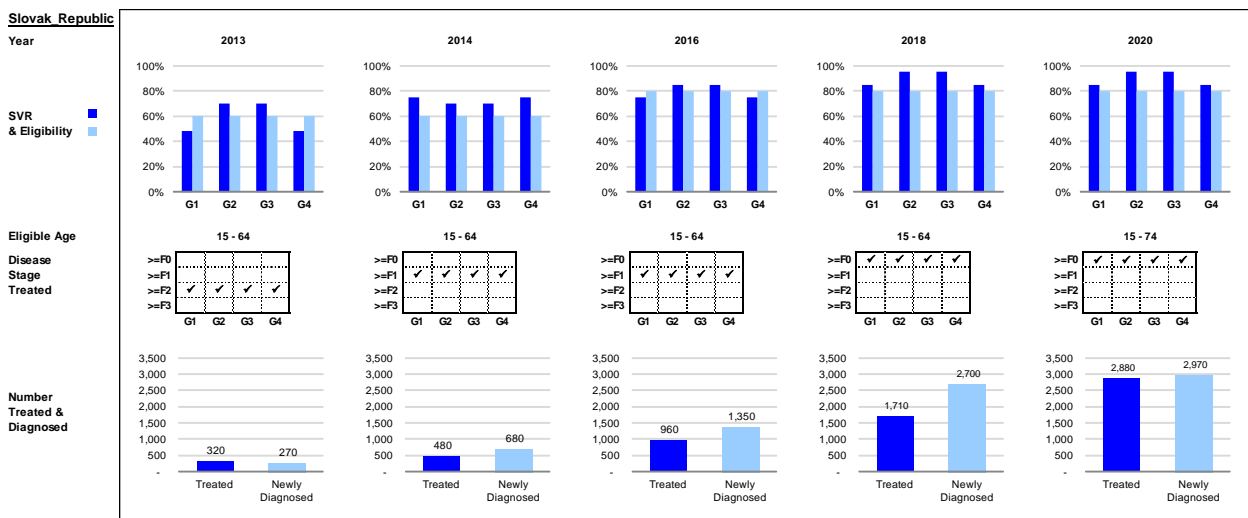


Figure 16. South Africa model inputs, by year

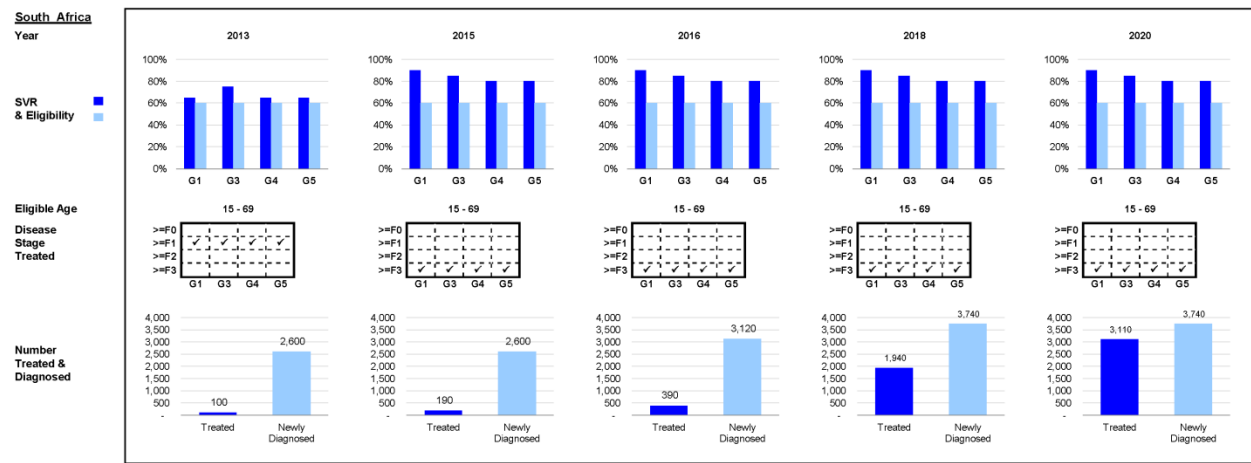


Figure 17. Change in HCV morbidity and mortality, by scenario, 2013-2030

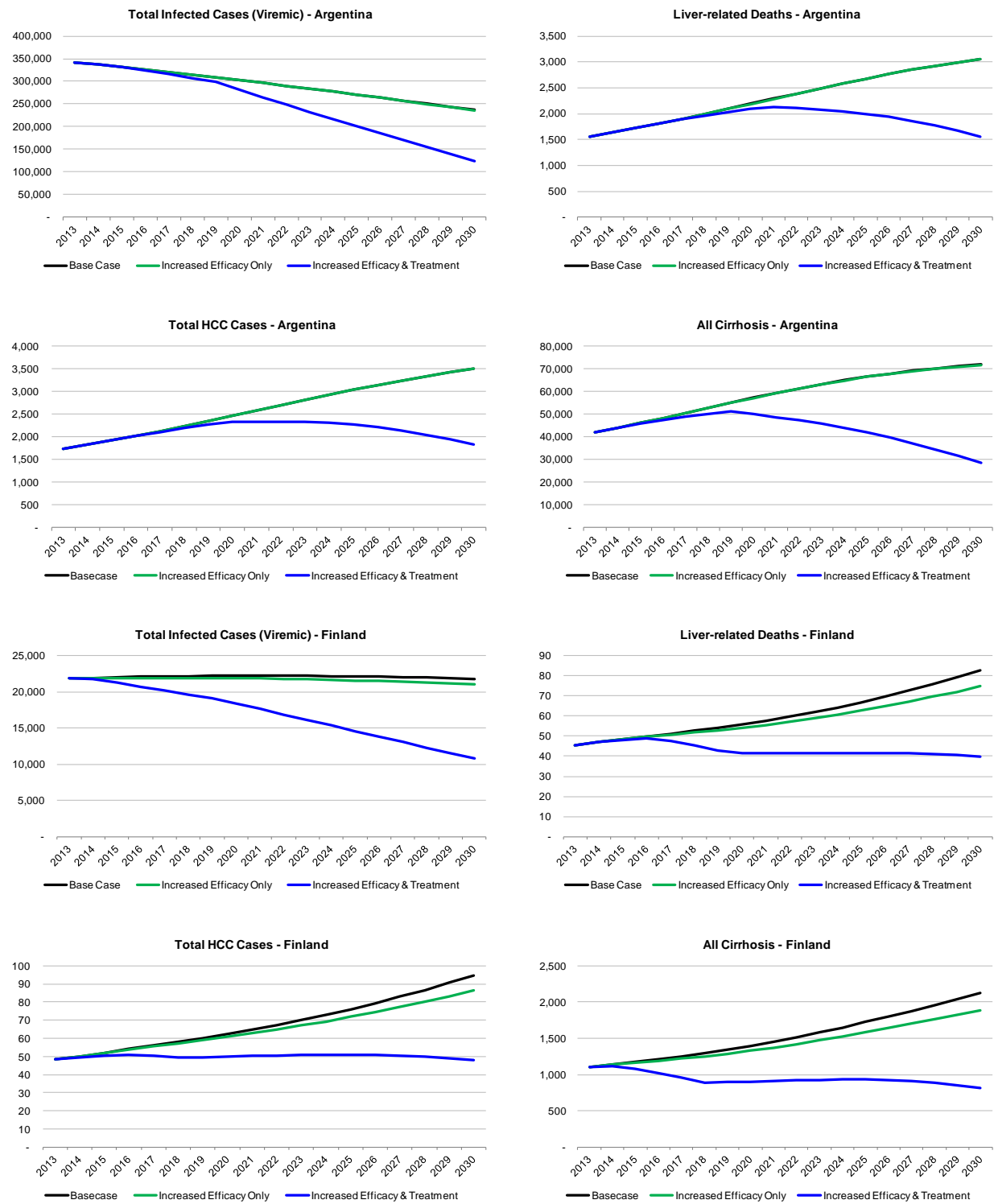


Figure 17. Change in HCV morbidity and mortality, by scenario, 2013-2030



Figure 17. Change in HCV morbidity and mortality, by scenario, 2013-2030

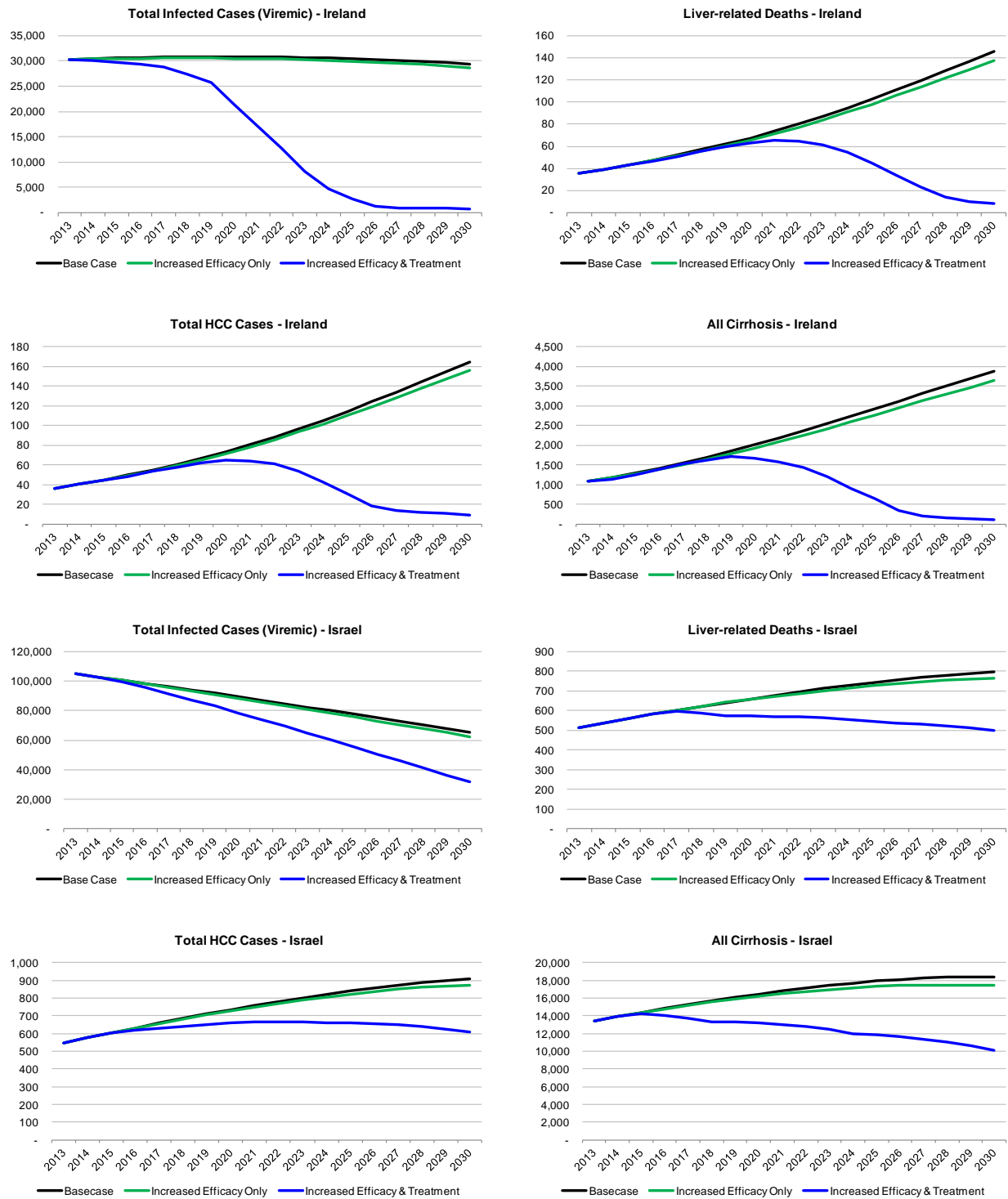


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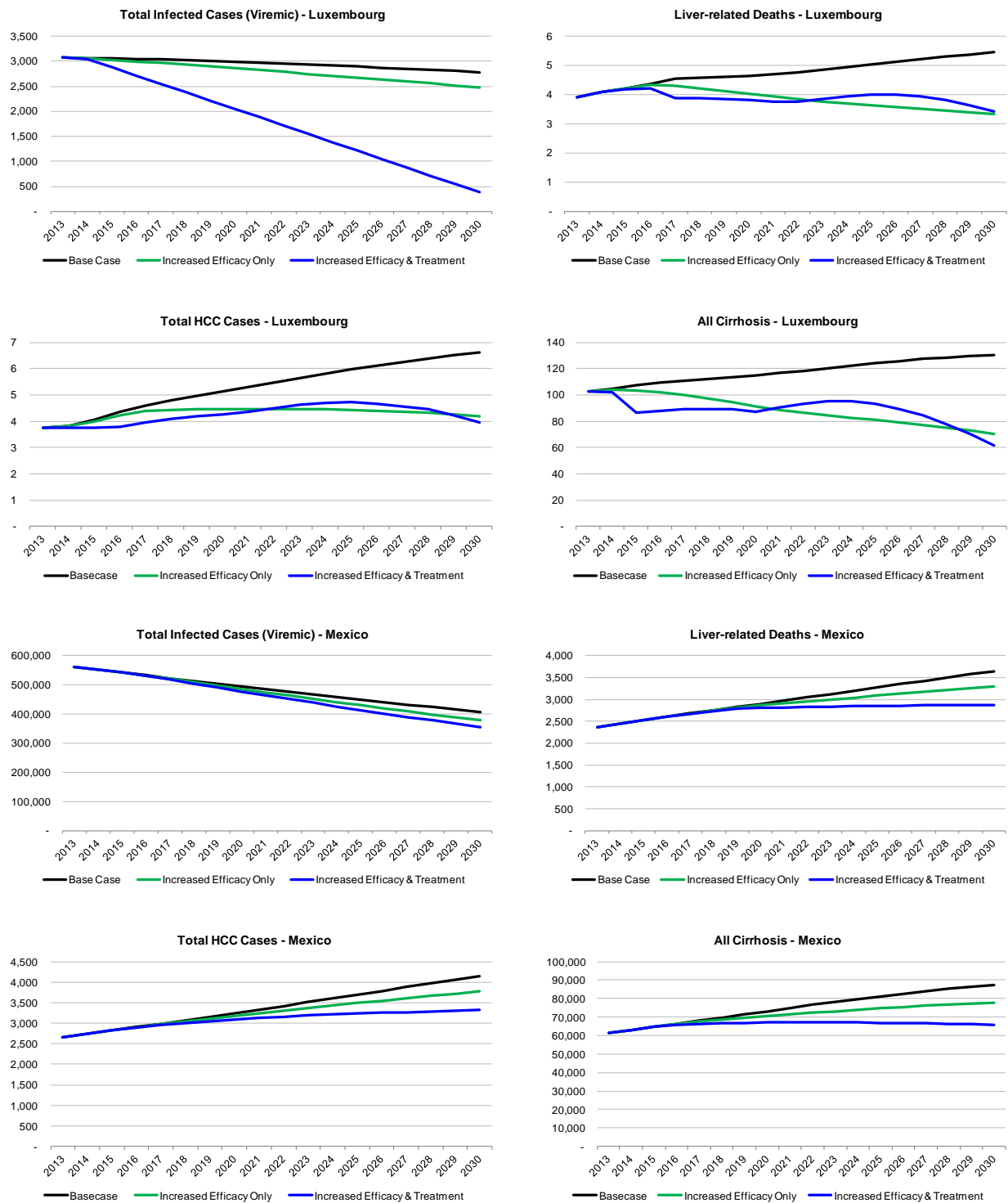


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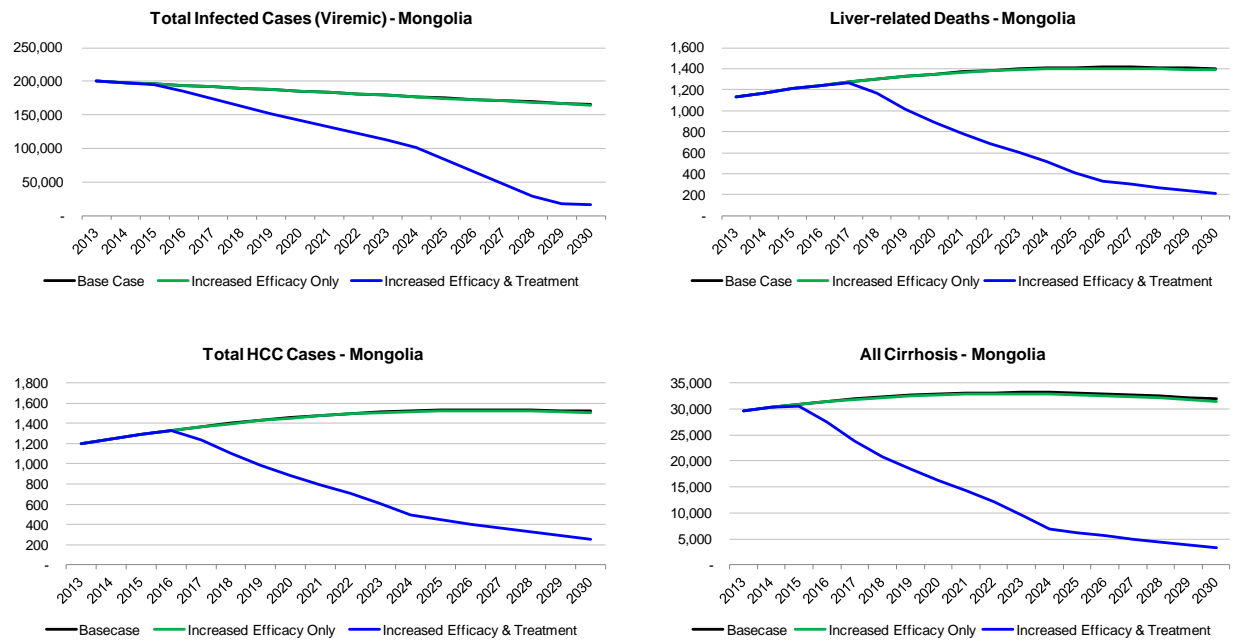


Figure 17. Change in HCV morbidity and mortality, by scenario, 2013-2030



Figure 17. Change in HCV morbidity and mortality, by scenario, 2013-2030

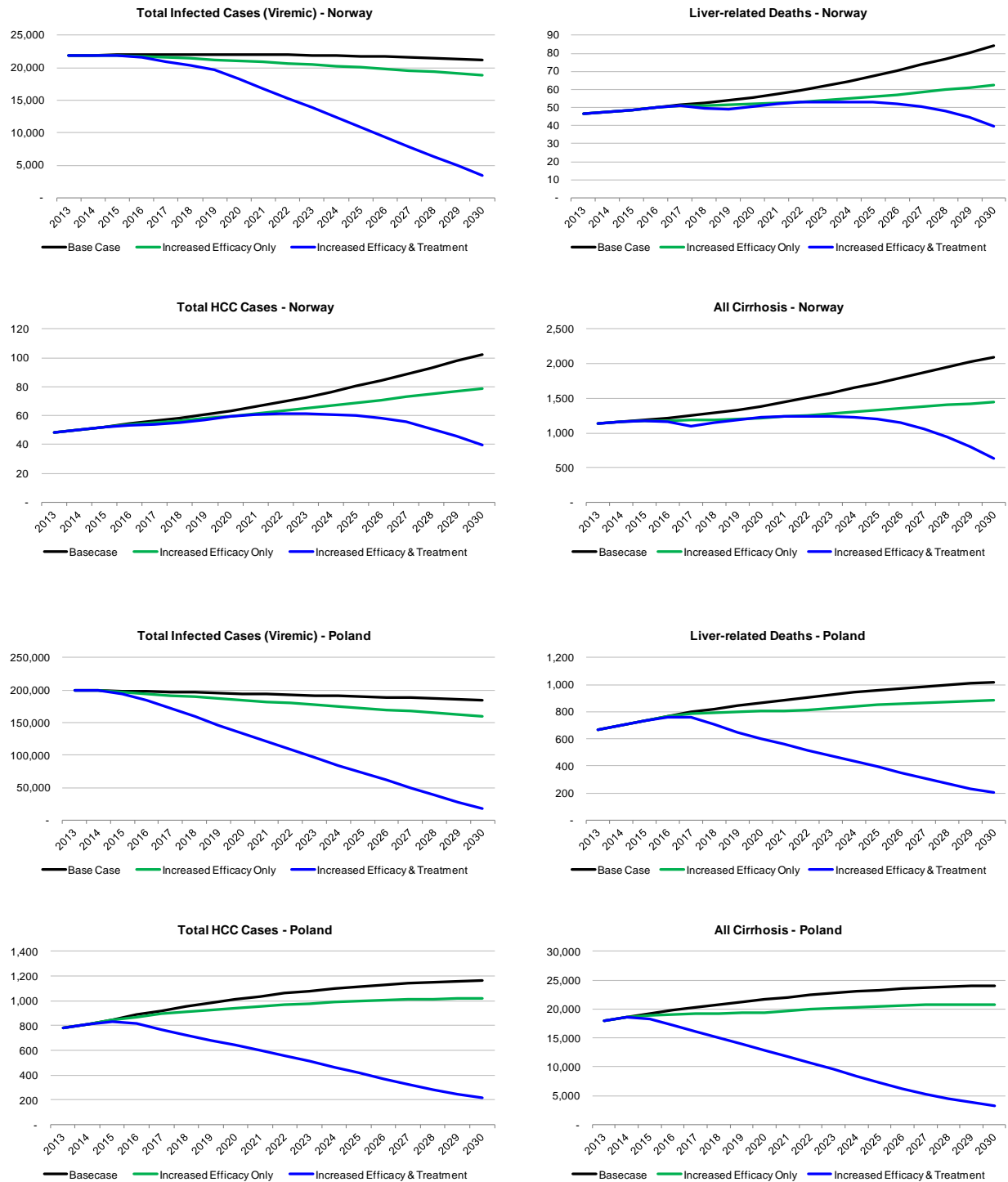


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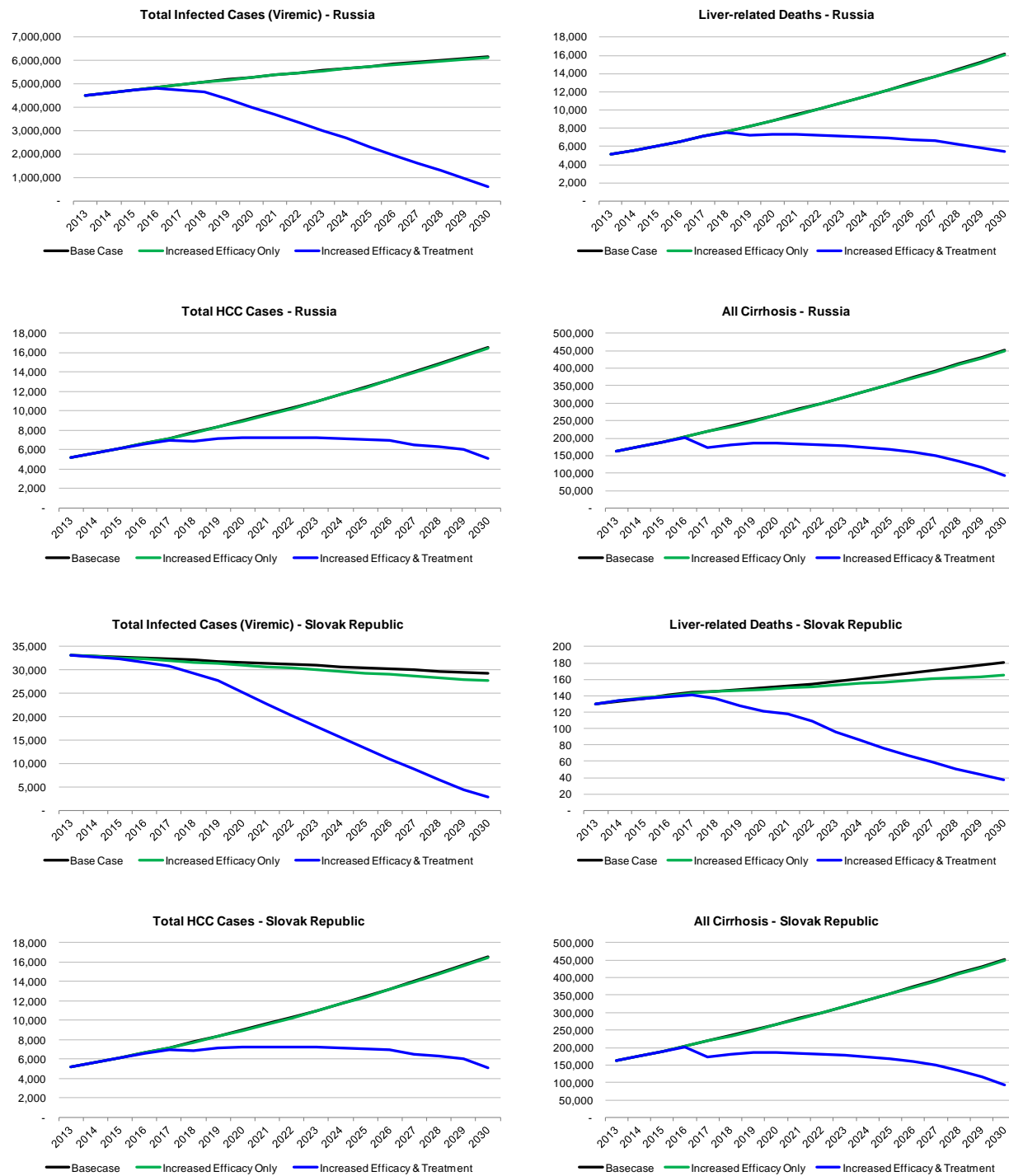


Figure 17. Change in HCV morbidity and mortality, by scenario, 2013-2030

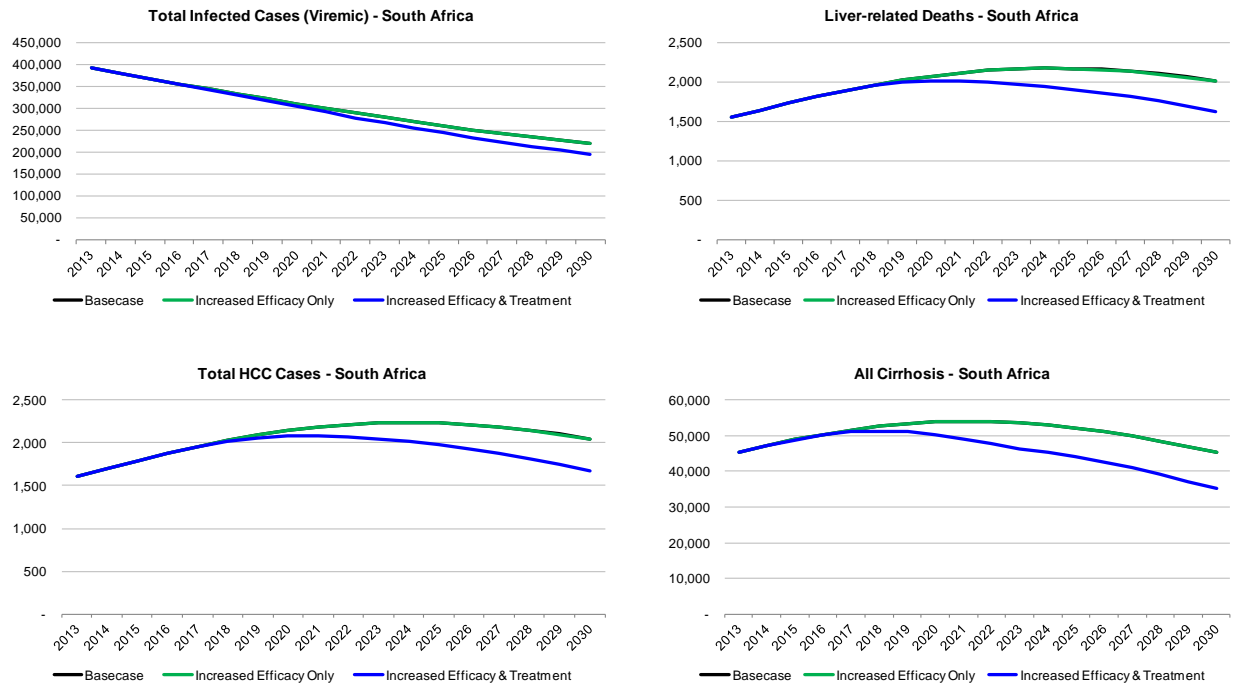


Figure 18. Distribution of HCV infected population by birth year cohort

