JOURNAL OF VIRAL HEPATITIS
JVH

Journal of Viral Hepatitis, 2015, **22** (Suppl. 4), 21–41 doi:10.1111/jvh.12476

The present and future disease burden of hepatitis C virus infections with today's treatment paradigm – volume 3

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Received September 2015; accepted for publication September 2015

SUMMARY. The total number, morbidity and mortality attributed to viraemic hepatitis C virus (HCV) infections change over time making it difficult to compare reported estimates from different years. Models were developed for 15 countries to quantify and characterize the viraemic population and forecast the changes in the infected population and the corresponding disease burden from 2014 to 2030. With the exception of Iceland, Iran, Latvia and Pakistan, the total number of viraemic HCV infections is expected to decline from 2014 to 2030, but the associated morbidity and mortality are expected to increase in all countries except for Japan and South Korea. In the latter two countries, mortality due to an ageing population will drive down prevalence, morbidity and mortality. On the other hand, both countries have already experienced a rapid increase in HCV-related mortality and morbidity. HCV-related morbidity and mortality are projected to increase between 2014 and 2030 in all other countries as result of an ageing HCV-infected population. Thus, although the total number of HCV countries is expected to decline in most countries studied, the associated disease burden is expected to

Abbreviations: G, genotype; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IDU, injection drug use; Peg-IFN, pegylated interferon; RBV, ribavirin; RNA, ribonucleic acid; SMR, standard mortality ratio; SVR, sustained viral response.

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increase. The current treatment paradigm is inadequate if large reductions in HCV-related morbidity and mortality are to be achieved.

Keywords: diagnosis, disease burden, epidemiology, hepatitis C, hepatitis C virus, incidence, mortality, prevalence, treatment.

INTRODUCTION

The global burden of hepatitis C virus (HCV) infections is both substantial and increasing [1,2]. It was recently estimated that global anti-HCV prevalence is 115 million individuals, 80 million of whom have active viraemic HCV infections [3]. Studies have shown an increase in HCV liver-related mortality [4], as well as cases of hepatocellular carcinoma (HCC) and liver transplants attributable to HCV [5–7]; however, robust epidemiological data on HCV and HCV-related morbidity are not available in all countries. To develop policies to address the growing HCV disease burden, individual countries will require more accurate morbidity and mortality data on a national level.

This study aimed to provide estimates for multiple countries of the current HCV disease burden and treatment paradigm in 2014, including prevalence, incidence, diagnosis, treatment and mortality. A disease burden model was then used to estimate the projected future disease burden by the year 2030 in each country if the current trends were to continue. This analysis is consistent with previously published work [8,9] to allow for comparison of results across all of the countries assessed so far.

METHODOLOGY

Inputs

The historical epidemiology of HCV was gathered through a literature search, analysis of unpublished data and discussion with expert panels [10]. When no input data were available, analogues (data from countries with a similar healthcare practice and/or risk factors) or expert inputs were used. Ranges were used to capture uncertainty in inputs with wider ranges implying greater uncertainty.

Model

A disease progression model was constructed in Microsoft Excel® (Microsoft Corp., Redmond, WA, USA) to quantify the size of the HCV-infected population, by the liver disease stages, from 1950 to 2030. Microsoft Excel was selected as a platform due to its transparency, availability and minimal need for operator training. The model was set up for sensitivity and Monte Carlo analysis using Crystal Ball®, (Oracle Corp., Redwood City, CA, USA) an Excel® add-in. Beta-PERT distributions were used for all uncertain inputs.

The model has been previously described in detail [9]. It started with the annual number of acute infections that progressed to chronic HCV (viraemic) infection after accounting for spontaneous clearance of the virus (Fig. 1). The progression of these new cases was followed along with all chronic infections from prior years. Unless specified, the scope of the model was limited to viraemic, HCV ribonucleic acid (RNA)-positive cases. Nonviraemic cases (those who spontaneously cleared the virus or were treated and cured) were not considered even though they would test positive to HCV antibodies and may still progress to more advanced stages of liver disease despite viral clearance [11]. The total number of cases, at each stage of the disease, was tracked by age and gender.

The historical number of HCV infections and the age and gender distributions were gathered through a literature search and discussions with an expert panel [10]. These data were used to estimate the historical number of new HCV infections, as described below.

New hepatitis C virus infections and re-infection

When available, reported or calculated annual estimates of new infections were used. In most countries, the number of new HCV infections was not available and was therefore back-calculated. At any point in time, the total number of HCV infections equals the sum of all new infections minus the number of spontaneously cleared, deceased and cured cases.

The number of new infections was back-calculated using a two-step process that first calculated the annual number of new cases, followed by the age and gender distribution of these cases. The annual number of new cases was calculated using the known number of total HCV infections in a given year in a country. The model calculated the annual number of all-cause mortality, liver-related deaths and

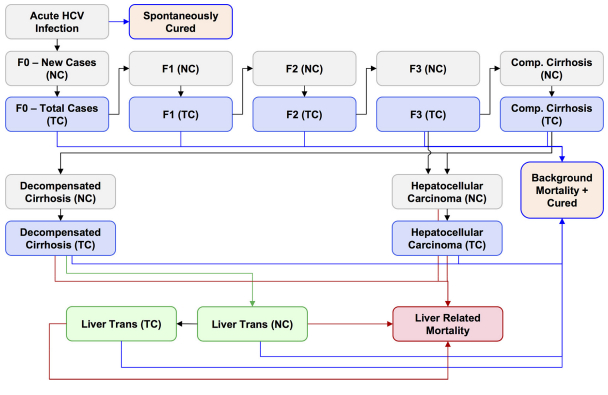

Fig. 1 The flow of the hepatitis C virus (HCV) disease progression model.

cured cases, as described below. The Excel® optimization add-in, Solver, was used to determine an average number of new infections per year. However, the annual number of new cases did not remain flat since 1950. Thus, an annual relative incidence value was used to describe the change in the number of new infections over time. Relative incidence was set to one in 1950, and a discussion with the expert panel was used to identify the years when new infections peaked using the risk factors common in the country (nosocomial infections, injection drug use, etc.).

When immigration from endemic high-risk countries was highlighted as an important source of new infections, the annual number of new cases due to immigration was calculated by gathering net annual immigration, by country of origin and from national databases regarding the anti-HCV prevalence in the country of origin.

In the second step, the age and gender of the acute infections were calculated using the age and gender distribution of the total infected population in a given year. The age and gender distributions of the new infections in 1966 and every 5 years thereafter were modified to match the known distribution of the prevalent population. The age and gender distributions in years 1950–1965 were set to equal 1966 and trended linearly between the 5-year increments. Age and gender allocation by year started in 1950 if when significant risk factors were present prior to 1966 (e.g. Japan).

It was assumed that in the absence of better information, future HCV infection and re-infection will remain the same as they are today. This is a more conservative approach than a dynamic model, which would show a reduction in HCV incidence with treatment of high-risk populations (treatment as prevention). This conservative approach was deemed appropriate given the uncertainties present for HCV epidemiology and lack of detailed data on infection and re-infection rates.

Progression rates

Disease progression was simulated by multiplying the total number of cases at a particular stage of the disease by a progression rate to the next stage. The rates were gathered from previous studies [1,12–19] or calculated using known number of HCC cases/mortality, as explained previously [9].

The number of new cases at a stage of the disease was calculated by multiplying the progression rate and the total number of cases at the previous stage of the disease in the previous year. The total number of cases was adjusted for ageing, all-cause mortality and cases cured in any given year.

Transition probabilities to HCC and HCC-related death were modified in Japan based on cancer registry data for liver cancer incidence and 5-year survival rates [20]. Because the ratio of incident HCC to incident decompensated cirrhosis is believed to be higher in Japan as compared to other countries [21], transition probabilities to decompensated cirrhosis were also adjusted. In addition, the HCV epidemic began prior to 1950 in Japan [22], so the model was modified to account for growth of the HCV-infected population prior to 1950.

All-cause mortality

The all-cause mortality rates by age and gender were gathered from the Human Mortality Database [23] unless stated otherwise. The rates were adjusted for incremental increase in mortality due to injection drug use (IDU) and transfusion, as described previously [24]. Unless specified, a standard mortality ratio (SMR) of 10 (95% uncertainty interval 9.5–29.9) was used for the portion of the HCV-infected population who were active IDU between ages 15 and 44 [25–30]. An SMR of 2.1 (1.3–17.6) was applied to all ages for the portion of the population infected due to transfusion [31]. In all countries studied, new HCV infections due to transfusion were no longer a risk factor. A linear declining rate was applied to obtain the per cent of total infections attributed to transfusion to zero by 2030. The adjustments to all-cause mortality for active IDU and transfusion were made using the following assumptions:

Estonia

The per cent of the HCV population infected through IDU and transfusion was not available in Estonia, so data from surrounding countries were used to inform expert consensus. In 1995, it was estimated that 30% of the HCV population was infected through transfusion, and in 2005, it was estimated that 15% of the infected population were IDU.

Hungary

In 2014, 7% of the viraemic population was infected via IDU. The percentage was back-calculated using estimates of 10 000 IDU in Hungary and an IDU HCV prevalence of 50% [32]. These estimates were based on previous needle exchange data, expert opinions and recently published data. In Hungary, experts estimate that 50% of the viraemic population was infected via transfusion in 2010.

Iceland

Based on data from the Centre for Health Security and Infectious Disease Control during an early period of reporting, an estimated 50% of infected cases reported IDU and an estimated 4% of infected cases reported a history of transfusion, but there are likely no new infections due to transfusion in recent years. Based on expert consensus, approximately 85% of cases in Iceland have a history of IDU.

Indonesia

In 2012, 2.5% of the HCV-infected population was active IDU. This percentage was back-calculated using estimates

of 70 000 IDU in Indonesia (N. Nugrahini 2015 personal communication) and an IDU HCV prevalence of 40–80%, based on data from a recent survey of viral diseases among IDU (N. Nugrahini 2015 personal communication). Applying a spontaneous clearance rate of 20% suggests there were between 22 400 and 43 680 viraemic infected IDU. In 1994, a general population survey in Jakarta estimated that 20% of the population was infected through transfusion [33].

Iran

In 2007, it was estimated that 75% of the infected population in Iran had been infected by IDU [34,35]. Based on expert opinion, 4% of all HCV cases were infected via transfusion procedures. The majority of new cases are due to IDU, which is reflected in the young age distribution.

Japan

Based on an estimated 325 000 IDU in 2002 with anti-HCV prevalence of 60% [36] and a viraemic rate of 70% [37], there were 131 000 chronically infected IDU in 2002, equivalent to 6% of the viraemic population in this year. In 1992, an estimated 35% of the HCV-infected population was infected through transfusion [38].

Latvia

In 2012/2013, approximately 11–18% of the HCV-infected population was active IDU. This percentage was back-calculated using estimates of 8000–12 700 IDU in Latvia [39] and an IDU anti-HCV prevalence of 75% [40]. In 2007, approximately 8% of the HCV-infected population had acquired their infection through blood transfusion [41].

Lebanon

In 2015, 9% of the HCV-infected population acquired their infection through IDU. This percentage was back-calculated using a reported 30% anti-HCV prevalence among IDU [42] and an estimate of 3000 IDU in Lebanon based on expert input. In 2007, 15% of the HCV-infected population had acquired their infection through blood transfusion [43].

Lithuania

In 2014, approximately 9% of the HCV-infected population was active IDU. This percentage was back-calculated using estimates from the ASIS database of the Lithuania State Mental Health Center. Of 5800 reported drug users in Lithuania, 4190 (70%) were active IDU (expert consensus). Furthermore, 2870 (70%) were reported to be HCV RNA-positive [44]. Additional studies suggest an anti-HCV prevalence of 90–95% [45,46] with a recent unpublished estimate from Vilnius of 95% anti-HCV among IDU (Liakina 2015 personal communication). In 1995, an estimated 15% of the HCV-infected population had acquired their infection through blood transfusion [47].

Pakistan

In 2005, it was estimated that 5% of the viraemic population in Pakistan were active IDU and that 6% of the viraemic population had been infected via transfusion [36,40,48,49]. The vast majority of new HCV infections in Pakistan are due to nosocomial transmission. There are additional risk factors in Pakistan including sharing of smoking utensils, sharing of toothbrushes, shaving by travelling barbers, unsterilized piercing tools and unsterilized tattoo and acupuncture procedures [50].

Romania

In 2005, there were approximately 101 000 IDU in Romania [36]. The anti-HCV prevalence among IDU in 2007 was 80% [51]. Applying that prevalence to the IDU population from 2005 indicates approximately 83 000 HCV + IDU in 2012. Using a viraemic rate of 85%, as determined by expert consensus, an estimated 12% of the total infected population was IDU in 2012. In 2008, 10% of the infected population had received their infection through transfusion [52].

Saudi Arabia

The per cent of the infected HCV population that were IDU was estimated at 9%. This rate was back-calculated using an estimated anti-HCV prevalence among IDU of 14% [53]. The per cent of HCV infections attributable to transfusions was reported as 15% [54].

Slovenia

In 2007, a study of 75% of the diagnosed anti-HCV population in Slovenia found that 34% acquired the infection through IDU, 10% through transfusion before 1993 and 3% through haemodialysis [55]. Sexual contact (2%), occupational exposure (1%), tattooing (0.5%), household contact (0.3%) and mother to child transmission (0.1%) accounted for the remaining known routes of transmission [55].

South Korea

In 2009, an estimated 5% of the HCV-infected population was active IDU, and 19% acquired HCV through transfusion [56].

UAE

It is estimated that 4% of HCV-positive UAE nationals are IDU. Expert consensus estimates a 20% HCV prevalence in IDU; this rate was combined with the rate of 0.5% IDU in the general population [57] to calculate the number of IDU with HCV and then divided by the total number of HCV-seropositive individuals. The proportion of HCV cases that are due to previous blood transfusion was estimated to be 40% according to expert consensus.

Diagnosed

The total number of diagnosed cases was collected and reported previously [10]. To estimate current and future total diagnosed cases, it was assumed that the number of newly diagnosed cases stayed the same as the last reported year.

Treated and cured

As described previously [10], the total number of treated patients with HCV was estimated. It was assumed that the number of treated patients stayed constant after the last reported year. It was also assumed that the number of treated patients for each genotype was proportional to the genotype distribution of the HCV-infected population [10].

The annual number of cured patients was estimated using the average sustained viral response (SVR) rate in a given year. A separate SVR was used for the major genotypes, as shown in Table 1. Different methods were used to estimate the average SVR. All countries took into consideration a weighted average of different treatment options in a given year – interferon based therapy in combination with ribavirin (RBV) (dual therapy) or with RBV and a protease inhibitor (triple therapy). Some also took into consideration the percentage of the population who were treatment-experienced and treatment-naïve on each treatment option, while other countries took into account the disease stages of the patients being treated (e.g. F1, F2, F3 and F4).

Treatment protocols

The pool of patients who could be treated was impacted by explicit or implicit treatment protocols. Explicit protocols were determined by national or international guidelines, whereas implicit protocols were determined by actual practice in the country. In 2014, decompensated cirrhotic patients were considered ineligible in all countries.

According to the literature, approximately 40–60% of patients with HCV are eligible for Peg-IFN/RBV [58,59]. The definition of eligibility included contraindications to the drugs (e.g. psychiatric conditions) as well as patient's preference. In this analysis, 60–95% of the patients were considered treatment-eligible for standard of care (Table 1).

In each country, the expert panel provided the most common stages of fibrosis considered for treatment (Table 1). Many countries use, or are starting to use, non-invasive testing methods to determine the level of fibrosis on patients. However, the Metavir scale was used in this model to represent the severity/stage of liver fibrosis. The age of the patients was also considered. Table 1 outlines the most common age bands considered for treatment. The data presented here do not imply that patients with lower Metavir score or older/younger patients were not treated in each country. Instead, the data provided a range for the majority of treated patients.

Future treatment protocols

In this analysis, it was assumed that the future treatment paradigm will remain the same as today. Thus, all assumptions (the number of acute cases, treated patients, per cent of patients eligible for treatment, treatment restrictions, the number of newly diagnosed annually and the average SVR by genotype) were kept constant in future years.

RESULTS

The results of the analysis for 2014 are shown in Table 1. Figure 2 shows the age distribution of the HCV-infected population by country. Table 2 compares the change in HCV disease burden in 2014 and 2030, while Figs 3 & 4 show the projected HCV disease burden between the years 1950 and 2030. It should be noted that decompensated cirrhosis figures include those who received a liver transplant.

Estonia

Expert consensus and acute HCV diagnosis data, provided by the Estonian Health Board, were used to estimate annual incidence. Incidence was estimated to have peaked in 2000 and was modelled to decrease relative to annual reports of acute HCV diagnosis. In 2014, 200 new cases were estimated.

It is estimated that there were 19 000 (13 000–20 900) viraemic individuals in 2014. Viraemic infections were estimated to have peaked at 20 900 in 2006. By 2030, viraemic infections were estimated to decrease to 13 700 (8300–15 400). In 2014, an estimated 6% of the viraemic population experienced cirrhosis, HCC or liver transplant. By 2030, this proportion was projected to increase to 17%. The number of HCC and decompensated cirrhosis cases was projected to increase through 2030, when cases will number 60 and 200, respectively, more than doubling the 2014 values.

Hungary

There are little data on the exact number of new infections in Hungary. Experts agree that new infections peaked in 1993 due to blood transfusions. After 1993, there was a rapid decrease in incidence, due to blood screenings. However, a rapid increase in new infections began in 2000 due to a rise in IDU-related infections. Among IDU, new users have very high infection rates. This is likely due to new designer drugs that have very short half-lives, so they can be injected several times per day, thus increasing transmission rates. There were an estimated 2200 new cases of HCV infections in Hungary in 2014.

Table 1 Hepatitis C virus (HCV)-infected population and treatment forecasts in 2014

	Estonia	Hungary	Iceland	Indonesia	Iran	Japan	Latvia	Lebanon
Country's population (000)	1300	9900	340	253 000	78 500	127 000	2000	5000
Total viremic infections (000)	19 (13 - 21)	52 (39 - 65)	1.1 (0.8 - 1.2)	1284 (447 - 2047)	186 (123 - 250)	1014 (470 - 1173)	43 (27 - 49)	7.7 (3.0 - 18)
Viremic prevalence (%)	1.5% (1.0% - 1.6%)	0.5% (0.3% - 0.6%)	0.3% (0.2% - 0.4%)	0.5% (0.2% - 0.8%)	0.2% (0.2% - 0.3%)	0.8% (0.4% - 0.9%)	2.1% (1.3% - 2.4%)	0.2% (0.1% - 0.4%)
Total diagnosed (viremic)								
Total cases	9600	24 400	900	126 000	62 000	740 000	19 000	1600
Annual newly diagnosed	190	2100	60	12 100	6000	8000	1300	160
Diagnosis rate (%)	51%	47%	83%	10%	33%	73%	45%	20%
Newly diagnosed rate (%)	1.0%	4.0%	5.6%	0.9%	3.2%	0.8%	3.1%	2.1%
Treated & cured								
Annual number treated	500	1200	30	230	4500	26 900	840	170
Annual number cured	230	660	20	120	3000	17 900	460	90
Average SVR (%)	46%	55%	67%	78%	67%	67%	55%	55%
Treatment rate (%)	2.6%	2.3%	2.8%	0.0%	2.4%	2.6%	2.0%	2.2%
New infections								
Total cases	200	2200	50	24 800	8900	3300	2000	280
Infection rate (per 100K)	16	22	15	10	11	3	97	6
Risk factors								
Number of active IDU	2800	3600	560	32 600	140 000	63 900	6400	690
% Active IDU	15%	7%	52%	3%	75%	6%	15%	9%
Previous blood transfusion	2600	20 900	30	131 000	4200	141 000	2900	820
% Previous blood transfusion	14%	40%	3%	10%	2%	14%	7%	11%
Mortality								
All cases	260	1290	10	18 700	2940	101 000	770	210
All cause mortality	220	1000	8	14 800	2800	65 400	680	170
Liver related mortality	40	290	2	3900	140	35 600	90	40
Current treatment protocols								
Treatment age	15 - 74	5 - 85+	20 - 64	15 - 64	20 - 64	15 - 74	15 - 85+	15 - 74
% Treatment eligible	60%	60%	60%	95%	60%	60%	60%	85%
Treated stages - G1	>= F0	>= F1	>= F1	>= F0	>= F1	>= F0	>= F0	>= F0
Treated stages - G2	>= F0	>= F0	>= F1	>= F0	>= F1	>= F0	>= F0	>= F0
Treated stages - G3	>= F0	>= F0	>= F0	>= F0	>= F0	>= F0	>= F0	>= F0
Treated stages - G4	>= F0	>= F1	>= F1	>= F0	>= F1	>= F0	>= F0	>= F0
SVR - G1 (%)	51%	55%	58%	76%	58%	65%	40%	50%
SVR - G2 (%)	75%	55%	85%	90%	70%	75%	80%	90%
SVR - G3 (%)	60%	55%	78%	76%	78%	65%	80%	70%
SVR - G4 (%)	45%	55%	58%	76%	61%	65%	40%	55%

(continued)

Table 1 *(continued)*

	Lithuania	Pakistan	Romania	Saudi Arabia	Slovenia	South Korea	UAE
Country's population (000)	3000	185 000	21 600	20 600	2100	49 500	1100
Total viremic infections (000)	34 (21 - 40)	7193 (5069 - 8126)	572 (420 - 593)	101 (75 - 181)	6.5 (4.5 – 7.3)	242 (161 - 274)	11 (7.6 - 11)
Viremic prevalence (%)	1.1% (0.7% - 1.3%)	3.9% (2.7% - 4.4%)	2.6% (1.9% - 2.7%)	0.5% (0.4% - 0.9%)	0.3% (0.2% - 0.4%)	0.5% (0.3% - 0.6%)	1.0% (0.7% - 1.0%)
Total diagnosed (viremic)							
Total cases	5500	1 055 000	90 000	21 500	3300	95 000	4300
Annual newly diagnosed	500	100 000	7500	2000	170	8000	360
Diagnosis rate (%)	17%	15%	16%	21%	51%	39%	40%
Newly diagnosed rate (%)	1.5%	1.4%	1.3%	2.0%	2.6%	3.3%	3.3%
Treated & cured							
Annual number treated	450	85 000	4100	380	150	4500	140
Annual number cured	210	51 300	1900	190	120	3300	70
Average SVR (%)	47%	60%	46%	50%	80%	73%	50%
Treatment rate (%)	1.3%	1.2%	0.7%	0.4%	2.3%	1.9%	1.3%
New infections							
Total cases	1000	231 000	10 600	2200	140	3900	80
Infection rate (per 100K)	35	125	49	11	7	8	8
Risk factors							
Number of active IDU	2900	338 000	70 500	8700	2200	12 100	490
% Active IDU	9%	5%	12%	9%	34%	5%	4%
Previous blood transfusion	1200	286 000	39 400	6800	270	35 100	4400
% Previous blood transfusion	4%	4%	7%	7%	4%	14%	40%
Mortality							
All cases	550	133 200	17 900	1080	80	8000	200
All cause mortality	480	109 000	15 200	870	60	5800	160
Liver related mortality	70	24 200	2700	210	20	2200	40
Current treatment protocols							
Treatment age	15 - 74	15 - 69	5 - 74	15 - 69	20 - 74	15 - 69	15 - 84
% Treatment eligible	65%	60%	70%	60%	80%	60%	60%
Treated stages - G1	>= F2	>= F0	>= F1	>= F0	>= F0	>= F0	>= F0
Treated stages - G2	>= F2	>= F0	>= F1	>= F0	>= F0	>= F0	>= F0
Treated stages - G3	>= F2	>= F0	>= F1	>= F0	>= F0	>= F0	>= F0
Treated stages - G4	>= F2	>= F0	>= F1	>= F0	>= F0	>= F0	>= F0
SVR - G1 (%)	40%	60%	50%	42%	80%	55%	33%
SVR - G2 (%)	80%	70%	50%	90%	80%	85%	75%
SVR - G3 (%)	65%	60%	50%	76%	80%	80%	66%
SVR - G4 (%)	75%	60%	50%	50%	80%	55%	78%

IDU, injection drug use; SVR, sustained viral response; Viraemic infections – active HCV infections who are RNA-positive; viraemic prevalence – prevalence of active HCV infections; viraemic diagnosed – the number individuals diagnosed with an active infection; annual newly diagnosed – the number of active (viraemic or RNA-positive) HCV infections diagnosed for the first time; diagnosis rate – total viraemic diagnosed cases divided by total viraemic infections; newly diagnosed rate – number of new viraemic diagnosed cases divided by total viraemic infections.

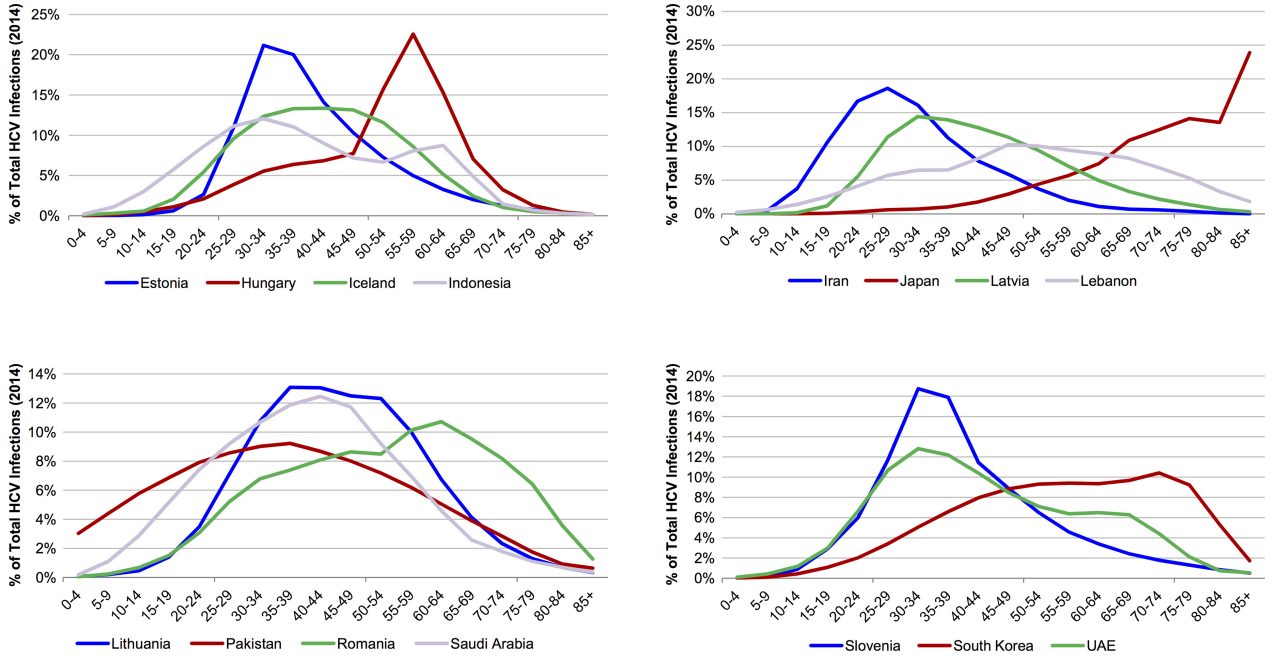

Fig. 2 Distribution of the 2014 hepatitis C virus (HCV)-infected population by age as a percentage of total number of cases.

It is estimated that there were 52 200 (39 100–65 200) viraemic individuals in 2014. Viraemic infections were estimated to peak at 52 300 in 2017 before decreasing to 50 800 cases in 2030. The number of HCC cases was estimated to increase 45% from a base of 280 cases in 2014 to 420 cases in 2030. The number of liver-related deaths in patients with chronic HCV was forecasted to increase by 60% from a base of 290 in 2014 to 450 in 2030. Decompensated cirrhosis and cirrhosis cases were projected to increase by 60% and 45% from a base of 390 and 4400, respectively, in 2014. HCV is shown not only as increasing liver-related mortality, but may also increase liver-independent all-cause mortality as well.

Iceland

Expert consensus was used to estimate annual incidence. In 2014, it was estimated that there were 50 new cases in Iceland.

It is estimated that there were 1100 (800–1200) viraemic individuals in 2014. Viraemic infections were estimated to increase beyond the year 2030, when there will be an estimated 1200 cases. In 2014, an estimated 6% of the viraemic population experienced cirrhosis, HCC or liver transplant eligibility. By 2030, this proportion was projected to increase to 12%. The number of HCC and decompensated cirrhosis cases was projected to increase through 2030, when cases will number 4 and 10, respectively, more than doubling the 2013 values.

Indonesia

Expert consensus was used to estimate annual incidence. Prior to 1992, a survey in Jakarta showed the primary risk of HCV transmission was through transfusion and haemodialysis. From 1992 to 1994, the Indonesian Red Cross stepped in to clean up the blood supply. During this time, Indonesia was seen as a model for the international community for clean blood. Although IDU was estimated to increase in the late 1990s, the efforts to achieve a clean blood supply and recent (2010) active harm reduction measures were considered to support a decreasing incidence. In 2014, it was estimated that there were 24 800 new cases.

It was estimated that there were 1 284 000 (447 000–2 047 000) viraemic individuals in 2014. Total viraemic infections were estimated to increase slightly to 1 303 000 by 2023 before returning to 1 288 000 by 2030. In 2014, an estimated 9% of the viraemic population experienced cirrhosis, HCC or liver transplant eligibility. By 2030, this proportion was projected to increase to 15%. The number of HCC and decompensated cirrhosis cases was projected to increase through 2030, when cases will number 5300 and 19 400, respectively, nearly doubling the 2014 values.

Iran

Expert consensus combined with prevalence data was used to estimate the number of new infections. A rapid increase

Table 2 Comparison of hepatitis C virus (HCV) disease burden in 2014 and 2030

	Estonia	Hungary	Iceland	Indonesia	Iran	Japan	Latvia	Lebanon	Lithuania	Pakistan	Romania	Saudi Arabia	Slovenia	South Korea	UAE
Viremic HCV Infections (000)															
2014 Est.	19	52	1.1	1284	186	1014	42	7.7	34	7193	572	101	6.5	242	11
2030 Est.	14	51	1.2	1288	213	271	49	7.4	35	7529	439	103	5.1	146	8
Percent Change	(30%)	(3%)	15%	0.3%	14%	(75%)	15%	(4.0%)	5.0%	5.0%	(25%)	2.0%	(20%)	(40%)	(25%)
HCC Cases															
2014 Est.	30	280	2	3000	110	169 000	70	30	50	25 200	1900	160	10	1800	30
2030 Est.	60	420	4	5300	330	68 400	130	30	120	32 800	2400	470	20	1500	40
Percent Change	110%	45%	155%	75%	195%	(60%)	90%	25%	130%	30%	25%	190%	80%	(18%)	35%
Liver Related Mortality															
2014 Est.	40	290	2	3900	140	35 600	90	40	70	24 200	2700	210	20	2200	40
2030 Est.	90	450	6	7700	430	14 300	180	40	150	30 800	3400	670	30	2000	60
Percent Change	120%	60%	180%	95%	215%	(60%)	95%	18%	125%	25%	30%	225%	90%	(10%)	45%
Decompensated Cirrhosis															
2014 Est.	90	390	4	9700	150	50 700	230	90	150	78 900	6500	210	30	4300	60
2030 Est.	200	630	10	19 400	660	15 900	450	110	340	97 900	8200	1300	70	3800	100
Percent Change	120%	60%	245%	100%	350%	(70%)	95%	17%	135%	25%	30%	510%	105%	(12%)	85%
Compensated Cirrhosis															
2014 Est.	980	4400	50	98 300	3500	349 000	2300	810	1600	501 000	62 900	5400	380	40 800	1000
2030 Est.	2100	6400	140	172 000	10 800	86 900	4400	1100	3900	662 000	78 300	15 400	670	32 900	1400
Percent Change	115%	45%	160%	75%	210%	(75%)	90%	30%	145%	30%	25%	185%	80%	(19%)	35%

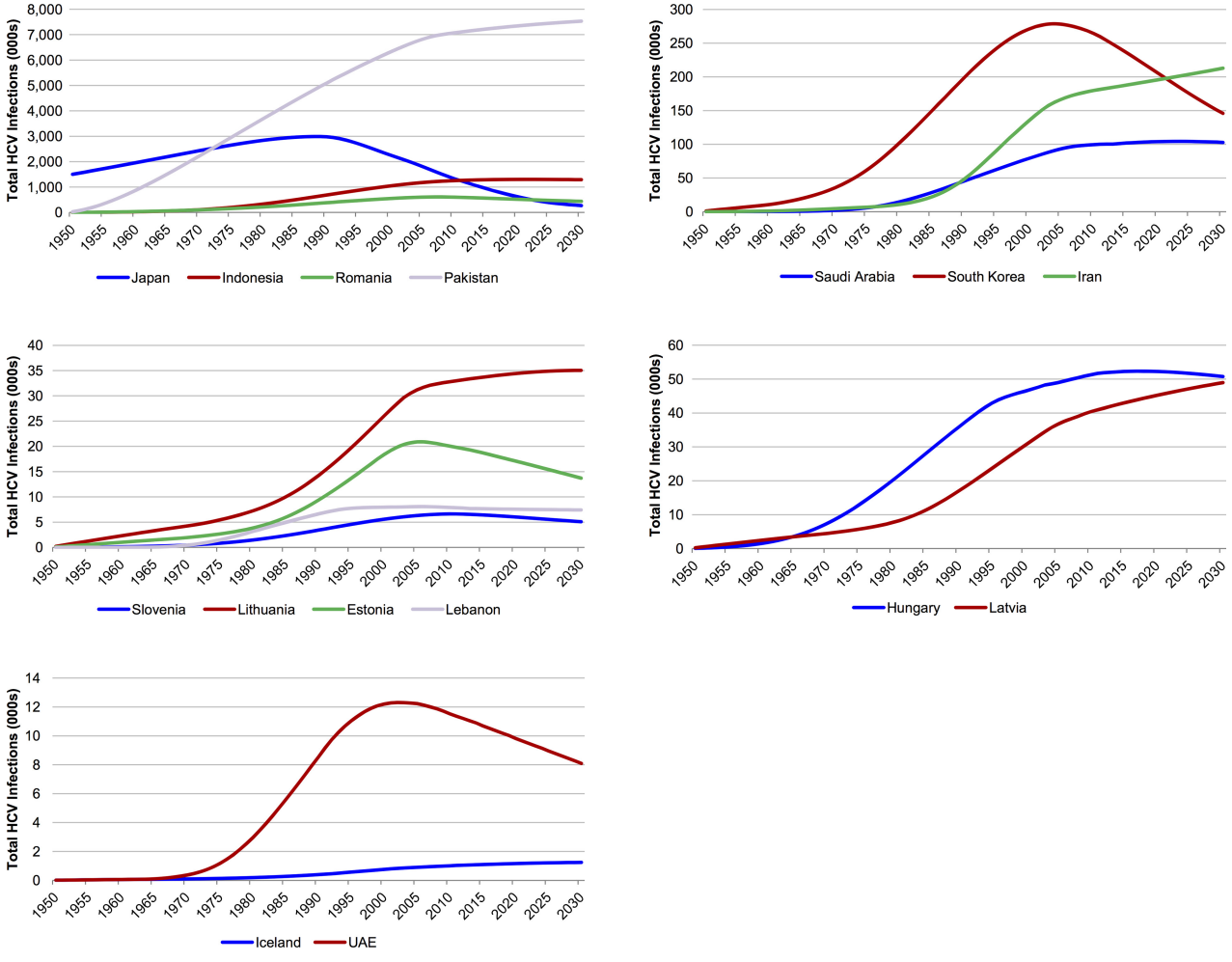

Fig. 3 Change in viraemic hepatitis C virus (HCV) infections over time.

in new infections, through IDU, occurred after the Iranian revolution in 1979 and continued until 1998, when the full impact of harm reduction programmes among injection drug users and blood screening resulted in a sharp decrease until 2005, upon which the incidence levelled out. There were an estimated 8900 new viraemic HCV cases in Iran in 2014.

In 2014, there were an estimated 186 000 (123 000–250 000) viraemic individuals in Iran, increasing 14% to 213 000 individuals in 2030. The number of HCC cases and liver-related deaths will increase by 195% and 215%, from a base in 2014 of 110 and 140, respectively, by 2030. Compensated and decompensated cirrhosis cases will increase 210% and 350% from a base of 3500 and 150, respectively, in 2014.

Japan

Expert consensus was used to estimate annual incidence. In 2014, it was estimated that there were 3300 new infections in Japan.

It was estimated that there are 1 014 000 (470 000–1 173 000) viraemic individuals in 2014. Viraemic infections were estimated to have peaked at 2 992 000 (88 000–355 000) in 1988. In 2014, an estimated 55% of the viraemic population experienced cirrhosis, HCC or liver transplant eligibility. By 2030, this proportion was projected to increase to 65%. The number of HCC and decompensated cirrhosis cases was projected to decrease through 2030, when prevalent cases will number 68 400 and 15 900, respectively, as result of liver-related and all-cause mortality.

Latvia

Expert consensus was used to estimate annual incidence. Incidence was estimated to have peaked in 2000 and decreased only gradually since that time. The gradual decrease was modelled due to continued transmission in the IDU population as well as in general community and medical settings where sterilization of tools is not mandated by law. In 2014, it was estimated that there were 2000 new cases occurring annually (100 per 100 000 persons) in Latvia.

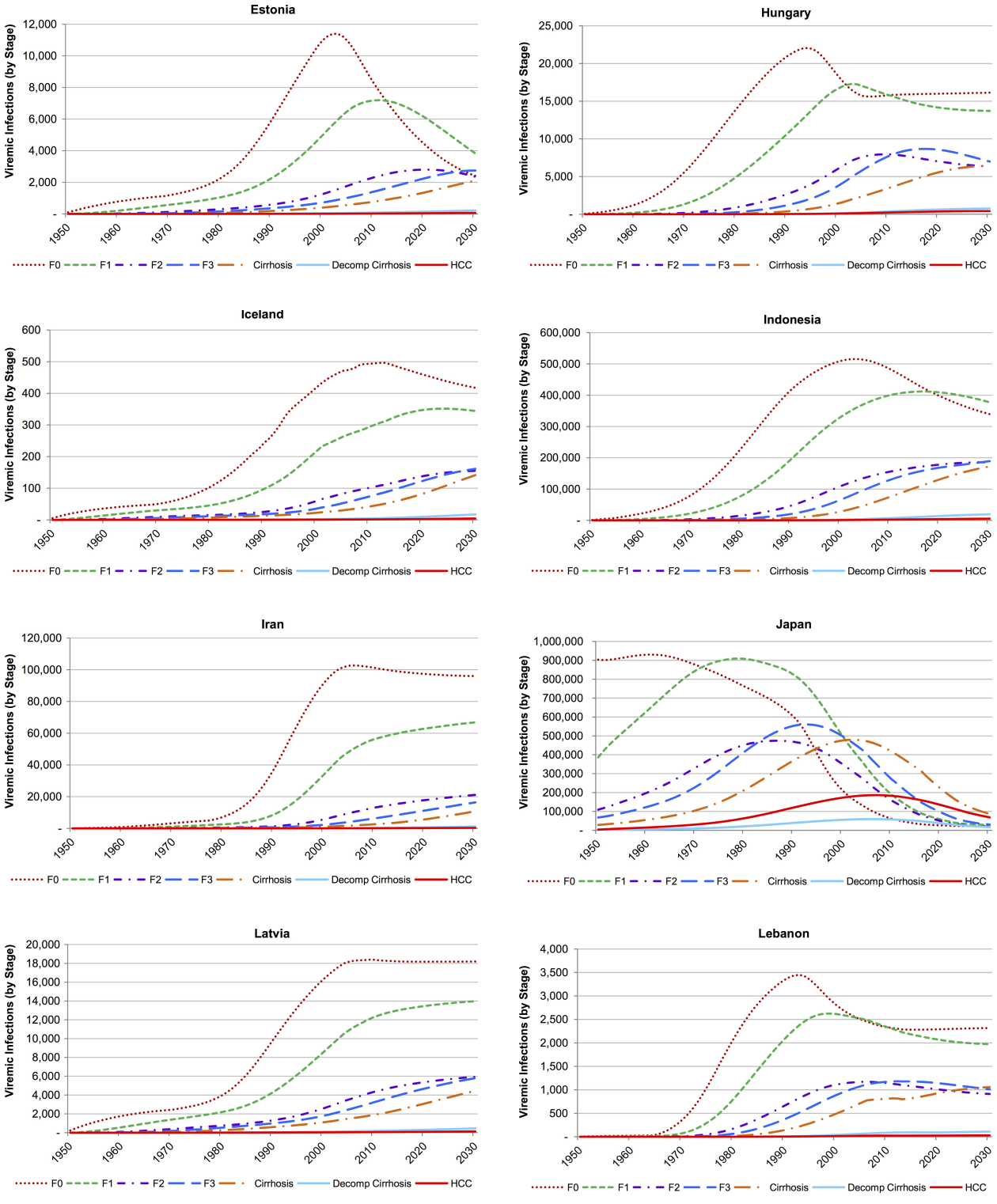

Fig. 4 Change in hepatitis C virus (HCV) disease burden over time.

It is estimated that there were 42 500 (27 400–49 000) viraemic individuals in 2014. Viraemic infections were estimated to increase to 49 000 (30 500–57 600) after 2030. The number of HCC cases was projected to increase 90%, from 70 cases in 2014 to 130 cases in 2030. The number of decompensated cirrhosis cases and liver-related deaths was projected to increase from 230 and 90 cases, respectively, in 2014 to 450 and 180 cases in 2030, a 95% increase for each.

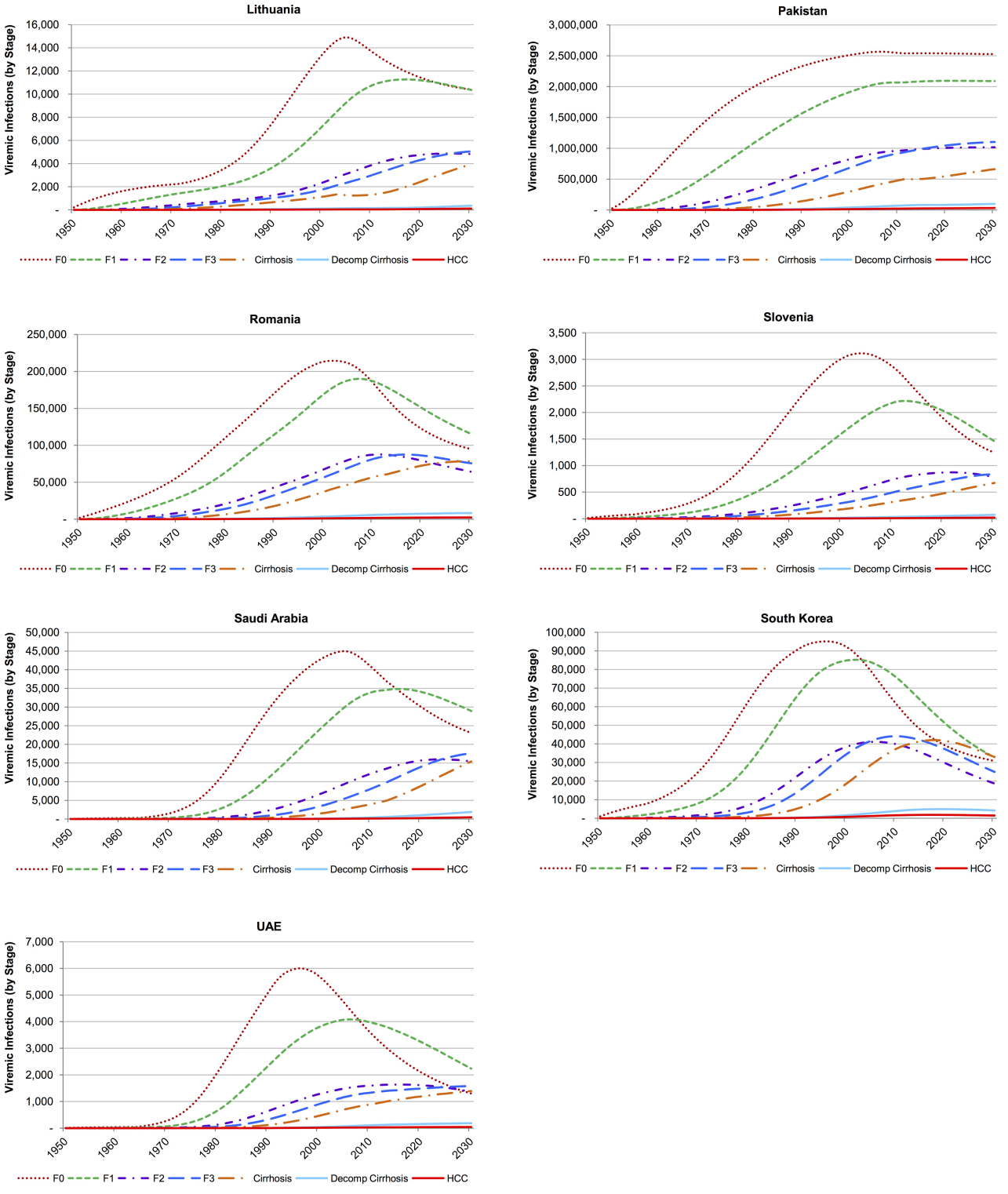

Fig. 4 continued

Lebanon

It was estimated based on expert consensus that incidence of HCV peaked in 1990. A sharp decline in new cases was estimated through the 1990s before levelling out and increasing slightly from 2000 to 2014. An estimated 280 new cases occurred in 2014.

In 2014, there were an estimated 7700 (3000–17 900) viraemic individuals in Lebanon. Viraemic infections were estimated to have peaked in 2006 at 8100 cases and were

projected to decline slightly between 2014 and 2030 to 7400 (2430–18 800) cases. The number of HCC cases attributable to HCV was projected to increase 25% by 2030 from a base of 30 cases. Compensated cirrhosis and decompensated cirrhosis were also projected to increase 30% and 17%, respectively, from a base of 810 and 90 cases in 2014.

Lithuania

Expert consensus was used to estimate annual incidence. Incidence was estimated to have peaked in 2000, decreased until 2005 and remained stable after 2005. In 2014, 1000 new cases were estimated, an incidence of 35 per 100 000.

It is estimated that there were 33 500 (21 100–40 300) viraemic individuals in 2014. Viraemic infections were estimated to peak at 35 100 (22 000–43 000) in 2030. In 2014, an estimated 6% of the viraemic population experienced cirrhosis, HCC or liver transplant eligibility. By 2030, this proportion was projected to increase to 13%. The number of HCC and decompensated cirrhosis cases was projected to increase through 2030, when cases will number 120 and 340, respectively, more than doubling the 2014 values.

Pakistan

The results of a national survey study combined with expert panel input were used to estimate the number of new infections [60]. Incidence peaked around 2005 and remained constant from that point forward. There were an estimated 231 000 new viraemic HCV cases in Pakistan in 2014.

In 2014, there were an estimated 7 193 000 (5 069 000–8 126 000) viraemic individuals in Pakistan, increasing to 7 529 000 individuals in 2030. The number of HCC cases and liver-related deaths will increase by 30% and 25% from a base in 2014 of 25 200 and 24 200, respectively, by 2030. Similarly, cirrhotic cases and decompensated cirrhosis cases will increase 30% and 25% from a base of 501 000 and 78 900, respectively, in 2014.

Romania

According to expert consensus, in 2008, reported incidence of HCV in Romania was nine per 100 000, with an estimated 10% of cases reported. This corresponds to approximately 10 600 incident HCV cases in Romania in 2014. HCV incidence was thought to have peaked before 2000.

It was estimated that there were 572 000 (420 000–593 000) viraemic individuals in 2014. Viraemic infections were estimated to have peaked at 611 000 cases in 2007 and were projected to continue to decline to 439 000 (328 000–461 000) cases in 2030. Liver-related mortality was projected to increase by 30% by 2030, from 2700 deaths in 2014 to 3400 in 2030. Cases of HCC were projected to increase 25% to 2400 cases in 2030 from 1900 cases in 2014. Compensated cirrhosis and decompensated cirrhosis were projected to increase by 25% and 30% from a base of 62 900 and 6500 cases in 2014, respectively.

Saudi Arabia

It was estimated, based on expert consensus, that there were approximately 2700 incident cases of HCV in 2010 (one case per 10 000 persons). The model showed incidence increasing through the 1970s and 1980s and peaking in the early 1990s at an estimated 4800 cases per year. It was thought that the rise in incidence was due largely to the coinciding development of medical infrastructure and increase in the number of invasive procedures and blood transfusions in Saudi Arabia before blood screening was implemented. It was estimated that there were 2200 new cases of HCV in 2014.

In 2014, the total number of viraemic cases of HCV was estimated at 101 000 (75 400–181 000). Viraemic prevalence was estimated to increase slightly to 103 000 (75 900–186 000) by 2030, a 2% change. HCC prevalence was estimated at 160 cases in 2014 and was projected to increase to 470 by 2030, a 190% increase. Liver-related mortality was expected to increase from 210 deaths in 2014 to 670 deaths in 2030, a 225% increase. Decompensated and compensated cirrhosis cases were projected to increase by 510% and 185%, respectively, by 2030 from a base of 210 cases and 5400 cases in 2014.

Slovenia

According to expert consensus, incidence in Slovenia is declining and was estimated at 140 cases in 2014. Expert input also determined that the incidence peaked before 1993, when blood screening began. IDU currently presents the biggest risk factor to the spread of HCV in Slovenia [61].

It was estimated that there were 6500 (4500–7300) viraemic individuals in 2014. Viraemic prevalence was estimated to peak in 2011 at 6700 cases. Assuming the current treatment paradigm remains constant, there will be an estimated 5100 (3100–5900) viraemic cases in 2030. An estimated 7% of the viraemic population experienced compensated cirrhosis, decompensated cirrhosis, HCC or liver transplant in 2014, and this proportion was projected to increase to 15% by 2030. Cases of compensated cirrhosis, decompensated cirrhosis and HCC were projected to increase by 80%, 105% and 80%, respectively, by 2030 under the current treatment paradigm.

South Korea

In 2014, it was estimated that there were 3900 new cases and there were 242 000 (161 000–274 000) viraemic

individuals. Viraemic infections were estimated to have peaked at 279 000 in 2004 and by 2030 were estimated to be 146 000 (88 600–175 000). In 2014, an estimated 19% of the viraemic population experienced cirrhosis, HCC or liver transplant eligibility. By 2030, this proportion was projected to increase to 25%, despite an overall decreasing number of advanced stage cases. The number of HCC and decompensated cirrhosis cases was projected to decrease 18% and 12% to 1500 and 3800 cases, respectively, in 2030. The number of liver-related deaths (2200 in 2014) will increase to 2300 annually in 2027, before decreasing to 2000 in 2030.

UAE

It was estimated that there were 80 new cases of HCV among UAE nationals in 2014. Incidence peaked at just over 900 cases per year around 1991 before levelling out to today's incidence rate around 2005. It was thought that the rise in incidence through the 1970s and 1980s was largely due to increased iatrogenic infection relating to the increase in access to medical care during that time. HCV blood screening began in the early 1990s, leading to a sharp decline in incidence over the next 10 years.

In 2014, the total number of viraemic cases was estimated at 10 900 (7600–11 100). If the pre-2014 standard of care were continued, prevalence would be expected to steadily decrease by 25% to 8100 (5500–8400) cases by 2030. HCC prevalence would be expected to increase from 30 to 40 cases between 2014 and 2030, a 35% increase. Liver-related mortality was projected to increase by 45% from an estimated 40 deaths in 2014 to 60 deaths in 2030. Decompensated and compensated cirrhosis prevalences were estimated at 60 and 1000 cases, respectively, in 2014 and were expected to increase by approximately 85% to 100 and by 35% to 1400 cases by 2030.

DISCUSSION

A modelling approach was used to forecast HCV morbidity and mortality. As the HCV disease burden changes over time, this approach allowed us to compare data across countries reported in different years [10] by estimating the disease burden in 2014 (Table 1).

As shown in Fig. 3, the total number of viraemic infections was expected to decline or remain flat in most countries in this analysis, with the exception of Iceland, Iran, Latvia and Pakistan. The changes in the total number of infections over time mainly reflect the past HCV incidence, age-specific HCV prevalence and improvements in the safety of blood products and standards of health care. The total number of HCV infections reported here is likely lower than other estimates, as this study focused on the number of viraemic cases in the population. Those who spontaneously cleared the virus or were treated and cured were not considered. The increase in the future total HCV infections is caused by a higher number of annual new HCV infections than mortality or cured. In Pakistan, the source of most new infections is iatrogenic, while in Latvia, Iran and Iceland, the new infections are attributed to IDU. Japan and South Korea both have relatively older HCV-infected populations (Fig. 2), and a rapid decline in total HCV infections is projected as the result of an increase in mortality, as the HCV-infected population ages. On the other hand, both countries have already experienced a rapid increase in HCV-related mortality and morbidity. In comparison, Iran has a very young infected population and HCV-related morbidity and mortality are expected to increase through 2030. This analysis focused on nationals in UAE and Saudi Arabia. The inclusion of migrant workers, who are typically younger, could result in a different age distribution and a different estimate for total HCV infections.

Figure 4 shows the change in disease burden over time, while Fig. 5 shows that the number of individuals with late-stage liver disease was expected to continue to grow past 2030 in most countries except for Japan and South Korea. The decrease in the total number of individuals with HCC and decompensated cirrhosis in these countries (Fig. 5) is due to an increase in mortality as the population ages. However, the percentage of the HCV-infected population, still alive, with advanced liver disease will increase 43% in both countries between 2014 and 2030.

As shown in Table 1, viraemic HCV prevalence ranged from 0.2% in Iran and Lebanon to 4% in Pakistan. The countries with the highest diagnosis rates were Iceland and Japan (85% and 75%, respectively), while Indonesia, Romania, Lithuania and Pakistan were estimated to have the lowest diagnosis rates (range: 10–17%). In addition, it was estimated that 0.8–6% of the infected population is newly diagnosed each year, with the lower end of the range represented by Japan and the upper end of the range represented by Iceland. However, it should be noted that as Iceland has diagnosed approximately 85% of their infected population, this high rate of newly diagnosed patients is not expected to continue indefinitely.

The country with the highest treatment rate was Iceland, where 3% of the infected population is treated annually, followed by Estonia, Japan, Iran, Hungary Slovenia, Lebanon, and Latvia with treatment rates ranging between 2% and 3%. Among the countries included in this analysis, three had treatment rates <1% (0.01–0.7%): Indonesia, Saudi Arabia and Romania.

Mortality (all-cause and liver-related) was driven by the age of the infected population (Fig. 2) as well as risk factors such as IDU and transfusion (Table 1). Older populations had a higher all-cause mortality rate [23] and, in addition, disease progression rates increased with age. Thus, older individuals were more likely to have advanced liver disease and liver-related deaths associated with HCV.

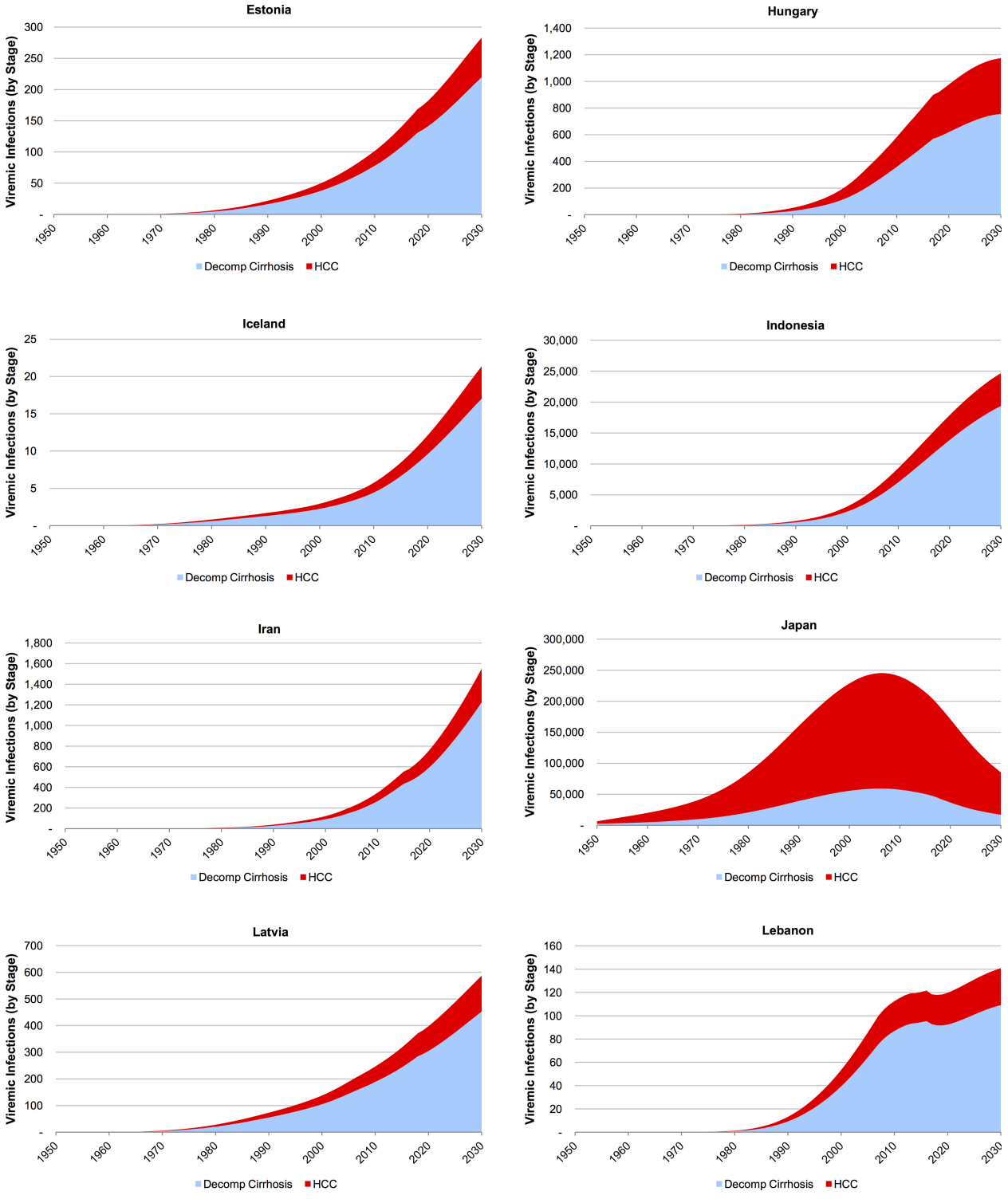

Fig. 5 Change in the number of decompensated cirrhosis cases and hepatocellular carcinoma (HCC) cases over time.

As stated in the Methodology section, active IDU cases also had a higher mortality rate due to the high-risk behaviour associated with drug use. Table 1 presents the percentage of the infected population who were actively injecting drugs. The all-cause mortality was adjusted accordingly for this portion of the population.

In each country, details of the current treatment protocols were gathered. For the purpose of the model, it was

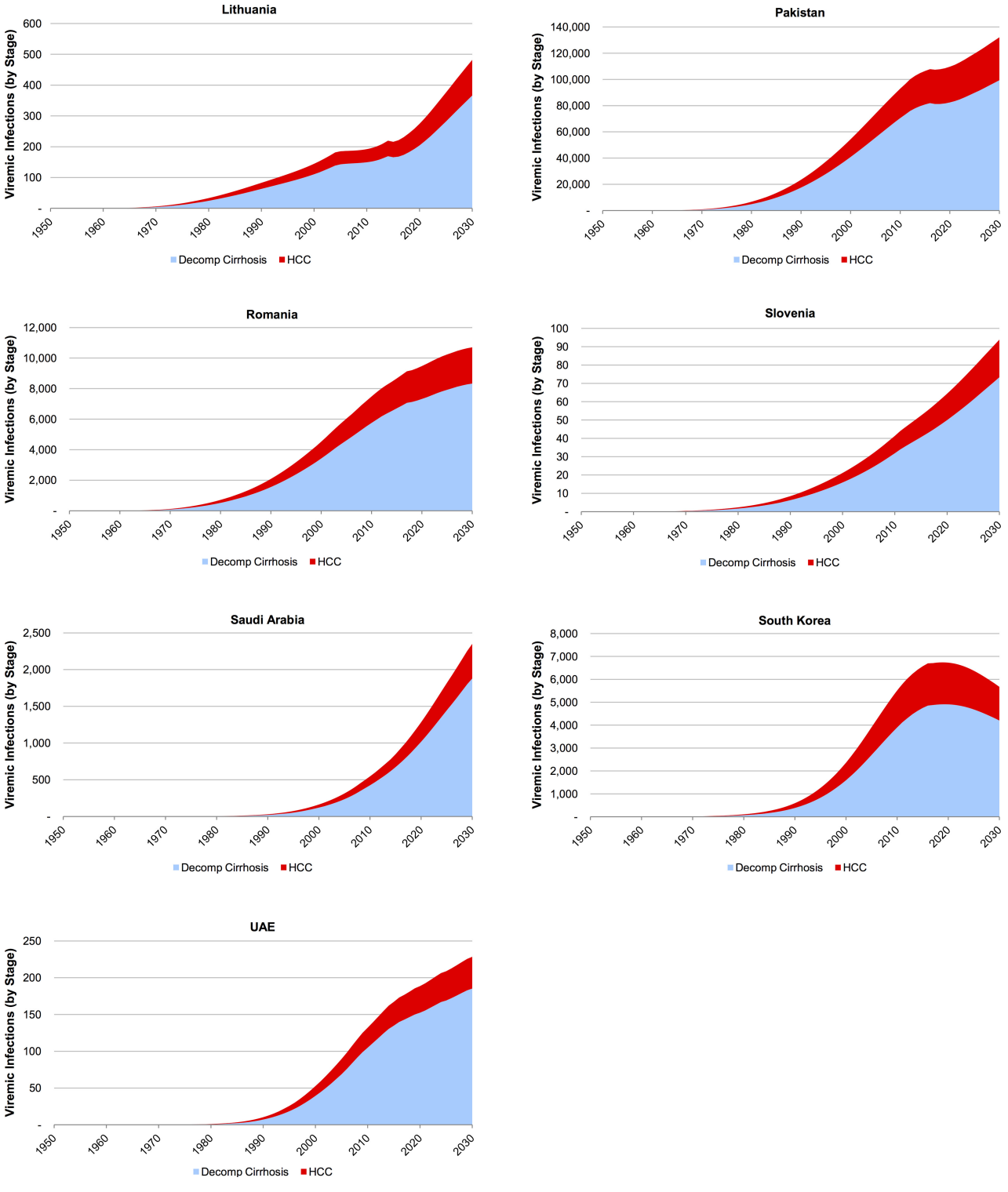

Fig. 5 continued

presumed that all treatment assumptions (including the number of treated patients, treatment eligibility, the number of newly diagnosed cases, SVR and treated patient segments) would remain constant between now and 2030. This was not meant to be a realistic scenario but was rather a baseline that could be used to compare the impact of new strategies to manage the future disease burden [62]. Thus, this work does not imply that the current treatment paradigm will remain as it is today. Instead, the scenarios shown here represent what would

be the outcome if the current paradigm were to continue unchanged.

There are several limitations that may influence the outcomes from this study. The distribution of new cases from 1950 to the most recent year of available data was back-calculated using relative incidence and an estimation of appropriate age and gender distribution. However, to estimate the number of new infections after the year of known prevalence, an analysis of the key risk factors was conducted in each country. These risk factors included incidence among IDU, nosocomial infection and the impact of immigration. A key limitation of this study is the assumption that the number of new cases will remain constant after 2014. Therefore, an increase in incidence seen in 2014 could result in a higher total prevalence in 2030.

A second limitation is the assumption that diagnosis in each country will be sufficiently high to provide a pool of patients available for treatment. In reality, as the diagnosis rate increases, it will become more difficult to find undiagnosed patients. Furthermore, even if diagnosed, not all patients may have easy access to care. Thus, the ability of a country to treat its HCV prevalent population may be limited by the number of available diagnosed eligible patients.

In addition, the model does not consider the potential disease progression of cured patients with HCV. Previous studies have indicated that it is possible for disease progression to continue in more advanced patients even after achieving SVR, although this progression will occur at a slower rate [11]. As the analysis presented in this study was limited to HCV viraemic individuals, the data may overestimate the reduction in cases of HCC and decompensated cirrhosis.

In conclusion, this study illustrates that, in most countries, overall viraemic HCV prevalence is projected to decrease due to a combination of an ageing prevalent population, treatment and a reduction in risk factors, mainly the improvements in the safety of blood products and harm reduction programmes for injection drug users. However, morbidity and mortality attributable to HCV are expected to increase as the current infected population progresses to advanced stages of liver disease. In most countries included in this analysis, the increased disease burden will likely not be controlled without significant changes being made in the overall treatment paradigm, including increases in screening, diagnosis and treatment. This implies that countries will need to evaluate different strategies to help make decisions on how to best manage the expected increase in their HCV-related disease burden.

ACKNOWLEDGEMENTS

This project was supported by Gilead Sciences. The study of HCV disease burden in Iran was supported by the Center for Disease Analysis.

CONFLICT OF INTERESTS

A. Sibley, S. Blach, C. Estes, J. Gunter, H. Razavi, D. Razavi-Shearer, K. Razavi-Shearer and J.D. Schmelzer have no conflict of interests. They are employees of the Center for Disease Analysis and are barred from accepting remuneration. 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 modelling research. R. Salupere has served as a consultant or speaker or has received research grants from AbbVie, Gilead Sciences, Janssen-Cilag, MSD and Roche. F.Z. Alfaleh has received research grants from Schering-Plough. A.A. Aljumah has served as a speaker and advisory board member for Gilead Sciences and Bristol-Myers Squibb. I. Altraif has received support from Roche, Merck/MSD, Janssen, AbbVie and Bristol-Myers Squibb. G. Horvath has served as a consultant and/or an investigator for, and has received consulting/speaker fees from AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Fresenius Kabi, Gilead Sciences, Janssen-Cilag, MSD/Merck and Roche. B. Hunyady has served as consultant/speaker/investigator and/or has received research grants from AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Fresenius Kabi, Gilead Sciences, Janssen-Cilag, MSD/Merck and Roche. Y.S. Lim is an advisory board member of Bayer Healthcare and Gilead Sciences and receives research funding from Bayer Healthcare, Bristol-Myers Squibb, Gilead Sciences and Novartis. M. Maimets has served as a consultant and received speaking fees from Janssen, AbbVie and Gilead. R.A. Sayegh is an advisory board member of Gilead, AbbVie and Bristol-Myers Squibb (Lebanon). J. Tanaka has received funding from AbbVie, Bristol-Myers Squibb, Chugai, Eisai, Gilead Sciences, Janssen, Otsuka and Sysmex. K.H. Han, A. Abourached, L.A. Lesmana, M. Makara, W. Jafri, A.M. Assiri, A. Goldis, F. Abaalkhail, Z. Abbas, A. Abdou, F. Al Braiki, F. Al Hosani, K. Al Jaberi, M. Al Khatry, M.A. Al Mulla, H. Al Quraishi, A. Al Rifai, Y. Al Serkal, A. Alam, S.M. Alavian, H.I. Alashgar, S. Alawadhi, L. Al-Dabal, P. Aldins, A.S. Alghamdi, R. Al-Hakeem, A. Almessabi, A.N. Alqutub, K.A. Alswat, M. Alzaabi, N. Andrea, M.A. Babatin, A. Baqir, M.T. Barakat, O.M. Bergmann, A.R. Bizri, A. Chaudhry, M.S. Choi, T. Diab, S. Djauzi, E.S. El Hassan, S. El Khoury, S. Fakhry, J.I. Farooqi, H. Fridjonsdottir, R.A. Gani, A. Ghafoor Khan, L. Gheorghe, M. Gottfredsson, S. Gregorcic, B. Hajarizadeh, S. Hamid, I. Hasan, A. Hashim, R. Husni, A. Jeruma, J.G. Jonasson, B. Karlsdottir, D.Y. Kim, Y.S. Kim, Z. Koutoubi, V. Liakina, A. Löve, R. Malekzadeh, M. Matičič, M.S. Memon, S. Merat, J.E. Mokhbat, F.H. Mourad, D.H. Muljono, A. Nawaz, N. Nugrahini, S. Olafsson, S. Priohutomo, H. Qureshi, P. Rassam, B. Rozentale, M. Sadik, K. Saeed, A. Salamat, F.M. Sanai, A. Sanityoso Sulaiman, A.I. Sharara, M. Siddiq, A.M. Siddiqui, G. Sigmundsdottir, B. Sigurdardottir, D. Speiciene, A. Sulaiman,

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