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SUPPLEMENT ARTICLE

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The present and future disease burden of hepatitis C virus infections with today's treatment paradigm: Volume 4

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

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Summary

Factors influencing the morbidity and mortality associated with viremic hepatitis C virus (HCV) infection change over time and place, making it difficult to compare reported estimates. Models were developed for 17 countries (Bahrain, Bulgaria, Cameroon, Colombia, Croatia, Dominican Republic, Ethiopia, Ghana, Hong Kong, Jordan, Kazakhstan, Malaysia, Morocco, Nigeria, Qatar and Taiwan) to quantify and characterize the viremic population as well as forecast the changes in the infected population and the corresponding disease burden from 2015 to 2030. Model inputs were agreed upon through expert consensus, and a standardized methodology was followed to allow for comparison across countries. The viremic prevalence is expected to remain constant or decline in all but four countries (Ethiopia, Ghana, Jordan and Oman); however, HCV-related morbidity and mortality will increase in all countries except Qatar and Taiwan. In Qatar, the high-treatment rate will contribute to a reduction in total cases and HCV-related morbidity by 2030. In the remaining countries, however, the current treatment paradigm will be insufficient to achieve large reductions in HCV-related morbidity and mortality.

KEYWORDS
diagnosis, disease burden, epidemiology, HCV, hepatitis C, incidence, mortality, prevalence, treatment

1 | INTRODUCTION

Hepatitis C virus (HCV) infection incurs a substantial global disease burden with dire implications for morbidity and mortality.[1] Analyses have shown significant associations between infection with HCV and outcomes such as cirrhosis, hepatocellular carcinoma (HCC) and liver transplants as well as a corresponding increased association with mortality.[2-4] With the emergence of effective direct-acting antiviral treatments for HCV, policies to address the HCV disease burden at the national and global levels will require the use of more accurate epidemiological data.[5] There remains, however, a lack of robust data on HCV- and liver-related mortality at the country level, as well as significant heterogeneity in pooled global estimates.[6] It was recently estimated that globally 71 million people have active viremic HCV infections.[7] This study aimed to provide estimates of incidence, prevalence, diagnosis, treatment and mortality in 2015 for multiple countries (Bahrain, Bulgaria, Cameroon, Colombia, Croatia, Dominican Republic, Ethiopia, Ghana, Hong Kong, Jordan, Kazakhstan, Malaysia, Morocco, Nigeria, Qatar and Taiwan). A disease burden model was then used to estimate the projected future disease burden by the year 2030 in each country. This analysis is consistent with previously published work to allow for comparison of results across all of the countries assessed.

2 | METHODOLOGY

2.1 | Inputs

The historical epidemiology of HCV was gathered through a literature search, analysis of unpublished data and discussion with expert panels.[8] When no input data were available, analogues (data from countries with a similar health care and/or risk profiles) or expert inputs were used. Ranges were used to capture uncertainty in inputs with wider ranges implying greater uncertainty.

2.2 | 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. The model has been previously described in detail.[9] 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®, an Excel® add-in by Oracle®. Beta-PERT distributions were used for all uncertain inputs.

The model starts with the annual number of acute infections that progressed to chronic HCV infection after accounting for spontaneous clearance of the virus (Figure 1). The progression of these new cases was followed along with all chronic infections from prior years, after accounting for mortality and cure. Unless specified, the scope of the model was limited to HCV-RNA-positive cases. Nonviremic cases (those who spontaneously cleared the virus or were treated and cured) were not considered even though they would test positive to HCV antibodies (anti-HCV) and may still progress to more advanced stages of liver disease despite viral clearance.[3] 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, was gathered through a literature search and discussions

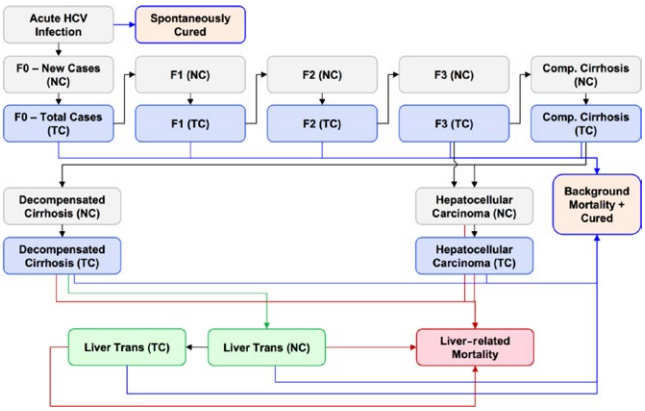

FIGURE 1 The flow of the HCV disease progression model

with an expert panel.[8] These data were used to estimate the historical number of new HCV infections, as described below.

2.3 | New HCV infections & 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 using a two-step process that first calculated the annual number of new cases and then calculated 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. The model calculated the annual number of all-cause mortality, liver-related deaths and cured cases, for that year as will be described below. The Excel® optimization add-in, Solver, was then used to determine an average number of new infections per year going back to 1950. The size and impact of the HCV-infected population prior to 1950 were considered negligible for the purposes of this analysis. An annual relative incidence value was used to describe the change in the number of new infections from 1950 to the year of known HCV prevalence. This was done to account for the fact that annual number of new cases did not remain flat since 1950. Literature reviews and discussions with the expert panel were used to identify the years when new infections peaked using the risk factors common in the country (transfusion-related infections, injection drug use [IDU], 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 known 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, and trended linearly between the 5-year increments. The age and gender distributions in years 1950-1965 were set to equal 1966.

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.

2.4 | 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 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 cured in any given year.

2.5 | All-cause mortality

The all-cause mortality rates by age and gender were gathered from the United Nations Population Database[10] unless stated otherwise. The rates were adjusted for incremental increase in mortality due to IDU and transfusion, as described previously.[11] 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 between ages of 15-44 years who were active injection drug users (active IDU).[12-17] An SMR of 2.1 (1.3-17.6) was applied to all ages for the portion of the population infected due to transfusion.[18] While blood transfusion still posed a risk in some of the low-income countries in this analysis, general consensus was that new HCV infections due to transfusion are on the decline as safer transfusion practices are implemented. A linear declining rate was applied to get the per cent of total infections attributed to transfusion to zero by 2030.

Country-specific adjustments to all-cause mortality for active IDU and transfusion were made using the following assumptions:

2.5.1 | Bahrain

In 2015, experts estimate that 30% of the HCV-infected populations were active IDU. According to a 2008 study of medical records from 183 HCV-infected patients, 35% had acquired their infection through past transfusion.[19]

2.5.2 | Bulgaria

In 2015, approximately 11% of the HCV-infected population was active IDU. This percentage was back-calculated using the estimates of

19 000 active IDU in Bulgaria of whom 62.7% were anti-HCV positive.[20,21] In 2006, an estimated 13% of the infected population had received their infection through transfusion.[22]

2.5.3 | Cameroon

Based on expert consensus, in 2015, <1% of the infected population was assumed to be active IDU, and 5% of the infected population was assumed to have been infected through blood transfusion. Infection due to traditional practices (circumcision, ritual cutting, etc.) poses a significant but as of yet unquantified risk for HCV infection in Cameroon.

2.5.4 | Colombia

Using Argentina as an analogue, it was estimated that approximately 9% of the infected population in 2001 had been infected via IDU.[20,21] Anti-HCV prevalence among active IDU in Colombia ranges from 1.70% to 20.9%, but the size of PWID population has not been well defined.[23,24] Still using Argentina as an analogue, it was estimated that in 2005, 21% of the HCV-infected population acquired the virus as a result of transfusion.[25]

2.5.5 | Croatia

Approximately 16% of the infected population is estimated to have acquired their infection from IDU. This was calculated according to expert input which held that 41% of the estimated 15 440 IDU in 2007[26] are anti-HCV positive, with 4430 chronically infected. In 2011, an estimated 38.7% of the HCV-infected population was infected through transfusion.[27]

2.5.6 | Dominican Republic

The rate of IDU is low in the Dominican Republic. According to expert input, 0.5% of HCV cases in 2015 were due to IDU. Transfusion accounted for an estimated 40% of cases in 2015, also according to expert input.

2.5.7 | Ethiopia

IDU is very uncommon in the Ethiopian population, and thus, none of the HCV-infected population was assumed to have received their infection through this means (expert consensus). Expert consensus estimates that 10% of the HCV population was infected through blood transfusion in 2014.

2.5.8 | Ghana

No formal study of IDU-associated HCV has been carried out in Ghana, but rates are believed to be very low. Expert consensus estimated that <1% of the 2015 infected population was infected through this means. Meanwhile, between 2008 and 2013, 1.20% of HCV cases were assumed to have occurred as a result of contaminated blood transfusions.[28]

2.5.9 | Hong Kong

In 2015, an estimated 16.5% of the infected population was active IDU. This percentage was calculated using estimates of 6000 active IDU in Hong Kong in 2011 and an anti-HCV prevalence of 56% among IDU.[29] In a study of 273 HCV-positive Chinese blood donors in Hong Kong, 37.9% received their infection through transfusion.[30]

2.5.10 | Jordan

Data on risk factors in Jordan are scarce. Estimates are thus based on analogue data from Lebanon. In Lebanon, experts estimate that 0.06% of the 2015 population were actively injecting drugs. Applying this rate to the total population in Jordan, along with a 27.5% anti-HCV prevalence as reported in Lebanese IDU[31] results in 1250 anti-HCV positive IDU in Jordan, corresponding to 4.3% of the infected population. Also using analogue data from Lebanon, an estimated 15.4% of infections in Jordan were assumed to be due to transfusion.[32]

2.5.11 | Kazakhstan

There have been no published studies regarding the prevalence of HCV among active injection drug users in Kazakhstan, and thus, Uzbekistan was used as an analogue. An estimated 7% of the infected population was active IDU.[33] This corresponds to about 2000 individuals. Uzbekistan was also used as an analogue source for transfusion-related HCV rates, with an estimated 41% of the infected population infected via transfusion in the year 2000.[33]

2.5.12 | Malaysia

Based on expert input, about 65% of the viremic population in 2009 was infected via IDU. In 2005, an estimated 42% of the HCV-infected population had been infected through a past blood transfusion, with the majority infected prior to 1994.[34]

2.5.13 | Morocco

The per cent of HCV-infected individuals who are active IDU was estimated to be 7.6% based on Libyan analogue data from 2008.[35,36] In a nationwide study carried out from 2005 to 2011, 16.1% of HCV-infected individuals in Morocco had experienced a blood transfusion.[37]

2.5.14 | Nigeria

In 2013, expert consensus estimated that 1% of the infected population was assumed to be active IDU, and 10% of the infected population was assumed to have been infected through blood transfusion.

2.5.15 | Oman

In 2010, clinical data showed that 22.6% of the infected population was active IDU and that 21.1% had become infected through past transfusion.[38]

2.5.16 | Qatar

Data on risk factors in Qatar are scarce. According to expert input, blood transfusion and dialysis are the most common risk factors among Qatari nationals, while active injection drug users are uncommon and make up <5% of the HCV-infected population in 2015. Analogue data from Saudi Arabia were used to estimate that 15% of the infected population has a history of blood transfusion.[39]

2.5.17 | Taiwan

Experts estimated that there are 60 000 active IDU in Taiwan in 2015. Applying an IDU anti-HCV prevalence of 81%,[40] there were an estimated 45 600 active IDU with viremic HCV, corresponding to 8.8% of the prevalent population in 2015. In 1992, 26.8% of the population had become infected through transfusion.[41]

2.6 | Diagnosed

The total number of diagnosed cases was reported previously.[8] To estimate future total diagnosed cases, it was assumed that the number of newly diagnosed cases stayed the same as the last reported year.

2.7 | Treated & cured

The total number of treated HCV patients was similarly reported previously.[8] 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.[8]

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 each of 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; pegylated-interferon (Peg-IFN)-based therapy in combination with RBV (dual therapy); Peg-IFN with RBV and a protease inhibitor (PI) (triple therapy); or direct-acting antiviral therapies (DAAs) with or without RBV. 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 (eg F1, F2, F3 and F4).

2.8 | 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 revealed by consultations with experts. Prior to 2015, decompensated cirrhotic patients were considered ineligible for treatment in all countries.

According to the literature, approximately 40%-60% of HCV patients are eligible for Peg-IFN/RBV.[42,43] The definition of eligibility included contraindications to the drugs (eg psychiatric conditions) as well as patient's preference. In this analysis, 50%-100% of the patients were considered treatment eligible for the 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, noninvasive testing methods to determine the level of fibrosis in 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 ranges 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.

2.9 | 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.

3 | RESULTS

The results of the analysis for 2015 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 between 2015 and 2030, while Figures 3 and 4 show the projected HCV disease burden between the years 1950-2030. It should be noted that decompensated cirrhosis figures include those who received a liver transplant.

3.1 | Bahrain

Annual incidence was modelled with expert input to peak in 1991, around the time systematic blood screening began. In 2015, it was estimated that there were 250 new cases in Bahrain (18.4 per 100 000).

It was estimated that there were 17 000 (11 000-17 700) viremic cases in 2015. The number of viremic cases peaked in 2015 and will continue to slowly decline by 5% between 2015 and 2030, resulting in 16 200 cases in 2030. In the same time frame, compensated and decompensated cirrhotic cases are expected to increase by 100% from a base of 1200 and 80 respectively. HCC is expected to increase by 100% from a base of 50 cases, while liver-related deaths are expected to increase by 100% from a base of 50 cases.

TABLE 1 HCV-infected population and treatment forecasts in 2015

	Bahrain	Bulgaria	Cameroon	Colombia	Croatia	Dominican Republic	Ethiopia	Ghana	Hong Kong
Country's population (000)	1400	7100	23 300	48 200	4300	10 500	98 900	27 000	7300
Total viremic infections (000)	17 (11-17)	92 (52-118)	159 (117-166)	382 (269-416)	26 (17-28)	69 (45-109)	649 (414-713)	400 (308-930)	15 (6-23)
Viremic prevalence (%)	1.3% (0.8%-1.5%)	1.3% (0.7%-1.7%)	0.7% (0.5%-0.7%)	0.8% (0.6%-0.9%)	0.6% (0.4%-0.7%)	0.7% (0.5%-1.6%)	0.6% (0.4%-0.7%)	1.5% (0.9%-4.1%)	0.2% (0.1%-0.3%)
Total diagnosed (viremic)									
Total cases	2900	17 700	6300	48 500	6400	6900	19 500	29 700	3400
Annual newly diagnosed	280	1200	110	3200	150	690	2000	2800	370
Diagnosis rate (%)	17%	19%	4%	13%	25%	10%	3%	7%	22%
Newly diagnosed rate (%)	1.6%	1.3%	0.1%	0.8%	0.6%	1.0%	0.3%	0.7%	2.4%
Treated & cured									
Annual number treated	50	720	500	1000	150	500	2000	20	190
Annual number cured	50	470	230	670	90	340	1000	0	180
Average SVR (%)	95%	65%	46%	67%	60%	67%	53%	0%	95%
Treatment rate (%)	0.3%	0.8%	0.3%	0.3%	0.6%	0.7%	0.3%	0.0%	1.3%
New infections									
Total cases	250	1200	5200	3200	190	930	15 300	12 300	330
Infection rate (per 100K)	18.4	16.9	22.3	6.6	4.5	8.8	15.4	45.6	4.5
Risk factors									
Number of active IDU	5100	10 300	16	3500	4100	340	0	4	2500
% Active IDU	30%	11%	0%	1%	16%	0%	0%	0%	17%
Previous blood transfusion	3400	7500	7100	47 700	7900	25 700	60 000	4500	3900
% Previous blood transfusion	20%	8%	4%	12%	30%	38%	9%	1%	26%
Mortality									
All cases	210	2060	6300	8400	460	1230	11 500	5310	370
All cause mortality	160	1600	5200	6300	370	990	9400	4400	260
Liver-related mortality	50	460	1100	2100	90	240	2100	910	110
Current treatment protocols									
Treatment age	15 - 64	20 - 74	20 - 64	15 - 74	20 - 69	15 - 69	15 - 69	20 - 64	15 - 69
% Treatment eligible	100%	55%	50%	55%	57%	58%	52%	55%	100%
Treated stages - G1	>= F3	>= F3	>= F0	>= F0	>= F1	>= F3	>= F1	>= F0	>= F0
Treated stages - G2	>= F3	>= F3	>= F0	>= F0	>= F1	>= F3	>= F1	>= F0	>= F0
Treated stages - G3	>= F3	>= F3	>= F0	>= F0	>= F1	>= F3	>= F1	>= F0	>= F0
Treated stages - G4	>= F3	>= F3	>= F0	>= F0	>= F1	>= F3	>= F1	>= F0	>= F0
SVR - G1 (%)	95%	65%	60%	60%	50%	67%	50%	65%	95%
SVR - G2 (%)	95%	65%	75%	75%	75%	67%	65%	65%	90%
SVR - G3 (%)	95%	65%	65%	65%	77%	67%	55%	65%	85%
SVR - G4 (%)	95%	65%	75%	75%	50%	67%	50%	65%	95%

TABLE 1 (Continued)

	Jordan	Kazakhstan	Malaysia	Morocco	Nigeria	Oman	Qatar	Taiwan
Country's population (000)	7600	17 600	30 700	34 400	184 000	4200	390	23 400
Total viremic infections (000)	24 (11-31)	331 (256-398)	384 (272-443)	310 (259-454)	2576 (1906-2673)	16 (14-21)	1 (0.46-4)	520 (350-922)
Viremic prevalence (%)	0.3% (0.1%-0.4%)	1.9% (1.5%-2.3%)	1.3% (0.9%-1.4%)	0.9% (0.8%-1.3%)	1.4% (1.0%-1.5%)	0.4% (0.3%-0.5%)	0.5% (0.2%-2.0%)	2.2% (1.5%-3.9%)
Total diagnosed (viremic)								
Total cases	5100	56 300	30 000	31 100	111 000	3100	600	223 000
Annual newly diagnosed	480	4000	2900	3100	1300	230	100	16 400
Diagnosis rate (%)	21%	17%	8%	10%	4%	20%	46%	43%
Newly diagnosed rate (%)	1.9%	1.2%	0.8%	1.0%	0.1%	1.5%	7.8%	3.2%
Treated & cured								
Annual number treated	150	1800	550	3000	300	80	170	8000
Annual number cured	80	1300	350	1800	160	40	160	5500
Average SVR (%)	53%	72%	64%	61%	53%	51%	94%	69%
Treatment rate (%)	0.6%	0.5%	0.1%	1.0%	0.0%	0.5%	13.2%	1.5%
New infections								
Total cases	630	7700	5900	5600	69 400	310	40	3100
Infection rate (per 100K)	8.3	43.7	19.2	16.3	37.8	7.5	10.1	13.2
Risk factors								
Number of active IDU	1100	23 200	250 000	23 600	25 800	3500	70	45 600
% Active IDU	4%	7%	65%	8%	1%	22%	5%	9%
Previous blood transfusion	2500	67 900	96 800	34 000	176 000	2500	80	55 000
% Previous blood transfusion	10%	21%	25%	11%	7%	16%	6%	11%
Mortality								
All cases	320	5220	7600	6000	84 000	170	21	19 500
All cause mortality	240	4300	6200	4600	75 900	130	16	13 100
Liver-related mortality	80	920	1400	1500	8100	40	5	6400
Current treatment protocols								
Treatment age	15 - 64	15 - 64	15 - 64	15 - 69	20 - 69	15 - 84	15 - 69	15 - 74
% Treatment eligible	57%	58%	54%	53%	52%	58%	100%	55%
Treated stages - G1	>= F0	>= F3	>= F2	>= F2	>= F2	>= F2	>= F0	>= F0
Treated stages - G2	>= F0	>= F3	>= F2	>= F2	>= F2	>= F2	>= F0	>= F0
Treated stages - G3	>= F0	>= F3	>= F2	>= F2	>= F2	>= F2	>= F0	>= F0
Treated stages - G4	>= F0	>= F3	>= F2	>= F2	>= F2	>= F2	>= F0	>= F0
SVR - G1 (%)	45%	65%	50%	50%	50%	50%	96%	65%
SVR - G2 (%)	75%	81%	70%	75%	75%	85%	95%	75%
SVR - G3 (%)	65%	84%	72%	65%	75%	50%	87%	75%
SVR - G4 (%)	59%	81%	55%	75%	50%	50%	92%	65%

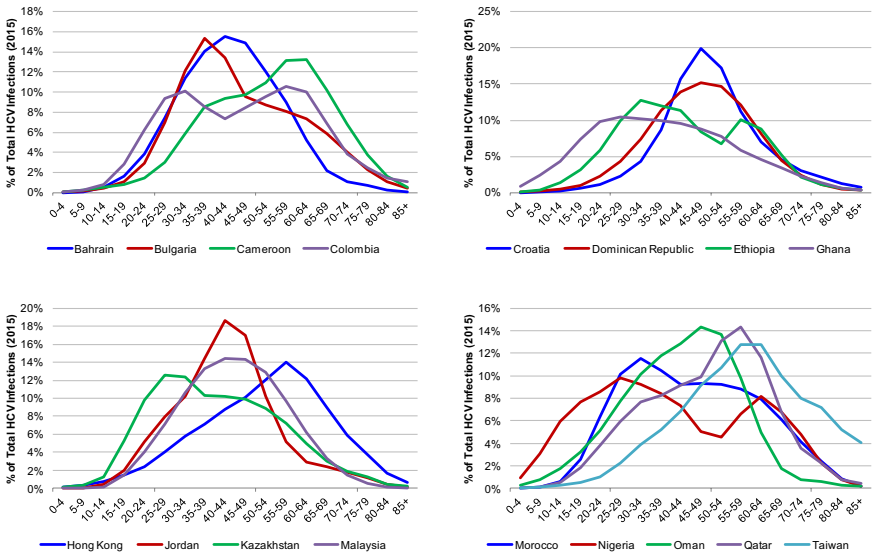

FIGURE 2 Distribution of the 2015 HCV-infected population by age as a percentage of total number of cases

3.2 | Bulgaria

Expert consensus was used to estimate annual incidence. In 2015, it was estimated that there were 1200 new cases in Bulgaria (16.9 per 100 000).

It was estimated that there are 92 200 (51 600-118 100) viremic cases in 2015. Viremic cases were estimated to have peaked at 97 900 in 2005 and are expected to decline by 18% between 2015 and 2030, resulting in 75 300 cases in 2030. In the same time frame, compensated and decompensated cirrhotic cases are expected to increase by 30% from a base of 8700 and 950 respectively. HCC is expected to increase by 30% from a base of 420 cases, while liver-related deaths are expected to increase by 30% from a base of 460 cases.

3.3 | Cameroon

An incidence curve was developed for Cameroon based on expert input and historical trends of nosocomial infections in the central African region.[44,45] Incidence was modelled to peak in the early 1990s and decline very gradually thereafter. In 2015, it was estimated that there were 5200 new cases in Cameroon (22.3 per 100 000).

It was estimated that there are 159 000 (117 000-166 000) viremic cases in 2015. The number of viremic cases peaked at 164 000 in 2007 and is expected to decline by 18% between 2015 and 2030, resulting in 131 000 cases in 2030. In the same time frame, compensated cirrhotic cases are expected to decrease by less than 1% from a base of a 2015 base of 20 500 and decompensated cirrhosis cases are expected to increase 3% from a 2015 base of 2200. HCC is expected to increase by 2% from a 2015 base of 960 cases while liver-related deaths are expected to increase by 2% from a base of 1100 cases.

3.4 | Colombia

Prevalence data, historical trends and expert input informed the estimated annual number of new cases. Incidence is assumed to have increased from the 1960s through the early 1990s. The commencement of blood screening in the mid-1990s led to a sharp drop in incidence stabilizing in 2013. In 2015, it is estimated that there were 3200 new viremic cases in Colombia (6.6 per 100 000).

In 2015, there were an estimated 382 000 (269 000-416 000) viremic cases in Colombia. Viremic cases will decrease 20% between 2015 and 2030 resulting in 306 000 cases in 2030. Compensated and decompensated cirrhosis cases will increase 45% and 70% from a 2015 base of 41 300 and 4100, respectively. Similarly, the number of HCC cases and liver-related deaths will increase by 70% and 60% by 2030 from 2015 bases of 1800 and 2100, respectively.

3.5 | Croatia

Expert consensus was used to estimate annual incidence. In 2015, it was estimated that there were 190 new cases in Croatia (4.5 per 100 000).

It was estimated that there are approximately 26 000 (17 000-28 200) viremic cases in 2015 with an estimated peak at 27 600 in 2007. The number of viremic cases is projected to decrease by 25% between 2015 and 2030, corresponding to 20 000 cases in 2030. Compensated and decompensated cirrhosis is expected to increase 100% and 200% from a 2015 base of 2300 and 110, respectively. Liver-related deaths and HCC are both projected to rise by 100% from a 2015 base of 90 cases.

3.6 | Dominican Republic

Expert consensus was used to estimate annual incidence. In 2015, it was estimated that there were 930 incident cases (8.8 per 100 000).

It was estimated that there are 68 600 (45 900-109 000) viremic cases in 2015. Viremic cases were estimated to have peaked at 68 800 in 2010. The viremic population is expected to decrease by 15% between 2015 and 2030 corresponding to 58 400 cases in 2030. The

TABLE 2 Comparison of hepatitis C (HCV) disease burden in 2015 and 2030

	Bahrain	Bulgaria	Cameroon	Colombia	Croatia	Dominican Republic	Ethiopia	Ghana	Hong Kong	Jordan	Kazakhstan	Malaysia	Morocco	Nigeria	Oman	Qatar	Taiwan
Viremic HCV infections (000)																	
2015 Est.	17	92	159	382	26	69	649	400	15	25	331	384	310	2576	16	1	520
2030 Est.	16	75	131	306	20	58	655	447	13	27	320	343	282	2327	16	0	289
Per cent change	(5%)	(18%)	(18%)	(20%)	(25%)	(15%)	1%	12%	(18%)	7%	(3%)	(11%)	(9%)	(10%)	3%	(90%)	(45%)
HCC cases																	
2015 Est.	50	420	960	1800	90	220	1800	1300	100	70	830	1200	1300	9700	40	5	6000
2030 Est.	120	550	990	3100	220	450	3800	2100	130	170	1400	2900	1800	10 000	110	1	5800
Per cent change	100%	30%	2%	70%	100%	100%	100%	70%	25%	100%	65%	100%	35%	3%	200%	(70%)	(4%)
Liver-related mortality																	
2015 Est.	50	460	1100	2100	90	240	2100	1400	110	80	920	1400	1500	10 900	40	5	6400
2030 Est.	120	600	1100	3300	220	490	4200	2300	140	190	1500	3200	2000	11 200	120	1	6000
Per cent change	100%	30%	2%	60%	100%	100%	100%	65%	25%	100%	65%	100%	35%	3%	200%	(70%)	(8%)
Decompensated cirrhosis																	
2015 Est.	80	950	2200	4100	110	480	4100	2900	210	150	1800	2700	3000	22 300	50	5	13 600
2030 Est.	190	1300	2300	7000	340	1000	8800	4900	280	390	3000	6700	4100	23 000	210	3	13 000
Per cent change	100%	30%	3%	70%	200%	100%	100%	70%	30%	200%	65%	100%	35%	3%	400%	(45%)	(5%)
Compensated cirrhosis																	
2015 Est.	1200	8700	20 500	41 300	2300	4900	43 000	27 600	2100	1600	18 000	28 600	28 300	212 000	870	110	115 000
2030 Est.	2600	11 200	20 400	59 900	4500	9300	80 300	43 900	2500	3600	28 900	59 400	36 100	214 000	2300	20	95 500
Per cent change	100%	30%	(0%)	45%	100%	90%	85%	60%	20%	100%	60%	100%	30%	1%	200%	(80%)	(17%)

Negative per cent change is represented with parentheses.

number of compensated and decompensated cirrhosis cases is projected to increase by 90% and 100% from 2015 bases of 4900 and 480, respectively. The number of liver-related deaths and HCC are both expected to increase by 100% as well from 2015 bases of 240 and 220 cases, respectively.

3.7 | Ethiopia

Incidence was estimated, with expert panel input, to have peaked in 1998, and decreased only gradually since that time. The gradual decrease was modelled due to continued transmission in the general community through tattooing and traditional practices and medical settings where sterilization of tools is not mandated by law (expert consensus). In 2015, it was estimated that there were 15 300 new cases occurring annually in Ethiopia (15.4 per 100 000).

It is estimated that there were 649 000 (414 000-713 000) viremic cases in 2015. Viremic cases were estimated to peak at 657 700 in 2023 before dropping to 655 000 cases by 2030. The numbers of compensated and decompensated cirrhosis cases are projected to increase by 85% and 100% from 2015 bases of 43 000 and 4100, respectively. Similarly, the number of liver-related deaths and HCC are expected to increase by 100% from 2015 bases of 2100 and 1800 cases, respectively.

3.8 | Ghana

Annual incidence was modelled with expert input to increase during the 1980s and 1990s, peak in the late 1990s and decrease thereafter to level off post-2010. In 2015, an estimated 12 300 new cases of HCV occurred in Ghana (45.6 per 100 000).

It is estimated that there are 400 000 (308 000-930 000) viremic cases in 2015. Viremic cases are estimated to peak at 449 000 in 2031. The viremic population is expected to increase by 12% between 2015 and 2030 resulting in 447 000 cases in 2030. Between 2015 and 2030, the number of compensated and decompensated cirrhosis cases is estimated to increase 60% and 70% from 27 600 and 2900 cases, respectively, in 2015. In the same time period, the number of cases of HCC and liver-related death is also expected to increase by 70% and 65% from 1300 and 1400 cases, respectively, in 2015.

3.9 | Hong Kong

It was estimated by expert consensus that there were 330 new cases in 2015 (4.5 per 100 000).

There were an estimated 15 200 (6100-23 200) viremic cases in Hong Kong in 2015. Viremic cases peaked in 2005 at 16 200 cases. Assuming the current treatment paradigm remains constant, viremic cases will decline by 18% from 2015 to 2030 resulting in 12 500 cases in 2030. Compensated and decompensated cirrhosis cases are projected to increase by 20% and 30% from 2015 bases of 2100 and 210 cases, respectively. Similarly, the number of liver-related deaths and HCC is expected to increase by 25%, from 2015 bases of 110 and 100 cases.

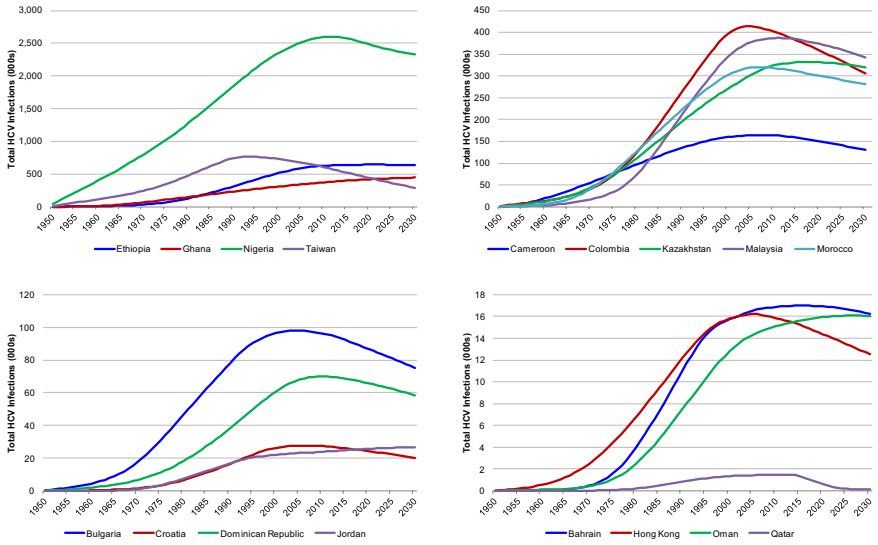

FIGURE 3 Change in viremic HCV infections over time

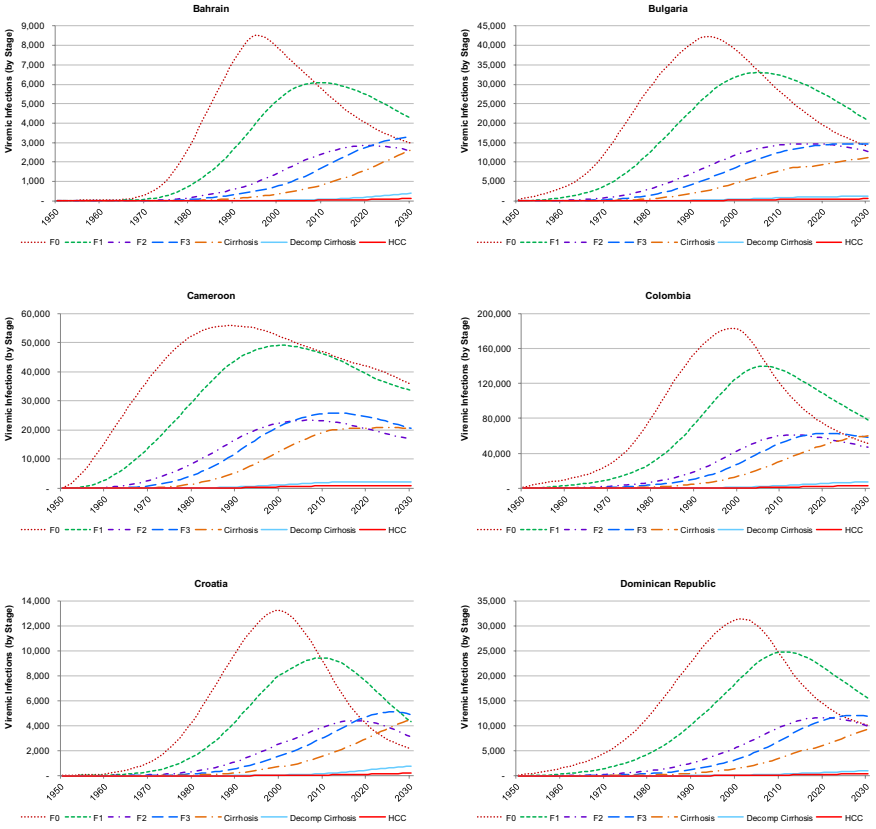

FIGURE 4 Change in HCV disease burden over time

3.10 | Jordan

Expert consensus was used to estimate annual incidence. In 2015, it was estimated that there were 630 new cases in Jordan (8.3 per 100 000).

It is estimated that there are 24 800 (11 300-30 800) viremic cases in 2015. Viremic cases are estimated to peak at 26 700 cases in 2033. A 7% increase ensues between 2015 and 2030, resulting in 26 600 cases in 2030. In the same time frame, compensated and decompensated cirrhotic cases are expected to increase by 100% and 200% from a base of 1600 and 150, respectively. HCC is expected to increase by 100% from a 2015 base of 70 cases, while liver-related deaths are expected to increase by 100% from a base of 80 cases.

3.11 | Kazakhstan

The number of new cases was estimated through a combination of expert consensus, prevalence data and historical trends. Incidence is assumed to have increased from the 1960's before stabilizing in the late

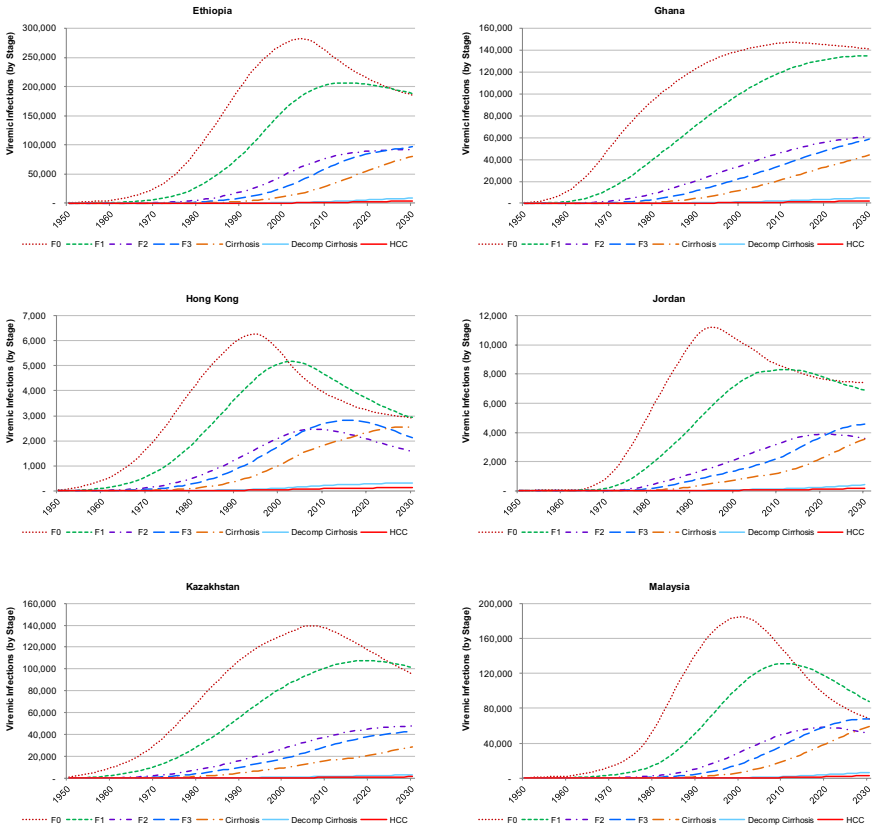

FIGURE 4 (Continued)

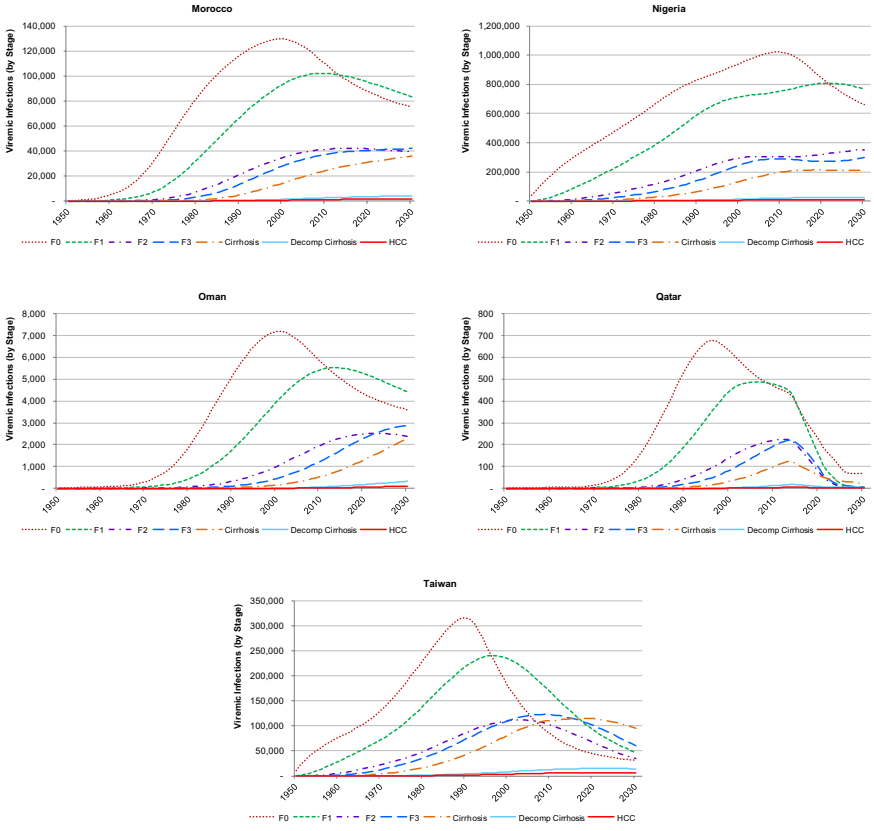

FIGURE 4 (Continued)

1980s. Once blood screening and other preventative measure came into full effect in the early 2000s there was a sharp drop in incidence and then stabilization. In 2015, it is estimated that there were 7700 new viremic cases of HCV in Kazakhstan (43.7 per 100 000).

In 2015, there were an estimated 331 000 (256 000-398 000) viremic individuals in Kazakhstan. Viremic cases are expected to peak at 332 000 cases in 2018 and then decrease to 320 000 cases in 2030, a 3% reduction from 2015. Compensated and decompensated cirrhosis cases will increase 60% and 65% from a 2015 base of 18 000 and 1800, respectively. The number of HCC cases and liver-related deaths will increase by 65%, from a base in 2015 of 830 and 920, respectively.

3.12 | Malaysia

Annual incidence was estimated with expert input. In 2015, it was estimated that there were 5900 new cases in Malaysia (19.2 per 100 000). Harm-reduction programs and screening of blood supply have reduced the number of new cases since the 1990s.

It was estimated that there are approximately 384 000 (272 000-443 000) viremic cases in 2015. Viremic cases were estimated to have peaked at 387 000 in 2011. Viremic cases are projected to decrease by 11% between 2015 and 2030 to 343 000 cases in 2030. Compensated and decompensated cirrhosis are both expected to increase 100% from a 2015 base of 28 600 and 2700, respectively. Similarly, liver-related deaths and HCC are both projected to rise by 100% from 2015 bases of 1400 and 1200 cases, respectively.

3.13 | Morocco

Expert consensus was used to estimate annual incidence. In 2015, it was estimated that there were 5600 new cases in Morocco (16.3 per 100 000).

It is estimated that there were 310 000 (259 000-454 000) viremic cases in 2015. Viremic cases were estimated to have peaked at 320 000 in 2007. The viremic population is expected to decline by 9% between 2015 and 2030 to 282 000 cases in 2030. The number of compensated and decompensated cirrhosis cases is projected to increase by 30% and 35% from 2015 bases of 28 300 and 3000, respectively. Similarly, the number of liver-related deaths and HCC is expected to increase by 35% from 2015 bases of 1500 and 1300 cases, respectively.

3.14 | Nigeria

Incidence was modelled with expert input to increase exponentially during the 1980s and 1990s, peak in 1998 and decrease slowly thereafter. In 2015, it was estimated that there were 69 400 new cases in Nigeria (37.8 per 100 000).

It is estimated that there are 2 576 000 (1 906 000-2 673 000) viremic cases in 2015. Viremic cases are estimated to have peaked at 2 602 000 in 2011. The viremic population is expected to decrease by 10% between 2015 and 2030 to 2 327 000 cases in 2030. Between 2015 and 2030, the number of compensated and decompensated cirrhosis cases is estimated to increase 1% and 3% from 212 000 and 22 300 cases, respectively, in 2015. In the same time period, both the number of cases of HCC and liver-related death are expected to increase by 3% from 9700 and 10 900 cases, respectively, in 2015.

3.15 | Oman

Expert consensus was used to estimate annual incidence. In 2015, it was estimated that there were 310 new cases in Oman (7.5 per 100 000). Incidence peaked in 1991, around the time systematic blood screening began.

It is estimated that there were 15 600 (14 000-20 500) viremic cases in 2015. Viremic cases are estimated to peak in 2026 at 16 100, only slightly higher than the 2015 estimate. Viremic cases are expected to increase by 3% between 2015 and 2030, resulting in about 16 000 cases in 2030. In the same time frame, compensated and decompensated cirrhotic cases are expected to increase by 200% and 400% from a 2015 base of 870 and 50 cases, respectively. HCC- and liver-related deaths are both expected to increase by 200%, both from a base of 40 cases in 2015.

3.16 | Qatar

Expert consensus was used to estimate annual incidence, and 40 new cases were estimated among Qatari nationals in 2015 (10.1 per 100 000).

It is estimated that there are 1300 (460-3600) viremic cases in 2015. Viremic cases are estimated to have peaked at 1500 in 2012, and they are projected to decrease by 90% between 2015 and 2030 due to the relatively high number of patients being treated with high SVR therapies. It is estimated that there will be 110 viremic cases in Qatar by 2030. In the same time frame, compensated and decompensated cirrhotic cases are expected to decrease by 80% and about 40% from a base of 110 and 5 cases, respectively. HCC- and liver-related deaths are expected to decrease by more than 60%, both from a base of 5 cases in 2015.

3.17 | Taiwan

It was estimated by expert consensus that there were 3100 new cases in 2015 (13.2 per 100 000).

It was estimated that there were 520 000 (350 000-922 000) viremic cases in Taiwan in 2015. Viremic cases were estimated to have peaked in 1993 at 769 000 cases. Assuming the current treatment paradigm remains constant, viremic cases will decline by 45% between 2015 and 2030 resulting in 289 000 cases in 2030. Compensated and decompensated cirrhosis cases are projected to decline by 17% and 5% respectively from 115 000 and 13 600 cases in 2015. HCC cases and liver-related deaths are also projected to decline by 4% and 8%, respectively, from 6000 and 6400 cases.

4 | DISCUSSION

The countries in this analysis vary widely in population size, demographics, epidemic history, current risk factors and endemicity, and

treatment rates. To account for the heterogeneity of countries considered and the changing disease burden over time, a modelling approach was used to estimate HCV morbidity and mortality in 2015 with forecasts to 2030. The standardized methodology used in this analysis presents an opportunity to compare the HCV disease burden across countries in a variety of contexts.

Globally, the prevalence of viremic HCV is around 1.0%.[7,46] Ten countries in this analysis had a viremic prevalence <1.0%, and three countries had a prevalence <0.5% (Hong Kong, Jordan and Qatar) in 2015 (Table 1). The number of viremic infections changes with time as the result of death, cure and ongoing transmission (Table 2 and Figure 3). The focus of this analysis is on viremic cases only; persons who spontaneously clear the virus or are cured through treatment are removed from the analysis. As a result, the disease burden estimates shown here represent only persons with active infection, and assumes no health burden of patients who have cleared the infection.

In most countries, the number of viremic cases is forecast to decline or remain flat, with the exception of Ethiopia, Ghana, Jordan and Oman. In Ghana, very few patients are treated, and the new infection rate is high (45.6 per 100 000). Additionally, the population is relatively young (average age in Ghana is <40, compared with an average age of 40-49 years for all countries studied), suggesting that the peak HCV morbidity and mortality are yet to come. In Oman, ongoing transmission is attributed to IDU. Although data gaps exist, and the estimate of IDU in Jordan is low, the practice (and associated increase in HCV transmission) is thought to be increasing (expert consensus). In Ethiopia, the increase in viremic cases is primarily due to ongoing community and nosocomial transmission.

Viremic cases are forecast to decline most substantially in Taiwan and Qatar, with a 45% and 90% reduction in cases expected by 2030, respectively. In both countries, the average age of the population is >50 years (Figure 2), and in Taiwan, mortality is the primary driver for the declining prevalence. In Qatar, however, a 13% treatment rate has accelerated the reduction in both viremic cases and end-stage liver disease (Figure 5). A point worth noting is that the analysis for Qatar included only Qatari nationals. Migrant workers and their families account for approximately 90% of the country's population, and including them in the analysis could impact the age distribution and burden of disease in Qatar.

Diagnosis rates closely followed the World Bank income group of the country in question such that the upper middle- and high-income countries analysed recorded on average higher diagnosis rates than lower middle- and low-income countries. Five countries had a diagnosis rate under 10% (Cameroon, Ethiopia, Ghana, Malaysia and Nigeria), and Qatar and Taiwan had diagnosis rates over 40%. Although the number of patients treated with high SVR therapies has been increasing at a global level,[46] treatment rates remain low for the majority of countries included in this analysis. Qatar's 13% treatment rate is the highest, far exceeding the rate of other countries; Taiwan has the second-highest rate, at 1.5% treated annually.

Figure 4 shows the change in disease burden between 2015 and 2030, while Figure 5 shows that the number of individuals with end-stage liver disease was expected to continue to grow beyond 2030 in most countries except for Qatar and Taiwan. The age of the infected

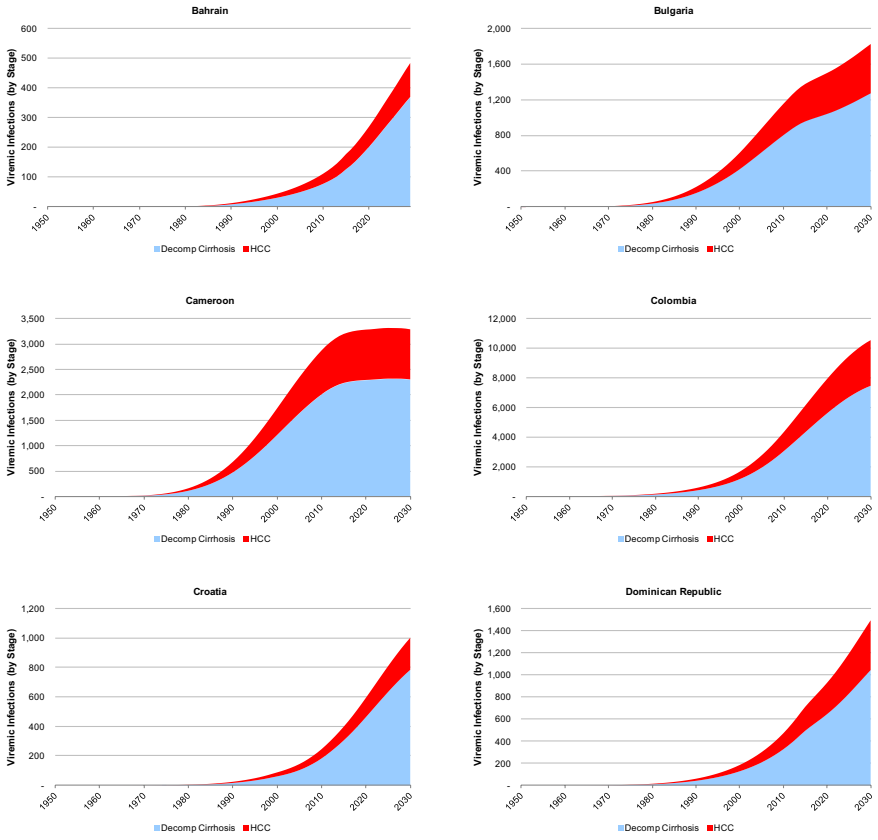

FIGURE 5 Change in the number of liver transplants, decompensated cirrhosis cases and HCC cases over time

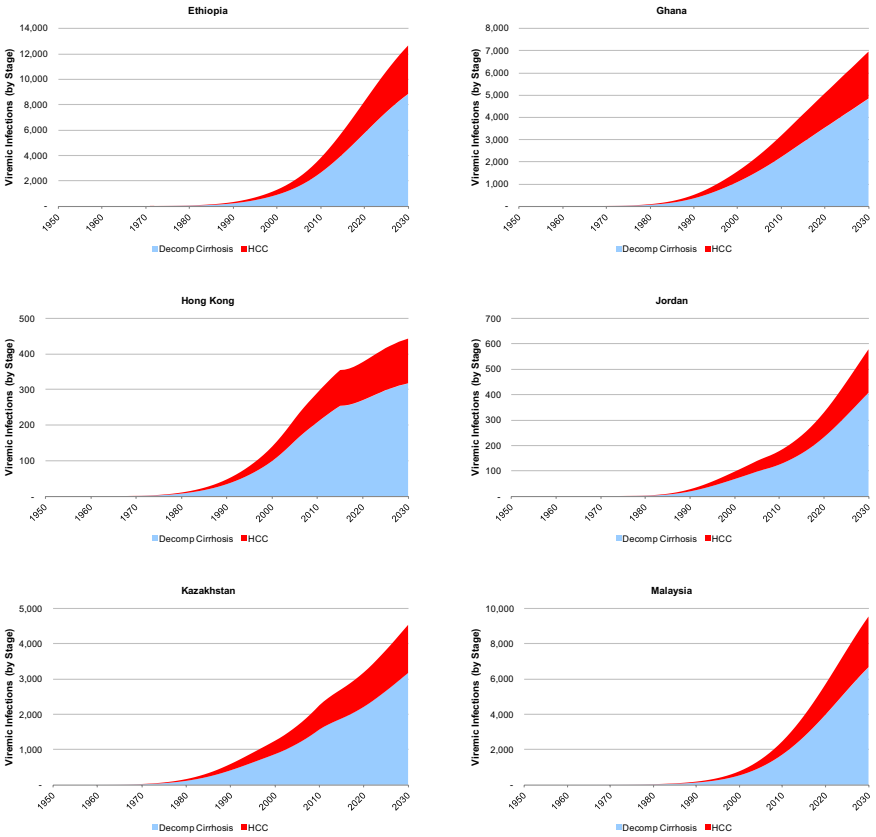

FIGURE 5 (Continued)

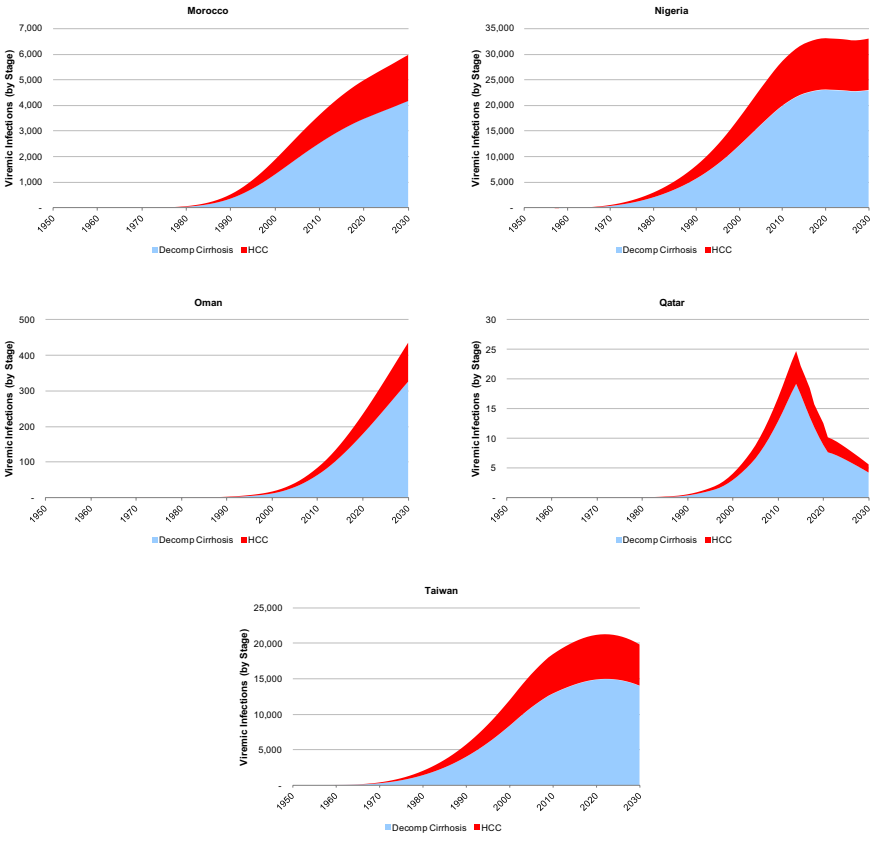

FIGURE 5 (Continued)

population (Figure 2) as well as risk factors such as IDU and transfusion (Table 1) largely determined mortality (all-cause and liver-related). In general, older populations have a higher all-cause mortality rate,[47] and, as HCV disease progression rates increase with age, older individuals were more likely to have HCV-related advanced liver disease and liver-related deaths. As mentioned previously, IDU cases have a higher mortality rate due to associated high-risk behaviour. Table 1 presents the proportion of the infected population who were actively injecting drugs. The all-cause mortality was adjusted accordingly for this portion of the population.

4.1 | Limitations

There are several limitations that may influence the outcomes from this study. Empirical incidence data starting in 1950 were impossible to get for all countries, so the distribution of new cases from 1950 to the most recent year of available data was back-calculated using prevalence from a known year, an estimation of the age and gender distribution of new cases and a relative incidence curve. All assumptions were reviewed extensively by the expert panels, and an analysis of key risk factors (eg IDU, nosocomial infection) was conducted in each country to inform incidence estimates after the year of known prevalence. In the absence of better information, the number of new cases was modelled to remain constant after 2015.

A second limitation is the assumption that diagnosis rates in each country will be sufficiently high to provide a pool of patients available and eligible 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. This is particularly relevant to the low-income countries in the analysis where HCV continues to be a neglected disease.

In addition, the model does not consider the potential continued disease progression of cured HCV patients. Previous studies have indicated that it is possible for hepatic inflammation and disease progression to continue to HCC in more advanced patients after achieving SVR,[48,49] even though this happens at a slower rate.[3] As the analysis presented in this study was limited to HCV viremic infections, the outcomes may overestimate the reduction in cases of HCC and decompensated cirrhosis.

4.2 | Conclusion

In conclusion, this study demonstrates that overall viremic HCV prevalence is decreasing in most of the analysed countries due to a combination of an aging-infected population, expanding availability of more effective treatments and a concurrent reduction in risk factors, mainly the improvements in the safety of blood products and harm-reduction programs for injection drug users. However, morbidity attributable and mortality attributable to HCV are expected to increase as the current infected population progresses to advanced stages of liver disease. This is especially the case in countries with a large but young infected population, coupled with low diagnosis and treatment rates. A reduced disease burden and eventual elimination are possible if significant improvements are made to the overall cascade of care continuum, especially increases in screening, diagnosis and treatment. Thus, countries will need to evaluate different management strategies to guide decisions on how to best control the expected increase in their HCV-related disease burden. A series of such management strategies are discussed in the next analysis in this volume.[50]

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CONFLICT OF INTEREST

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