Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study

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Summary

Background The 69th World Health Assembly approved the Global Health Sector Strategy to eliminate hepatitis C virus (HCV) infection by 2030, which can become a reality with the recent launch of direct acting antiviral therapies. Reliable disease burden estimates are required for national strategies. This analysis estimates the global prevalence of viraemic HCV at the end of 2015, an update of—and expansion on—the 2014 analysis, which reported 80 million (95% CI 64–103) viraemic infections in 2013.

Methods We developed country-level disease burden models following a systematic review of HCV prevalence (number of studies, n=6754) and genotype (n=11 342) studies published after 2013. A Delphi process was used to gain country expert consensus and validate inputs. Published estimates alone were used for countries where expert panel meetings could not be scheduled. Global prevalence was estimated using regional averages for countries without data.

Findings Models were built for 100 countries, 59 of which were approved by country experts, with the remaining 41 estimated using published data alone. The remaining countries had insufficient data to create a model. The global prevalence of viraemic HCV is estimated to be 1·0% (95% uncertainty interval 0·8–1·1) in 2015, corresponding to 71·1 million (62·5–79·4) viraemic infections. Genotypes 1 and 3 were the most common cause of infections (44% and 25%, respectively).

Interpretation The global estimate of viraemic infections is lower than previous estimates, largely due to more recent (lower) prevalence estimates in Africa. Additionally, increased mortality due to liver-related causes and an ageing population may have contributed to a reduction in infections.

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Introduction

Hepatitis C virus (HCV) infection is of growing international concern due to its substantial effect on morbidity and mortality.[1–6] A leading cause of cirrhosis, hepatocellular carcinoma (HCC), liver transplantation, and liver-related death worldwide, the HCV-related disease burden continues to increase as the infected population advances to late stage liver disease.[7,8] The disease inflicts an immense health and economic burden on countries due to the infection's hepatic and extrahepatic effects.[9–14]

In 2016, the 69th World Health Assembly approved the Global Health Sector Strategy to eliminate hepatitis infection by 2030,[15] and WHO introduced global targets for the care and management of HCV including "a 90% reduction in new cases of chronic hepatitis C, a 65% reduction in hepatitis C deaths, and treatment of 80% of eligible people with chronic hepatitis C infections".[16] To achieve these goals, countries need to develop national policies based on up-to-date and reliable epidemiological evidence.[17–19] However, data are often are outdated and conflicting, making evidence-based policy making and resource allocation difficult. We aimed to review and analyse available data to estimate the current HCV disease burden at the national level to support countries in their efforts to develop national strategies.

In 2014, we estimated the global HCV prevalence and genotype distribution following a comprehensive review of indexed sources and grey literature (eg, government reports) published between 2000 and 2013.[20] The analysis focused on quantifying the number of viraemic infections (HCV RNA positive). By comparison, earlier studies[21–23] had reported anti-HCV positive infections, which are serological evidence of past or present HCV infection. In 2015, the Polaris Observatory was created to monitor and forecast the disease burden for hepatitis B and C. This analysis builds on the previous efforts with an updated literature review and the addition of disease burden modelling to develop more accurate estimates of 2015 year-end viraemic HCV prevalence at the country level and aggregated to the global level.

Methods

This analysis represents the integration of a literature review, a Delphi process that used country expert interviews to identify missing inputs and to approve all inputs and outputs, and modelling to estimate the 2015 HCV prevalence. The details of data collection, scoring of data sources, Delphi process, and modelling, beyond the description in this section, are summarised in the appendix.

For the **Polaris Observatory** see http://polarisobservatory.com/

See Online for appendix

Research in context

Evidence before this study

In 2014, we estimated the global prevalence and genotype distribution of hepatitis C virus (HCV) infection following a comprehensive review of indexed sources and grey literature (eg, government reports) published between 2000 and 2013. The analysis focused on quantifying the number of viraemic infections (HCV RNA positive). Three global prevalence studies published before 2014 followed a traditional systematic review and meta-analysis procedure and reported anti-HCV positive infections, which are serological evidence of past or present HCV infection.

Added value of this study

The present analysis represents both an update to and substantial expansion of previous efforts to quantify the HCV prevalence and disease burden. A Delphi process was used to complement a traditional systematic review by adding a level of validation through discussions with country experts. 400 experts were consulted to approve the inputs and outputs of 59 country models. This work is additionally unique in that it uses a disease burden model to forecast the 2015 year-end HCV prevalence, accounting for the impact of a changing population due to ageing, treatment and cure, and mortality. 100 countries, representing more than 85% of the world's population, were included in the analysis. Data from these countries were used to estimate the regional prevalence, and regional prevalence rates were then applied to countries with missing data to estimate the global HCV prevalence.

Implications of all the available evidence

In 2016, the 69th World Health Assembly approved the Global Health Sector Strategy to eliminate hepatitis infection by 2030, and the WHO introduced global targets for the care and management of HCV including "a 90% reduction in new cases of chronic hepatitis C, a 65% reduction in hepatitis C deaths, and treatment of 80% of eligible people with chronic hepatitis C infections". The global HCV prevalence rate reported in this study is much lower than previous estimates have suggested. While some of this decline can be attributed to more recent (lower) prevalence estimates in Africa, increased mortality due to liver-related causes and an ageing population may have also contributed to a reduction in infections. The dissemination of the data presented here is crucial for the development of national and regional strategies to achieve these international targets.

Search strategy and selection criteria

We identified available data published between Jan 1, 2000, and March 31, 2016, through searches of PubMed, Embase, and non-indexed reports (appendix p 14). Non-indexed government reports, personal communication with country experts, and additional studies identified through manual searches of references noted in publications were included when better data were not available. The scope of the analysis included all countries. Articles were scored based on how well they could be extrapolated to the general population, the study sample size, and the year of analysis.[20]

HCV disease burden modelling

From a methodological perspective, the biggest difference between our analysis and previous analyses is the use of a Markov model to estimate the HCV prevalence in 2015. The reason for this addition is that HCV prevalence changes over time.[24–26] After culling and scoring available studies, a Microsoft Excel-based (version 2007) Markov-type model, described previously,[24–26] was populated with the highest-scoring epidemiological data for the country of interest (appendix p 15).

For the approved models, a Delphi process was used to gain country expert consensus and validate inputs (appendix p 17). Experts were identified through HCV-related scientific contributions, or through referrals and recommendations from leading researchers. Two or more meetings were held to get consensus around input variables and outputs, and validate the outputs against available empirical data.

For the estimated models, for countries where meeting with local experts could not be scheduled, published estimates were used. All published studies were reviewed and scored by two epidemiologists, and the highest scored study was used for modelling (appendix pp 15–16). When input other than prevalence rate was unavailable for a country, input was extrapolated from countries within the same Global Burden of Disease (GBD) region.

GBD regional prevalence and genotype were calculated as the weighted average of the 2015 outputs from approved and estimated models, and the regional rates were then applied to the 2015 populations of countries with missing data to estimate the global HCV prevalence and genotypes. Countries without a formal GBD designation were assigned an imputed GBD region (appendix p 18).

Statistical analysis

Uncertainty intervals (UIs) and sensitivity analyses were done with Crystal Ball (release 11.1.3708.0), an Excel add-in by Oracle. Beta-PERT distributions[27] were used for all uncertain inputs. Monte Carlo simulation was used to estimate 95% UI. It was assumed that prevalence uncertainty estimates in all countries were independent. The uncertainty range for each country was calculated based on range inputs for prevalence, transition rates, and mortality rate (appendix pp 6–13, 19–23). These were used to calculate regional and global uncertainty ranges. For these estimates, two sources of uncertainty had to be taken into consideration—country-level uncertainty in prevalence

and its effect on the regional and global prevalence. The 2015 country prevalence estimates and 95% UIs were consolidated and defined as assumption variables. A 1/0 switch was developed to include or exclude countries from the regional prevalence calculation, and was also defined as an assumption. A sensitivity analysis was run to identify countries that accounted for the greatest variation in the base global prevalence through their estimated prevalence uncertainty and their inclusion in regional averages.

Role of the funding source

This study was funded by the John C Martin Foundation through the Polaris Observatory. The funders had no role in the study design, data collection and analysis, interpretation of data, decision to publish, or preparation of the manuscript. CE, DR-S, HN, HR, IGa, IGo, JDS, JGu, KP, KR-S, KM, SB, and SR had access to the raw data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

We identified 9177 studies published between Jan 1, 2013, and March 31, 2016, through PubMed (n=4556) and Embase (n=4621) searches. Following the removal of duplicates (n=2408), 6754 studies were selected for review and inclusion in the final analysis. When combined with prevalence studies published before 2013[20] and expert input, prevalence estimates were available for 113 countries, accounting for 92% of the world's population. Among all countries with a prevalence estimate, viraemic rate was available for 81 countries, and age and sex distributions were available for 89 countries, accounting for 82% and 85% of the world's population in 2015, respectively (appendix pp 19–23).

The literature search for genotype data identified 11 342 studies through PubMed and Embase, and the results were combined with unpublished data provided by country experts. Genotype distribution was available for 115 countries (table 1; appendix pp 24–29), which accounted for 90% of the world's population in 2015. Models were built for 100 countries—the inputs and outputs for 59 countries were approved by country experts and for 41 countries were estimated using published data alone. To develop a model, at least one high quality prevalence study and one or more supporting inputs (ie, age and sex, genotype, viraemic rate, treatment rate) were necessary. The remaining countries had insufficient data to create a model.

Countries with approved and estimated modelled prevalence as well as countries for which prevalence was extrapolated from regional averages are shown in the appendix (p 30; figure 1), as are the quality scores of input prevalence data for approved and estimated countries. The 2015 viraemic HCV prevalence of the

	Viraemic prevalence, 2015*	Viraemic population (1000s), 2015*	Genotypes†									
			1a	1b	1c	1 (other)	2	3	4	5	6	Mixed or other
Asia Pacific, high income												
Japan	0·7% (0·3–0·8)	857 (364–1024)	0	64·8%	0	0	34·2%	0	0	0	0	1·0%
South Korea	0·5% (0·3–0·5)	231 (148–261)	3·0%	45·4%	0	4·3%	45·3%	0·8%	0·2%	0	1·0%	0
Asia, Central												
Armenia	..	..	5·2%	36·2%	0	1·7%	18·9%	38·0%	0	0	0	0
Azerbaijan	1·9% (1·3–2·1)	190 (125–212)	2·9%	64·2%	0	0	6·7%	26·0%	0·2%	0	0	0
Georgia	4·2% (3·0–4·2)	165 (120–169)	1·9%	37·6%	0	0	24·5%	34·3%	0	0	0	1·7%
Kazakhstan	2·8 (1·9–3·2)	508 (334–572)	2·5%	52·5%	0	0	10·0%	35·0%	0	0	0	0
Mongolia	6·4% (4·3–7·9)	194 (131–237)	0	98·8%	0	0	1·2%	0	0	0	0	0
Tajikistan	..	..	0	82·7%	0	0	5·8%	7·7%	0	0	0	3·8%
Uzbekistan	4·3% (3·0–5·0)	1292 (902–1524)	2·9%	64·2%	0	0	6·7%	26·0%	0·2%	0	0	0
Asia, East												
China	0·7% (0·5–0·8)	9795 (6675–10 832)	1·4%	56·8%	0	0	15·4%	8·7%	0	0	6·3%	11·4%
Hong Kong	0·2% (0·1–0·3)	15 (6–22)	4·3%	62·4%	0	0	3·2%	2·8%	0	0	27·4%	0
Taiwan	2·1% (1·3–3·7)	489 (310–877)	2·6%	45·5%	0	0·7%	39·5%	1·0%	0·2%	0	0·5%	10·1%
Asia, South												
Afghanistan	0·5% (0·3–0·8)	181 (85–258)	35·2%	2·8%	0	0	0	62·0%	0	0	0	0
India	0·5% (0·4–0·8)	6245 (4748–10 957)	9·0%	16·1%	0	3·3%	0	64·1%	7·3%	0·3%	0	0
Nepal	..	..	11·3%	6·6%	0	21·4%	0	58·4%	0	0	0	2·4%
Pakistan	3·8% (2·8–3·9)	7172 (5363–7487)	4·8%	1·2%	0	1·0%	3·8%	79·0%	1·6%	0·1%	0·1%	8·3%

(Table 1 continues on next page)

	Viraemic prevalence, 2015*	Viraemic population (1000s), 2015*	Genotypes†									
			1a	1b	1c	1 (other)	2	3	4	5	6	Mixed or other
(Continued from previous page)												
Asia, Southeast												
Cambodia	1·6% (0·9–1·7)	257 (147–272)	0	24·0%	0	0	0	20·0%	0	0	56·0%	0
Indonesia	0·5% (0·2–0·8)	1289 (443–2046)	25·6%	39·0%	0	3·0%	9·3%	9·4%	3·6%	0	0	10·0%
Laos	..	..	0	4·4%	0	0	0	0	0	0	95·6%	0
Malaysia	1·2% (0·8–1·3)	382 (240–405)	0	0	0	35·8%	0·7%	62·3%	0·7%	0	0·4%	0
Myanmar	..	..	4·1%	6·9%	0	0	0·7%	39·3%	0	0	49·0%	0
Philippines	0·6% (0·3–0·6)	614 (353–651)	70·7%	2·5%	0	0	26·4%	0	0·2%	0	0·2%	0
Sri Lanka	..	..	0	46·9%	0	0	37·5%	0	0	0	0	15·6%
Thailand	0·7% (0·4–0·7)	463 (255–487)	4·4%	13·0%	0	0	0	47·8%	0	0	34·8%	0
Vietnam	1·1% (0·6–1·2)	1066 (580–1116)	30·0%	17·1%	0	0	1·1%	1·1%	0	0	50·8%	0
Australasia												
Australia	1·0% (0·7–1·0)	230 (178–244)	18·5%	15·7%	0	15·4%	5·6%	42·2%	1·3%	0	1·1%	0·2%
New Zealand	1·0% (0·6–1·3)	48 (30–62)	44·0%	11·0%	0	0	7·0%	35·0%	0	0	1·0%	2·0%
Caribbean												
Cuba	0·3% (0·1–0·7)	35 (14–77)	17·0%	81·0%	0	0	0	0	0	0	0	2·0%
Dominican Republic	0·6% (0·4–1·0)	68 (42–108)	58·9%	19·4%	0	3·7%	9·6%	0·5%	0·2%	0	0	7·7%
Guadeloupe	0·3% (0·2–0·6)	1 (1–3)	0	0	0	80·0%	0	20·0%	0	0	0	0
Martinique	..	..	23·6%	56·7%	0·9%	0	6·9%	7·8%	3·6%	0·3%	0·3%	0
Suriname	..	..	0	0	0	0	100·0%	0	0	0	0	0
Europe, Central												
Albania	..	..	6·0%	50·0%	0	0	20·0%	8·0%	16·0%	0	0	0
Bosnia and Herzegovina	..	..	4·0%	69·3%	0	0	4·0%	21·3%	1·3%	0	0	0
Bulgaria	1·2% (0·7–1·6)	87 (46–122)	5·3%	72·3%	0	0	0	11·6%	0	0	0	10·8%
Croatia	0·6% (0·4–0·7)	26 (17–28)	13·1%	37·4%	0	8·3%	2·2%	35·6%	3·4%	0	0	0
Czech Republic	0·4% (0·2–0·5)	43 (22–49)	13·2%	52·8%	0	0	0·5%	31·1%	2·4%	0	0	0
Hungary	0·5% (0·3–0·6)	52 (29–55)	9·1%	79·9%	0	1·6%	0·9%	6·7%	1·7%	0·1%	0	0
Macedonia	..	..	0	0	0	55·4%	0	44·6%	0	0	0	0
Montenegro	..	..	19·6%	35·0%	0	0	1·1%	24·7%	19·6%	0	0	0
Poland	0·5% (0·4–0·6)	184 (136–224)	2·0%	83·0%	0	0	0·1%	10·0%	4·9%	0	0	0
Romania	2·5% (1·8–2·6)	547 (397–566)	5·4%	92·6%	0	0	0	0·8%	1·2%	0	0	0
Serbia	..	..	0	0	0	57·9%%	3·7%	23·2%	6·7%	0	0	8·5%
Slovakia	0·6% (0·4–0·7)	33 (20–37)	0	0	0	89·9%	1·5%	6·6%	0·5%	0	0·5%	1·0%
Slovenia	0·3% (0·2–0·3)	6 (4–7)	6·9%	8·2%	0	53·0%	2·1%	29·3%	0·4%	0·1%	0	0
Europe, Eastern												
Belarus	..	..	5·0%	53·2%	0	0	2·5%	25·7%	13·6%	0	0	0
Estonia	1·4% (0·9–1·6)	18 (12–20)	1·0%	71·7%	0	0	3·0%	24·2%	0	0	0	0
Latvia	2·2% (1·4–2·6)	43 (28–50)	46·1%	4·3%	0	13·4%	3·6%	31·9%	0·7%	0	0	0
Lithuania	1·1% (0·7–1·3)	33 (20–39)	2·1%	69·3%	0	3·8%	5·6%	19·2%	0	0	0	0
Russia	3·3% (2·3–3·5)	4748 (3238–4960)	2·1%	52·8%	0	0	8·1%	36·3%	0·1%	0	0	0·6%
Ukraine	..	..	1·6%	42·1%	0	0	1·6%	28·8%	0·8%	0	0	25·1%
Europe, Western												
Austria	0·2% (0·1–0·4)	21 (6–30)	20·0%	52·0%	0	0	5·0%	19·0%	4·0%	0	0	0
Belgium	0·6% (0·2–0·7)	64 (23–75)	0	50·0%	0	9·0%	6·0%	19·0%	14·0%	2·0%	0	0
Denmark	0·3% (0·3–0·3)	19 (14–20)	34·0%	12·0%	0	0	8·0%	43·0%	3·0%	0	0	0
Finland	0·4% (0·3–0·5)	23 (16–26)	10·2%	11·6%	0	3·3%	11·4%	48·8%	0·9%	0·1%	0·1%	13·6%

(Table 1 continues on next page)

	Viraemic prevalence, 2015*	Viraemic population (1000s), 2015*	Genotypes†									
			1a	1b	1c	1 (other)	2	3	4	5	6	Mixed or other
(Continued from previous page)												
France	0·3% (0·1–0·3)	194 (93–222)	14·8%	29·7%	0	15·3%	9·1%	19·7%	9·2%	2·0%	0·2%	0
Germany	0·3% (0·1–0·4)	205 (90–313)	25·0%	33·0%	0	4·0%	6·4%	27·4%	3·3%	0·2%	0·2%	0
Greece	1·1% (0·7–1·5)	132 (82–169)	11·5%	28·4%	0·2%	5·1%	7·0%	34·0%	13·9%	0	0	0
Iceland	0·3% (0·2–0·4)	1 (1–1)	41·1%	1·8%	0	0	0·8%	55·3%	1·0%	0	0	0
Ireland	0·6% (0·4–0·9)	30 (20–42)	42·0%	14·0%	0	0	4·0%	39·0%	1·0%	0	0	0
Israel	1·2% (0·7–1·3)	100 (60–103)	12·0%	57·0%	0	0	8·0%	20·0%	3·0%	0	0	0
Italy	1·1% (0·7–2·7)	680 (455–1641)	11·0%	44·0%	0	3·0%	15·0%	10·0%	7·0%	0	0	10·0%
Luxembourg	0·9% (0·6–1·0)	5 (3–6)	0	0	0	55·3%	4·3%	33·6%	6·4%	0	0	0
Malta	0·3% (0·2–0·4)	1 (1–2)	45·0%	15·0%	0	0	1·0%	37·0%	2·0%	0	0	0
Netherlands	0·1% (0·0–0·2)	16 (5–26)	14·8%	15·6%	0	18·8%	9·7%	29·3%	10·5%	0	0	1·3%
Norway	0·4% (0·3–0·5)	21 (15–24)	18·0%	18·0%	0	4·0%	9·0%	50·0%	1·0%	0	0	0
Portugal	0·8% (0·7–1·1)	89 (74–120)	42·7%	21·4%	0	4·0%	1·3%	17·9%	12·5%	0	0	0·2%
Spain	0·8% (0·3–1·2)	386 (159–557)	24·0%	53·5%	0	0	2·0%	8·2%	9·7%	0	0	2·5%
Sweden	0·4% (0·3–0·4)	38 (28–43)	40·0%	10·0%	0	0	20·0%	30·0%	0	0	0	0
Switzerland	1·0% (0·6–1·1)	78 (45–87)	26·0%	26·0%	0	0	8·5%	29·2%	10·3%	0	0	0
UK	0·3% (0·1–0·3)	189 (91–211)	24·4%	11·9%	0	8·8%	7·3%	43·8%	3·8%	0	0	0
Latin America, Andean												
Peru	0·5% (0·3–0·6)	167 (99–182)	74·0%	12·0%	0	0	2·0%	10·0%	0	0	0	2·0%
Latin America, Central												
Colombia	0·8% (0·6–0·9)	409 (272–436)	5·7%	82·8%	0	0	8·5%	2·8%	0	0	0	0
Mexico	0·4% (0·3–0·5)	532 (304–557)	45·4%	24·9%	0	0	21·8%	7·2%	0·3%	0·1%	0	0
Panama	0·3% (0·2–0·3)	12 (7–14)	..	..	..	..	..	..	..	..	..	..
Venezuela	0·4% (0·2–0·4)	118 (59–126)	37·0%	26·0%	0	0·4%	33·0%	4·0%	0	0	0	0
Latin America, Southern												
Argentina	0·8% (0·3–1·2)	326 (144–490)	20·3%	38·1%	0	0·8%	21·7%	17·8%	1·3%	0	0	0
Chile	0·3% (0·2–0·5)	57 (31–94)	7·9%	72·7%	0	0	2·0%	16·5%	0·6%	0·3%	0·1%	0
Latin America, Tropical												
Brazil	0·9% (0·6–0·9)	1787 (1293–1896)	31·0%	33·4%	0	0·4%	4·6%	30·2%	0·2%	0·1%	0	0
North Africa/Middle East												
Algeria	1·0% (0·3–1·7)	388 (140–674)	1·4%	86·2%	0	1·2%	8·5%	0·9%	1·2%	0·2%	0	0·5%
Bahrain	1·2% (0·8–1·3)	17 (11–18)	14·1%	21·1%	0	1·6%	3·9%	15·6%	25·0%	0	0	18·8%
Egypt	6·3% (4·5–6·7)	5625 (4007–6044)	0	4·0%	0	6·0%	0	0	90·0%	0	0	0
Iran	0·2% (0·2–0·3)	199 (129–226)	39·7%	12·1%	0	1·3%	1·4%	27·7%	0·9%	0	0	16·9%
Iraq	0·2% (0·2–0·3)	85 (60–97)	1·4%	12·9%	0	0	0	17·1%	52·9%	0	0	15·7%
Jordan	0·3% (0·1–0·4)	25 (11–29)	23·1%	19·2%	0	0	0	0	57·7%	0	0	0
Kuwait	..	..	0	0	0	15·0%	2·5%	2·5%	80·0%	0	0	0
Lebanon	0·2% (0·1–0·4)	8 (3–18)	6·6%	40·4%	0	0	3·7%	14·1%	33·8%	1·4%	0·1%	0
Libya	0·7% (0·5–0·7)	42 (32–43)	4·2%	6·4%	0	6·9%	7·0%	7·4%	14·6%	0	0	53·5%
Morocco	0·8% (0·5–0·9)	263 (190–328)	6·5%	40·3%	0	0	41·6%	1·0%	0·6%	0·1%	0	10·0%
Oman	0·4% (0·3–0·4)	16 (12–18)	5·5%	30·0%	0	10·1%	2·1%	32·6%	16·5%	0	0	3·2%
Occupied Palestinian territory	..	..	18·5%	9·8%	0	0	0	0	64·1%	0	0	7·6%
Qatar	1·6% (1·3–1·8)	38 (30–40)	1·9%	10·7%	0	3·6%	0·9%	10·3%	72·4%	0·1%	0	0
Saudi Arabia	0·3% (0·2–0·9)	105 (79–189)	0	0	0	38·6%	3·6%	5·2%	52·6%	0	0	0
Syria	3·0% (1·3–3·5)	554 (245–653)	3·4%	18·8%	0	6·3%	0·8%	1·8%	59·0%	10·0%	0	0

(Table 1 continues on next page)

	Viraemic prevalence, 2015*	Viraemic population (1000s), 2015*	Genotypes†									
			1a	1b	1c	1 (other)	2	3	4	5	6	Mixed or other
(Continued from previous page)												
Tunisia	0·9% (0·2–1·1)	108 (25–123)	5·1%	76·6%	0	0	5·1%	3·7%	7·3%	0	0	2·2%
Turkey	0·6% (0·3–1·0)	492 (271–763)	12·9%	80·4%	0	0	1·5%	3·7%	1·5%	0	0	0
United Arab Emirates	1·3% (0·5–1·6)	131 (50–159)	5·4%	9·4%	0	25·6%	2·2%	35·0%	22·0%	0	0	0
Yemen	0·8% (0·5–0·9)	211 (143–258)	..	..	..	..	..	..	..	..	..	..
North America, high income												
Canada	0·6% (0·4–0·7)	212 (136–246)	36·5%	21·5%	0	6·1%	14·1%	20·2%	0·3%	0	0	1·3%
Puerto Rico	1·0% (0·6–1·6)	36 (23–60)	39·8%	27·1%	0	15·2%	12·1%	3·8%	1·8%	0	0·2%	0
USA	0·9% (0·7–1·2)	2936 (2231–3826)	46·2%	26·3%	0	0	10·7%	8·9%	6·3%	..	1·1%	0·5%
Oceania												
Fiji	0·1% (0·0–0·3)	1 (0·2–3)	..	..	..	..	..	..	..	..	..	..
Papua New Guinea	1·2% (0·9–4·2)	94 (70–328)	..	..	..	..	..	..	..	..	..	..
Samoa	0·1% (0·1–0·2)	0·2 (0·1–0·4)	..	..	..	..	..	..	..	..	..	..
Sub-Saharan Africa, Central												
Central African Republic	0·3% (0·2–0·4)	16 (11–18)	0	0	0	0	8·6%	8·6%	82·8%	0	0	0
DR Congo	..	..	0	0	0	0	3·2%	0	96·8%	0	0	0
Equatorial Guinea	..	..	0	0	0	35·0%	1·7%	3·3%	60·0%	0	0	0
Gabon	7·0% (5·1–7·3)	124 (90–129)	0	0	0	5·8%	2·2%	0	92·0%	0	0	0
Sub-Saharan Africa, East												
Burundi	1·0% (0·8–4·0)	120 (93–459)	5·6%	0	0	0	0	1·7%	92·7%	0	0	0
Ethiopia	0·6% (0·4–0·7)	647 (410–726)	8·8%	2·7%	0	2·0%	13·5%	9·5%	60·0%	0	0	3·5%
Kenya	0·2% (0·1–0·3)	115 (42–126)	10·0%	0	0	0	90·0%	0	0	0	0	0
Madagascar	0·2% (0·2–0·3)	56 (39–81)	0	52·9%	0	0	47·1%	0	0	0	0	0
Mozambique	..	..	27·8%	22·2%	0	0	0	22·2%	0	27·8%	0	0
Sub-Saharan Africa, Southern												
South Africa	0·7% (0·4–0·9)	356 (227–441)	2·3%	22·1%	0	7·1%	1·2%	12·6%	12·4%	35·7%	0	6·7%
Sub-Saharan Africa, West												
Burkina Faso	1·3% (1·0–1·4)	247 (189–256)	3·1%	9·4%	0	0	56·3%	15·6%	3·1%	0	0	12·5%
Cameroon	0·7% (0·5–0·8)	164 (117–184)	0	0	0	40·0%	20·0%	0	40·0%	0	0	0
Chad	1·1% (0·8–1·3)	162 (111–184)	0	0	0	7·7%	7·7%	0	84·6%	0	0	0
The Gambia	0·8% (0·5–1·3)	17 (10–27)	0	0	0	19·4%	58·1%	6·5%	0	0	0	16·1%
Ghana	1·4% (1·1–3·4)	399 (305–944)	0·1%	0·2%	0	12·8%	87·0%	0	0	0	0	0
Guinea-Bissau	..	..	0	0	0	1·8%	98·2%	0	0	0	0	0
Nigeria	1·4% (1·0–1·4)	2553 (1902–2651)	0	0	0	82·3%	5·9%	7·4%	4·4%	0	0	0

*2015 year-end estimate is a model output projection based on historic data. †Genotype distribution data are either taken from the literature or based on regional averages in the absence of country-specific data.

Table 1: **Modelled 2015 hepatitis C viraemic prevalence and chronically infected population (all ages) and genotype distribution**

same countries is shown in figure 1A, while the prevalence of all countries, including those with an extrapolated prevalence, is shown in figure 1B. The number of HCV infections by country is shown in figure 1C. The numerical prevalence and total infections for approved and estimated countries are shown in table 1. The model input data for prevalence, quality score, year of prevalence estimate, uncertainty range, viraemic rate, source of prevalence age distribution, and all corresponding references are included in the appendix (pp 19–23).

The global prevalence of viraemic HCV is estimated to be 1·0% (95% UI 0·8–1·1) in 2015, corresponding to 71·1 million (62·5–79·4) viraemic infections. Regional estimates for HCV prevalence in 2015 are shown in table 2. The countries that accounted for 80% of total global HCV infections are shown in figure 2.

The top ten country-level uncertainties that made the largest contribution to the global uncertainty are shown in figure 3. The top ten uncertainties listed account for 92% of the total variance in the global prevalence. The uncertainty in the total number of infections in India had

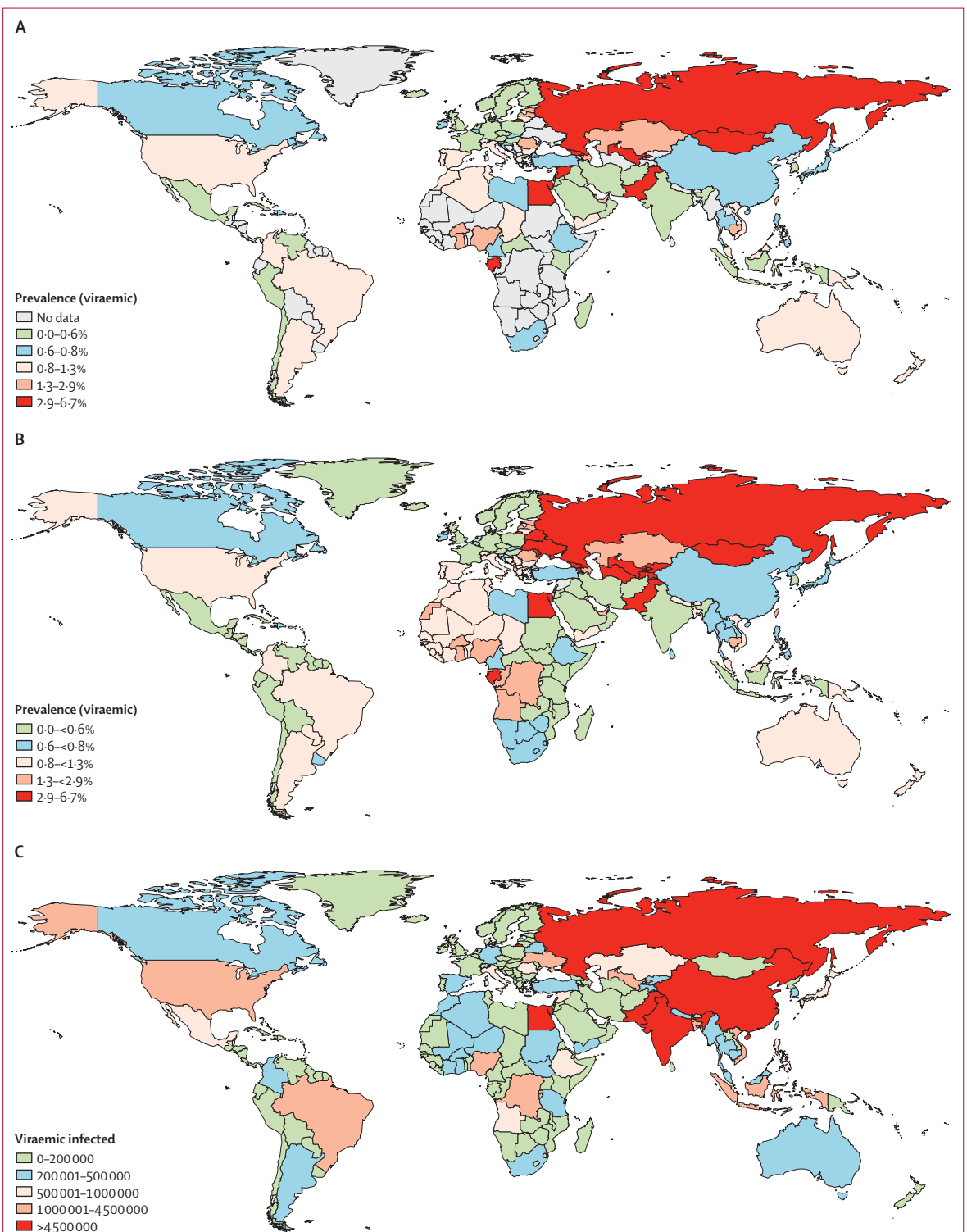

Figure 1: **HCV prevalence estimates (end of 2015)**
2015 viraemic prevalence in countries with approved or estimated models (A), viraemic prevalence in all countries (B), and number of viraemic infected people in all countries (C). HCV=hepatitis C virus.

	Viraemic HCV prevalence (95% UI)	Population (millions)	Viraemic HCV infected (millions; [95% UI])
Asia Pacific, high income	0·6% (0·3–0·7)	183	1·1 (0·6–1·3)
Asia, Central	3·6% (2·8–3·9)	88	3·2 (2·5–3·4)
Asia, East	0·7% (0·5–0·8)	1439	10·5 (7·3–11·6)
Asia, South	0·9% (0·7–1·3)	1742	15·3 (12·3–22·7)
Asia, Southeast	0·7% (0·5–0·8)	654	4·7 (3·2–5·2)
Australasia	1·0% (0·8–1·0)	29	0·3 (0·2–0·3)
Caribbean	0·5% (0·4–0·8)	45	0·2 (0·2–0·4)
Europe, Central	1·0% (0·8–1·0)	118	1·2 (0·9–1·2)
Europe, Eastern	3·3% (2·1–3·4)	206	6·7 (4·2 –7·0)
Europe, Western	0·5% (0·4–0·8)	426	2·3 (1·9–3·2)
Latin America, Andean	0·5% (0·3–0·6)	59	0·3 (0·2–0·3)
Latin America, Central	0·5% (0·4–0·5)	247	1·3 (0·9–1·3)
Latin America, Southern	0·6% (0·3–0·9)	64	0·4 (0·2–0·6)
Latin America, Tropical	0·9% (0·6–0·9)	211	1·8 (1·3–2·0)
North Africa/Middle East	1·7% (1·4–1·9)	498	8·5 (6·8–9·2)
North America, high income	0·9% (0·7–1·1)	362	3·2 (2·4–4·0)
Oceania	1·1% (0·8–3·7)	11	0·1 (0·1–0·4)
Sub-Saharan Africa, Central	2·1% (0·1–6·9)	115	2·4 (0·1–8·0)
Sub-Saharan Africa, East	0·5% (0·4–0·7)	425	2·1 (1·6–2·9)
Sub-Saharan Africa, Southern	0·7% (0·4–0·9)	76	0·5 (0·3–0·7)
Sub-Saharan Africa, West	1·3% (1·1–1·4)	399	5·1 (4·3–5·7)
Total	1·0% (0·8–1·1)	7397	71·1 (62·5–79·4)

HCV=hepatitis C virus. UI=uncertainty interval.

Table 2: **Regional prevalence and number of infected individuals (all ages)**

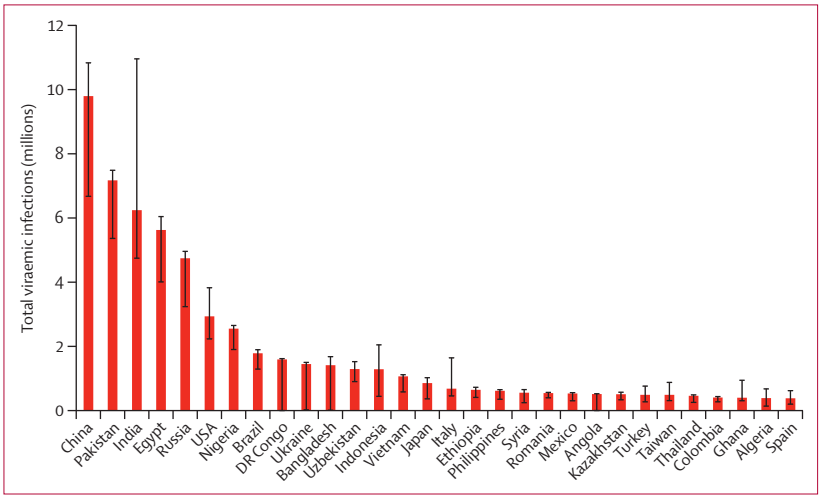

Figure 2: **Countries accounting for 80% of the total viraemic HCV infections**
HCV=hepatitis C virus.

the largest effect on our forecast. If the total number of infections in India is 11·0 million, rather than 6·2 million, the global estimate would be 76·6 million infections instead of 71·1 million. This takes into account the additional infections in India as well as the effect of India's prevalence on the regional prevalence, which is then applied to countries without data. Removing India's prevalence completely and using the regional prevalence instead (for India and other countries in the region without data) was the third largest driver of uncertainty. The global prevalence would be 75·9 million in this case, because other countries in the region (with data) have a higher prevalence than India, and regional prevalence is dampened by India. A similar observation is made in sub-Saharan Africa, Central region, where only the Central African Republic (prevalence 0·3%) and Gabon (7·04%) had reported prevalence estimates. Removing Central African Republic from the analysis would result in Gabon being used for the regional average and an estimate of 76·7 million infections globally (figure 3).

A separate sensitivity analysis looked at the effect of excluding estimated countries from the analysis and basing the global prevalence on approved countries only. In this scenario, the estimated global prevalence would be 0·7% (95% CI 0·6–0·8) with a total number of HCV infections of 38 million (34–41).

The HCV genotype distribution of the modelled countries is shown in table 1. These distributions were based on published studies referenced in the appendix (pp 24–29). Appendix p 29 contains data for data quality scores of the underlying study and sources for genotype 1a/b breakout if they were not reported in the primary study. The estimated genotype distribution by GBD region is shown in figure 4A, while the data are combined with total viraemic HCV infections by GBD region and shown in figure 4B. At the global level, genotype 1 dominated (44% of all infections), followed by genotype 3 (25%) and genotype 4 (15%). Genotype 1 dominated in high-income and upper-middle income countries (60% of all infections), whereas genotype 3 (36%) was common in lower middle-income countries, and genotype 4 (45%) was common in low-income countries.

Discussion

Our analysis represents both an update to and substantial expansion of previous efforts to quantify the HCV prevalence and disease burden. A Delphi process was used to complement a traditional systematic review by adding a level of validation through discussions with country experts. 400 experts were consulted to approve the inputs and outputs of 59 country models. This work is additionally unique in that it uses a disease burden model to forecast the 2015 year-end HCV prevalence, accounting for the impact of a changing population due to ageing, treatment and cure, and mortality.

The 2015 global prevalence estimate of 1·0% (95% CI 0·8–1·1) or 71·1 million (62·5–79·4) infections is substantially lower than that in previous estimates.[22,23] Previous studies were based on older and higher prevalence estimates for China and India (appendix p 31). However, the more recent studies[17,28] show a much lower infection rate in these countries. In addition, most studies are done in the adult population; however, when

estimates are applied to a country's total population, disease burden is overestimated. Furthermore, the earlier studies reported anti-HCV prevalence that is evidence of past or present infection rather than active infection. Our previous estimate took all these factors into account for a global estimate of 80 million (95% CI 64–103) viraemic infections.[20] Since the last study, we completed interviews in 59 countries, and Nigeria and Cameroon reported much lower HCV prevalence based on unpublished national studies. This reduced the overall prevalence in the region. In addition, the modelling took into consideration the effect of mortality (liver related and all cause) and treatment. The overall effect was a reduction in the global prevalence estimate, which was still within the uncertainty intervals of our previous estimate.[20] The current estimate reports a more narrow uncertainty range as a result of the updated methodology and incorporating country interviews.

Modelling the prevalence captured the change in the epidemiology of HCV infection. Globally, the total number of viraemic HCV infections has been decreasing since 2007 (appendix p 31); however, there were major variations between regions. Of the modelled countries, ten showed a 10% or greater growth in prevalence since 2007 due to foreign workforce from endemic countries (Qatar and the United Arab Emirates), iatrogenic infections (Azerbaijan, India, Iraq, Syria, and Uzbekistan), and infections among people who inject drugs (Iran, Russia, and Latvia). In most other countries, the rate of mortality (the rate of all-cause and liver related) was higher than new infections, leading to a decrease in total infections. Historically, prevalence was increasing in every region until blood screening started in early to mid-1990s.

However, development of an accurate global estimate remains a problem because of scarcity and low quality of data. Of 250 recognised countries in the world, HCV prevalence estimates were available for 113 countries (not all countries were modelled due to lack of available secondary data needed for a model). Globally, 91 countries have a population less than 1·5 million and only eight of these countries reported their HCV prevalence. 92 (60%) of the countries with a larger population had HCV prevalence studies. Of these, 21 countries had studies with a quality score of 3, 49 had a quality score of 2, and 22 had a quality score of 1 (appendix pp 19–23, 30). 13 of the countries with a quality score of 1 were in Europe and included Austria, Belgium, Finland, Germany, Italy, Portugal, and Norway, and 20 were high-income countries. Thus, the quality of the epidemiology data did not correlate with countries' income and robust national surveillance studies in the general population are needed to better quantify HCV burden. Larger countries had much larger effect on the global estimates. China (quality score=3), Pakistan (score=3), India (score=1), Egypt (score=3), Russia (score=2), and USA (score=3) accounted for 51% of total HCV infections globally (figure 2).

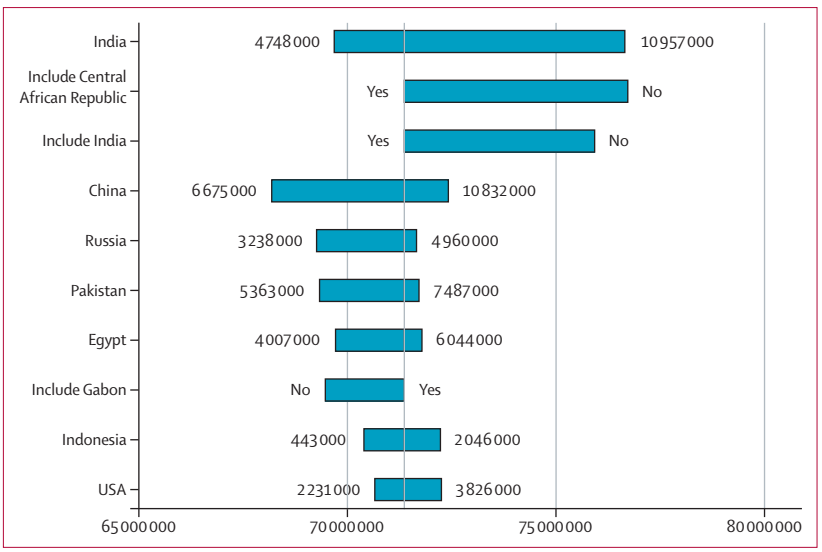

Figure 3: **Sensitivity analysis of 2015 global HCV prevalence viraemic infections, all ages (top 10)**

The prevalence range (the estimated prevalence and accompanying UI) reported here attempts to capture all uncertainties considered. Future revisions to the prevalence range will most probably come from estimates for countries without reported studies (grey countries in figure 1A), which included a large number of countries in Africa as well as some in Central and South America and Eastern Europe. As shown above, country interviews can provide more recent unpublished prevalence estimates. To test the effect of having approved estimates, a sensitivity analysis was done in which all estimated (non-approved) countries were removed from the analysis. In this scenario, the total estimated number of infections (globally) was 38 million. This result could be explained by a selection bias as a result of interviews being conducted in countries with a low prevalence.

Overall, care was taken to minimise biases that could have the largest effect on the global estimate. In 59 countries, interviews with country experts were used to identify relevant unpublished data and approve inputs and outputs. Panel meetings run the risk of confirmation, observer, and recall bias; however, facilitator training and meeting structure were designed to minimise the effect of these biases. Over the course of the project, ten facilitators were trained to lead country interviews. Each meeting required two attendees, one facilitator, and one note-taker. After each meeting, the note-taker provided feedback on how to improve future facilitations. In addition, for all models, the data inputs, model calibration, and outputs were reviewed by a second independent epidemiologist before being incorporated into the global estimate.

The genotype distribution, by region, did not change substantially (figure 4) since the last study[20] with the exception of further refinement of data for genotype 1.

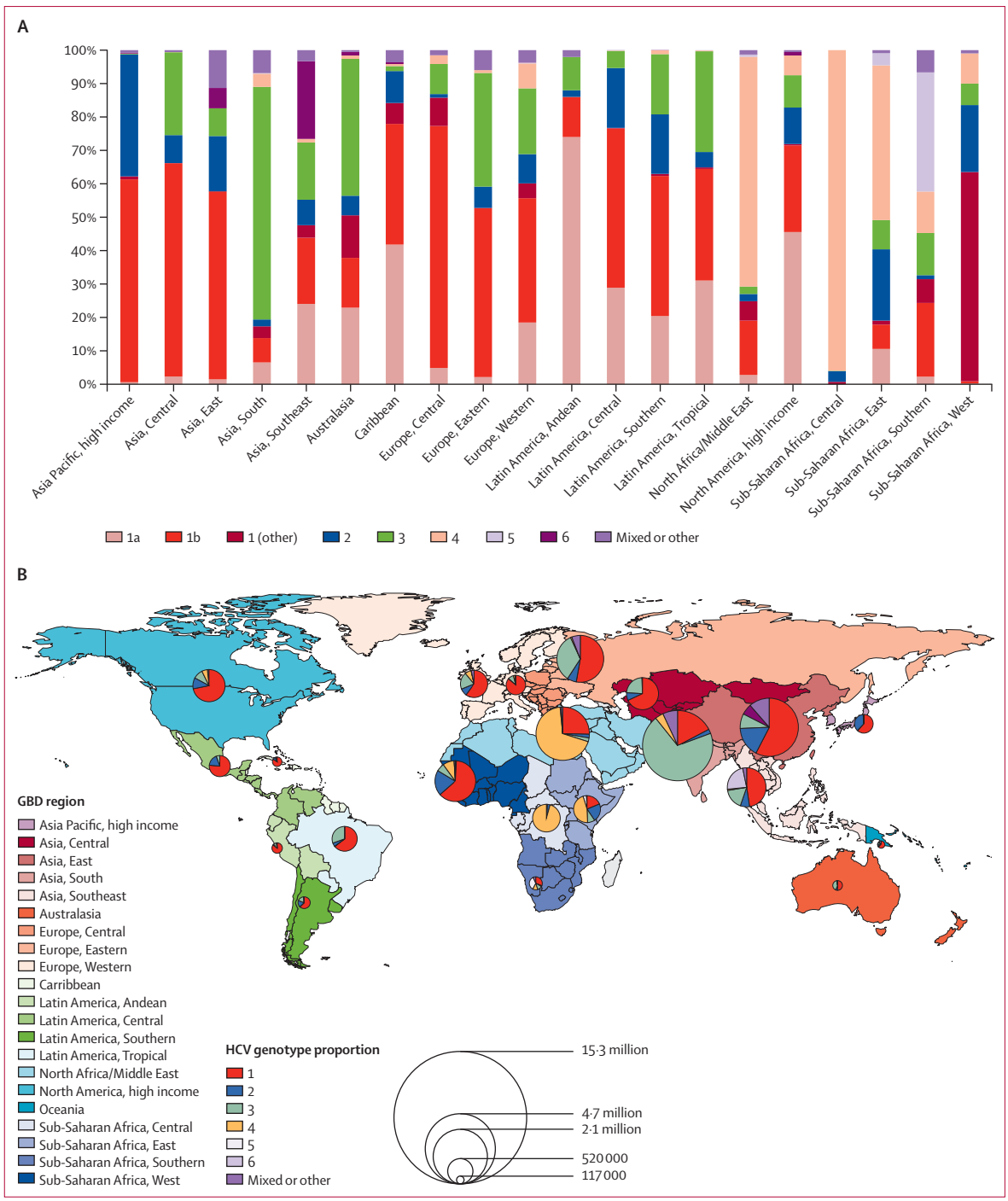

***Figure 4*: Genotype distribution**
By GBD region (A) and HCV genotype and total infected by GBD region (B). GBD=Global Burden of Disease.

When genotype 1a and 1b data were not available in the highest scored study, secondary studies were used. This refinement was requested by experts because these subgenotypes still show a different response rate to the available therapies. A new analysis was also added (figure 4B) that combined genotypes and total infections by region. The broad distribution of genotypes across different income settings highlights the importance of pan-genotypic therapies for elimination of HCV.

Many of the limitations of the original study[20] were addressed here; however, several limitations remained. As mentioned above, availability of data and the quality of

available data limited the accuracy of the forecasts (especially in sub-Saharan Africa). Ranges were used to address the uncertainty in the available data. Additionally, in the modelled countries the treated population was segmented by genotype proportionally to the genotype distribution of the HCV-infected population. If individuals with specific genotypes were treated preferentially, then the genotype distribution of the prevalent population could be different than what is forecasted here. The use of a model to forecast 2015 HCV prevalence introduced another limitation—the accuracy of the model. When available, the outputs of the model were validated against empirical data to reduce errors due to the modelling. However, another limitation was the uncertainty in empirical data. Two recent studies have shown that cases of hepatocellular carcinoma are under-reported by 37–50% in Sweden and Melbourne, Australia.[29,30] This would result in an underestimation of cases of hepatocellular carcinoma by our models.

We forecast a continual decline in total HCV infections as we move forward. In 2015, an estimated 950 000 patients were treated for HCV, with two-thirds of those treatments with direct acting antivirals.[24] An estimated 700 000 individuals achieved sustained viral response and were removed from the infected population. This accounts for only 1% of the total infected population who are treated and cured annually. However, as countries develop their national hepatitis elimination strategies and expand prevention, screening, and treatment, a more rapid decline in total viraemic infections is forecasted.

Contributors

CE, DR-S, HN, HR, IGa, IGo, JGu, JDS, KP, KR-S, KM, SB, and SR prepared the first draft and finalised the draft based on comments from other authors. All other authors provided data, analysed data, reviewed results, provided guidance on methodology, and provided critical feedback on the report.

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