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Global epidemiology and genotype distribution of the hepatitis C virus infection

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Summary

The treatment of chronic hepatitis C virus (HCV) infection has the potential to change significantly over the next few years as therapeutic regimens are rapidly evolving. However, the burden of chronic infection has not been quantified at the global level using the most recent data. Updated estimates of HCV prevalence, viremia and genotypes are critical for developing strategies to manage or eliminate HCV infection. To achieve this, a comprehensive literature search was conducted for anti-HCV prevalence, viraemic prevalence and genotypes for all countries. Studies were included based on how well they could be extrapolated to the general population, sample size and the age of the study. Available country estimates were used to develop regional and global estimates. Eighty-seven countries reported anti-HCV prevalence, while HCV viraemic rates were available for fifty-four countries. Total global viraemic HCV infections were estimated at 80 (64–103) million infections. Genotype distribution was available for ninety-eight countries. Globally, genotype 1 (G1) was the most common (46%), followed by G3 (22%), G2 (13%), and G4 (13%). In conclusion, the total number of HCV infections reported here are lower than previous estimates. The exclusion of data from earlier studies conducted at the peak of the HCV epidemic, along with adjustments for reduced prevalence among children, are likely contributors. The results highlight the need for more robust surveillance studies to quantify the HCV disease burden more accurately.

Introduction

The treatment of hepatitis C virus (HCV) infection has the potential to change significantly over the next few years as new all-oral treatment options become available with a shorter duration of treatment and more manageable side effects. With the advent of new antivirals, boasting improved sustained virologic response (SVR), HCV infection will be curable in nearly all patients. Previous studies have shown that HCV infection can be eliminated in the next 15–20 years with focused strategies to screen and cure current infections as well as prevent new infections [1,2]. However, a good understanding of the number of HCV infections is required to develop strategies to eliminate HCV.

A number of previous studies have reported global, regional and country level prevalence estimates of HCV infection. The original studies conducted by the World Health Organization (WHO) [3–7] outlined global and country level estimates. More recent analyses provided updated prevalence estimates, but were limited to select countries [1,8–13]. Finally, a recent study published a revised estimate of global HCV prevalence [14], but provided only regional estimates. Most previous global, regional and country level analyses have failed to reconcile estimates based on age-distribution and active infection. Most country-level studies were conducted in the adult population; however, when estimates were applied to a country's entire population, disease burden was likely overestimated. In addition, studies focused on anti-HCV (antibody positive) testing overestimated disease burden because they include those who have been cured, either spontaneously or through treatment.

Knowledge of the distribution of HCV genotypes has important clinical implications since the efficacy of current and new therapies differ by genotype. Until pan-genotypic therapies reach the market, SVR, duration of treatment and cost of treatment will be impacted by the genotype distribution. To date, there are no published studies assessing HCV genotype at the global level; however, it is understood that there are notable geographical differences.

The objective of the current study was to conduct a comprehensive review of recently published literature to estimate anti-HCV prevalence, viraemic (RNA positive) prevalence, number of anti-HCV and viraemic infections and genotype distribution. In addition, because more than half of the countries in the world do not have robust studies of the HCV infected population, a secondary objective of this analysis was to extrapolate available data to countries without prevalence estimates, to generate a global estimate of HCV disease burden.

Keywords: Genotype; Epidemiology; Hepatitis C; Prevalence; HCV infections.
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Abbreviations: HCV, hepatitis C virus; SVR, sustained viral response; WHO, World Health Organization; GBD, global burden of disease; PWID, people who inject drugs.

Key Points

Total HCV infections

- The total global prevalence of anti-HCV was estimated to be 1.6% (1.3-2.1%), corresponding to 115 (92-149) million past viraemic infections
- The majority of these infections, 104 (87-124) million, were among adults (defined as those older than 15 years old) with an anti-HCV infection rate of 2.0% (1.7-2.3%)
- The viraemic (RNA positive) prevalence was forecasted to be 1.1% (0.9-1.4%), corresponding to 80 (64-103) million viraemic infections
- Again, most of these viraemic infections were among adults who accounted for 75 (62-89) million viraemic infections or a viraemic prevalence of 1.4% (1.2-1.7%)

Genotype distribution

- Globally, genotype 1 was most common, accounting for 46% of all infections, followed by genotypes 3 (22%), and genotypes 2 and 4 (13% each). Subtype 1b accounted for 22% of all infections at the global level
- There were significant variations across regions with genotype 1 dominating in Australasia, Europe, Latin America and North America (53-71% of all cases) and G3 accounting for 40% of all infections in Asia
- Genotype 4 was most common (71%) in North Africa and the Middle East, but when Egypt was excluded, it accounted for 34% while genotype 1 accounted for 46% of infections across the same region

Methodology

HCV prevalence

A comprehensive literature search was conducted in PubMed and EMBASE, using the following search terms, respectively: "[Country Name] and [hepatitis c or hcv] and [prevalence]" and "['hepatitis c or hcv] and [prevalence]". Additional studies were identified through manual searches of references noted in the publications. Non-indexed government reports and personal communication with experts within countries were also included. Regions included in the analysis were those defined by the Global Burden of Diseases, Injuries, and Risk Factors 2010 (GBD) study [15,16].

Article titles and abstracts were reviewed for relevance and the following data were extracted from full articles or abstracts: anti-HCV prevalence, viraemic prevalence, studied population (e.g., pregnant women, health care patients, screening participants, military recruits, blood donors, etc.), sample size, data collection/analysis date, analysis scope (urban, rural, both and unknown), region(s) studied (one hospital/clinic, multi hospitals/clinics, city, multi city, region, multi region, national, other and unknown) and analysis type (meta-analysis, modelling, review article, surveillance study and other/unknown).

Exclusion criteria

Studies in non-representative populations, (e.g., people who inject drugs (PWID's), haemophiliacs, minority ethnic groups, refugees, etc.), studies with a sample size of less than 1000 and studies published prior to 2000 were excluded from the analysis.

Quality score

A multi-objective decision analysis approach [17–20] was used to derive a score of 0–10 for each study, using three measures: how well the reported data could be extrapolated to the general population, sample size and year of analysis. Supplementary Table 1 shows the 0–10 scoring system used to determine how well the reported data could be extrapolated to the general population. The log of the sample size was scaled as 0–10 where all studies with a sample size greater than 10,000 received a score of 10. Analyses conducted from 2000 to 2003 received a score of 6, 2004–2010 a score of 8 and >2010 a score of 10. A final score was calculated using a weighting of 60% for the extrapolation score and 20% each for sample size and study year. For simplicity, the 0–10 scores were converted to a data quality scale of 1–3 (study score of 0.0–<4.0 received a data quality score of 1, 4.0–<8.0 = 2, and 8.0–10.0 = 3). Modelling studies were automatically given a data quality score of 2. Studies without a formal assessment, but deemed to be of quality for inclusion, were given a score of 1.

Studies with the highest score were considered for the base assumption with the exception of China, India and Nigeria where a meta-analysis of all studies after 2000, which were representative of the general population, were used to develop a base estimate (see Supplementary Table 2). Blood donor studies were excluded from base estimates because they represent healthy screened adults, but were used for low prevalence estimates when applicable. When insufficient data was available to determine a range in a country, data from neighboring countries (or countries in the region) were used. When applicable, a wide range was used for countries with a high level of uncertainty.

The UN population database was used for the 2013 country population by five-year age cohort [21]. The number of anti-HCV and viraemic HCV infections was calculated by multiplying the country's population and the appropriate HCV prevalence.

HCV prevalence in adults

Most studies reported HCV prevalence in the adult population. For the purpose of this exercise, the definition of adults was assumed to include all individuals aged $\geqslant$15 years. When a study included data in children, prevalence in adults was calculated using the reported prevalence by age groups. In addition, when studies that calculated HCV prevalence in 2013 by age group were available [1,8,13], the adult prevalence from those studies was considered. Countries where adjustments were made to capture only the adult population and/or HCV infection in 2013 included: Australia, Bangladesh, Belgium, Brazil, Cameroon, Canada, Czech Republic, Denmark, Ethiopia, Finland, France, Germany, Ireland, Luxembourg, New Zealand, Pakistan, Portugal, Slovakia, Spain, Sweden, Switzerland, Thailand, Tunisia, United Kingdom and Yemen.

Table 1. Reported HCV prevalence/infected population (adjusted for the adult population) and genotype distribution.

Region/ country	Adult anti-HCV prevalence	Viraemic rate	Adult viraemic prevalence	Adult anti-HCV population (000)	Adult viraemic population (000)	Genotypes									
						1a	1b	1c	1 (other)	2	3	4	5	6	Mixed/ other
Asia Pacific, High Income															
Japan	1.5% (0.5%-2.2%)	78.1%	1.1% (0.4%-1.7%)	1603 (542-2432)	1252 (423-1899)		64.7%			34.2%					1.0%
Korea, Republic of	0.8% (0.2%-2.1%)	56.1%	0.4% (0.1%-1.2%)	327 (96-868)	183 (54-487)	3.0%	45.4%	1.3%	3.0%	45.3%	0.8%	0.2%		1.0%	
Asia, Central															
Armenia						5.0%	36.0%			18.0%	37.0%				3.0%
Azerbaijan	3.1% (1.0%-6.7%)			223 (73-491)											
Georgia	6.7% (5.6%-7.3%)			239 (200-260)		3.0%	59.0%			11.0%	27.0%				
Kazakhstan	3.3% (1.0%-6.7%)			403 (122-818)											
Kyrgyzstan	2.5% (1.6%-6.7%)			95 (62-259)											
Mongolia	10.8% (8.7%-15.6%)	69.6%	7.5% (6.1%-10.9%)	223 (180-322)	155 (125-224)		98.8%			1.2%					
Tajikistan	3.1% (1.1%-6.7%)			161 (58-353)			82.7%			5.8%	7.7%				3.8%
Turkmenistan	5.6% (1.1%-6.7%)			208 (41-251)											
Uzbekistan	11.3% (6.4%-13.1%)	39.2%	4.4% (2.5%-5.1%)	2334 (1322-2706)	916 (519-1062)	2.9%	64.2%			6.7%	26.0%				
Asia, East															
China	1.3% (0.4%-2.0%)	60.0%	0.8% (0.2%-1.2%)	14,765 (4429-22,260)	8,859 (2658-13,356)	1.4%	56.8%			24.1%	9.1%			6.3%	2.1%
Taiwan	4.4% (2.5%-6.3%)	74.5%	3.3% (1.9%-4.7%)	881 (500-1261)	656 (373-939)	2.6%	45.5%		0.7%	39.5%	1.0%	0.2%		0.5%	10.0%
Asia, South															
Afghanistan	1.1% (0.6%-1.9%)	58.1%	0.6% (0.4%-1.1%)	179 (103-310)	104 (60-180)										
Bangladesh	1.3% (0.2%-2.2%)	77.8%	1.0% (0.2%-1.7%)	1384 (219-2444)	1077 (171-1902)										
India	0.8% (0.4%-1.0%)	80.8%	0.7% (0.4%-0.8%)	7458 (3907-8879)	6026 (3157-7174)				24.0%		54.4%	5.8%	0.2%		15.6%
Pakistan	6.7% (1.6%-10.0%)	87.4%	5.8% (1.4%-8.7%)	8054 (1977-12,041)	7039 (1728-10,524)	4.8%	1.2%	0.2%	0.8%	3.8%	79.0%	1.6%	0.1%	0.1%	8.3%
Asia, Southeast															
Indonesia	0.8% (0.4%-2.0%)	65.7%	0.5% (0.3%-1.3%)	1421 (711-3554)	934 (467-2335)	12.5%	36.5%	12.5%		20.2%	17.4%	1.0%			
Cambodia	2.3% (2.3%-14.7%)	75.8%	1.7% (1.7%-11.1%)	240 (240-1533)	182 (182-1162)		24.0%				20.0%			56.0%	
Laos							4.4%							95.6%	
Sri Lanka							46.9%			37.5%					15.6%
Myanmar	1.7% (1.0%-2.7%)	55.6%	0.9% (0.5%-1.5%)	676 (380-1064)	376 (211-591)	4.1%	6.9%			0.7%	39.3%			49.0%	
Malaysia	1.5% (0.3%-7.7%)	71.9%	1.1% (0.2%-5.5%)	329 (66-1691)	237 (47-1216)				31.9%		58.6%	6.0%	3.5%		
Philippines	0.9% (0.3%-2.0%)			609 (214-1296)		70.7%	2.5%			26.4%		0.2%		0.2%	
Thailand	2.7% (1.8%-3.7%)	62.7%	1.7% (1.2%-2.3%)	1475 (1009-2007)	925 (633-1259)	19.9%	13.8%			0.3%	44.2%			21.8%	
Viet Nam		68.0%				12.4%	17.3%		0.7%	15.2%				54.4%	
Australasia															
Australia	1.7% (1.2%-1.8%)	74.6%	1.2% (0.9%-1.4%)	314 (227-349)	234 (169-260)	20.4%	17.2%		16.9%	5.2%	36.8%	1.9%		1.6%	
New Zealand	1.9% (0.8%-2.2%)			67 (29-77)		40.0%	15.0%			8.0%	35.0%	0.5%		1.0%	
Caribbean															
Cuba						17.0%	81.0%								2.0%
Dominican Republic						59.0%	3.6%			9.5%	2.4%				19.0%

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Table 1. (*continued*)

Region/ country	Adult anti-HCV prevalence	Viraemic rate	Adult viraemic prevalence	Adult anti-HCV population (000)	Adult viraemic population (000)	Genotypes									
						1a	1b	1c	1 (other)	2	3	4	5	6	Mixed/ other
Europe, Central															
Albania						6.0%	50.0%			20.0%	8.0%	16.0%			
Bulgaria	1.1% (0.3%-2.4%)			67 (19-150)											
Bosnia and Herzegovina						4.0%	69.3%			4.0%	21.3%	1.3%			
Czech Republic	0.7% (0.2%-0.7%)	70.0%	0.5% (0.1%-0.5%)	60 (18-64)	42 (13-45)	7.7%	27.2%		31.1%	0.5%	31.1%	2.4%			
Croatia						13.1%	37.4%		8.3%	2.2%	35.6%	3.4%			
Hungary	0.8% (0.4%-2.7%)	84.6%	0.7% (0.3%-2.3%)	68 (34-229)	57 (29-194)	22.0%	58.5%		13.6%	0.9%	3.4%	1.7%			
Macedonia									55.4%		44.6%				
Montenegro						19.6%	35.0%			1.1%	24.7%	19.6%			
Poland	0.9% (0.6%-1.1%)	70.0%	0.6% (0.4%-0.8%)	279 (192-370)	196 (134-259)				79.4%	0.1%	13.8%	4.9%		0.1%	1.6%
Romania	3.2% (2.9%-3.6%)	91.3%	2.9% (2.7%-3.2%)	595 (542-654)	543 (495-597)	5.4%	92.6%				0.8%	1.2%			
Serbia									57.9%	3.7%	23.2%	6.7%			8.5%
Slovakia	1.4% (0.9%-2.0%)	49.2%	0.7% (0.4%-1.0%)	66 (41-92)	32 (20-45)				89.9%	1.5%	6.6%	0.5%		0.5%	1.0%
Slovenia		74.6%							56.0%	5.0%	37.8%	1.2%			
Europe, Eastern															
Belarus	1.3% (0.9%-2.9%)	69.0%	0.9% (0.6%-2.0%)	100 (68-226)	69 (47-156)	5.1%	53.8%				38.5%	2.6%			
Estonia						1.0%	71.0%			3.0%	24.0%				
Lithuania	2.9% (0.7%-3.0%)			73 (19-77)		1.8%	59.8%		3.3%	8.7%	26.3%				
Latvia	2.4% (1.7%-3.3%)	71.4%	1.7% (1.2%-2.4%)	42 (30-58)	30 (21-41)	1.5%	87.7%			1.5%	9.2%				
Moldova	4.5% (2.3%-4.5%)			130 (67-130)											
Russia	4.1% (1.2%-5.6%)			4932 (1395-6736)		0.9%	54.8%			8.2%	35.1%				1.1%
Ukraine	3.6% (0.9%-4.5%)			1385 (333-1726)											
Europe, Western															
Austria	0.5% (0.1%-0.7%)	73.4%	0.4% (0.1%-0.5%)	36 (7-51)	27 (5-37)	20.3%	51.6%			5.0%	19.0%	4.0%		0.1%	
Belgium	0.9% (0.1%-1.2%)	80.0%	0.7% (0.1%-1.0%)	86 (11-113)	69 (9-91)		50.4%	8.6%		6.0%	19.0%	14.0%	2.0%		
Switzerland	1.5% (0.7%-1.8%)			105 (48-120)		25.9%	25.9%			8.5%	29.2%	10.3%	0.1%	0.1%	0.0%
Cyprus	0.6% (0.5%-1.9%)	71.4%	0.4% (0.3%-1.3%)	5 (4-18)	4 (3-13)										
Germany	0.6% (0.3%-0.9%)	66.7%	0.4% (0.2%-0.6%)	401 (216-647)	267 (144-432)	25.0%	33.0%		4.5%	6.4%	27.4%	3.3%	0.2%	0.2%	
Denmark	0.7% (0.5%-0.7%)	62.2%	0.4% (0.3%-0.5%)	33 (22-34)	21 (14-21)	34.0%	12.0%			8.0%	43.0%	3.0%			
Spain	1.7% (0.4%-2.6%)	68.6%	1.2% (0.3%-1.8%)	688 (159-1049)	472 (109-719)	25.5%	43.8%			3.1%	19.6%	8.0%			
Finland	0.7% (0.6%-0.9%)			31 (27-41)		15.0%	17.0%			16.0%	46.0%	6.0%			
France	0.6% (0.4%-1.1%)	65.0%	0.4% (0.3%-0.7%)	303 (234-578)	197 (152-376)	14.8%	29.7%		15.4%	9.1%	19.7%	9.2%	2.0%	0.2%	
United Kingdom	0.6% (0.4%-1.2%)	68.5%	0.4% (0.2%-0.8%)	307 (182-624)	210 (125-428)	24.4%	11.9%		8.8%	7.3%	43.8%				3.8%
Greece	1.9% (0.5%-2.6%)			178 (47-248)		12.5%	32.6%		0.0%	7.0%	34.0%	13.9%			
Ireland	1.1% (0.7%-1.6%)	75.0%	0.8% (0.5%-1.2%)	40 (24-58)	30 (18-44)				55.0%	4.0%	39.0%	1.0%	0.1%		1.2%
Israel	2.0% (0.9%-2.0%)	75.5%	1.5% (0.7%-1.5%)	110 (50-110)	83 (38-83)				69.0%	8.0%	20.0%	3.0%			
Italy	2.0% (1.6%-7.3%)	73.3%	1.5% (1.2%-5.4%)	1048 (839-3826)	768 (615-2805)	4.2%	57.5%		3.0%	26.0%	3.6%	3.8%	0.3%		1.5%

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Table 1. (*continued*)

Region/ country	Adult anti-HCV prevalence	Viraemic rate	Adult viraemic prevalence	Adult anti-HCV population (000)	Adult viraemic population (000)	Genotypes									
						1a	1b	1c	1 (other)	2	3	4	5	6	Mixed/ other
Luxembourg	0.9% (0.6%-0.9%)			4 (2-4)					55.3%	4.3%	33.6%	6.4%	0.4%		
Netherlands	0.2% (0.1%-0.4%)			31 (10-51)		14.8%	15.7%		18.8%	9.7%	29.3%	10.5%			1.1%
Norway	0.7% (0.6%-0.9%)	79.5%	0.6% (0.5%-0.7%)	29 (25-37)	23 (20-29)	28.1%	28.1%		1.8%	10.5%	28.1%				3.5%
Portugal	1.8% (0.5%-2.9%)			164 (42-259)		12.4%	39.8%			2.4%	34.0%	7.0%		0.2%	4.0%
Sweden	0.7% (0.5%-0.7%)	77.0%	0.5% (0.4%-0.5%)	53 (37-55)	41 (29-42)	38.2%	7.0%			19.3%	33.8%	1.7%			
Latin America, Andean															
Peru	1.2% (0.4%-1.6%)			251 (95-338)		74.0%	12.0%			2.0%	10.0%				2.0%
Latin America, Central															
Colombia						5.7%	82.8%			8.5%	2.8%				
Mexico	1.4% (1.1%-1.6%)	76.6%	1.1% (0.8%-1.2%)	1225 (962-1400)	938 (737-1072)	14.9%	32.2%		23.2%	21.8%	7.2%	0.3%	0.1%		0.3%
Venezuela	1.5% (0.3%-2.6%)			326 (70-571)			43.4%		21.7%	34.4%					0.5%
Latin America, Southern															
Argentina	1.5% (0.5%-2.5%)	80.0%	1.2% (0.4%-2.0%)	471 (163-785)	377 (131-628)	21.7%	40.9%	0.9%		24.7%	10.6%	1.3%			
Chile						7.9%	72.7%			2.0%	16.5%	0.6%	0.3%	0.1%	
Latin America, Tropical															
Brazil	1.6% (1.1%-1.6%)	80.5%	1.3% (0.9%-1.3%)	2409 (1704-2495)	1939 (1371-2008)	31.0%	33.4%		0.4%	4.6%	30.2%	0.2%	0.1%		
North Africa/Middle East															
Algeria	1.4% (0.2%-2.5%)			396 (68-708)		12.2%	57.0%			11.3%	10.0%	4.7%	0.9%		4.0%
Egypt	14.7% (10.3%-18.0%)	67.7%	10.0% (7.0%-12.2%)	8306 (5820-10,170)	5623 (3940-6885)		2.3%		3.8%		0.8%	93.1%			
Iran	0.5% (0.2%-1.0%)	81.8%	0.4% (0.2%-0.8%)	295 (118-590)	241 (97-483)	39.7%	12.1%		1.3%	1.4%	27.5%	0.9%			18.4%
Iraq	3.2% (0.3%-3.2%)			650 (61-650)		1.4%	12.9%				17.1%	52.9%			15.7%
Jordan						40.0%	33.3%					26.7%			
Kuwait									19.4%	0.7%	6.9%	54.2%			18.8%
Lebanon						25.4%	16.9%			4.9%	6.3%	45.8%	0.7%		
Libya	1.2% (1.2%-2.3%)			53 (53-101)		4.9%	14.6%		13.2%	14.9%	16.7%	35.7%			
Morocco	1.6% (0.6%-1.9%)	70.9%	1.1% (0.4%-1.4%)	376 (148-460)	267 (105-326)	0.7%	75.2%			22.7%		0.7%			0.7%
Oman															
Palestine						18.5%	9.8%					64.1%			7.6%
Qatar	0.9% (0.5%-1.5%)			17 (9-27)											
Saudi Arabia	1.5% (0.6%-7.3%)	51.6%	0.7% (0.3%-3.8%)	297 (123-1494)	153 (63-771)				25.9%	4.4%	2.9%	60.0%	0.3%	0.3%	6.3%
Syria									28.5%	0.8%	1.8%	59.0%	10.0%		
Tunisia	1.3% (0.3%-2.5%)	80.0%	1.0% (0.2%-2.0%)	107 (26-208)	86 (21-166)	1.4%	82.6%			10.1%	1.4%				4.3%
Turkey	1.0% (0.6%-2.1%)	82.0%	0.8% (0.5%-1.7%)	529 (334-1170)	434 (274-959)	8.1%	83.7%			2.2%	4.9%	1.1%			
United Arab Emirates		68.0%				15.0%	12.0%			3.0%	23.8%	46.2%			
Yemen	2.2% (1.1%-3.5%)			322 (161-511)											
North America, High Income															
Canada	1.1% (0.6%-1.3%)	74.0%	0.8% (0.5%-1.0%)	332 (179-394)	245 (133-291)	34.2%	20.1%		5.7%	15.4%	22.3%	2.3%			
United States	1.3% (1.2%-2.4%)	76.9%	1.0% (0.9%-1.8%)	3347 (3090-6180)	2575 (2377-4754)	46.2%	26.3%			10.7%	8.9%	6.3%		1.1%	0.5%

(*continued on next page*)

Table 1. (*continued*)

Region/ country	Adult anti-HCV prevalence	Viraemic rate	Adult viraemic prevalence	Adult anti-HCV population (000)	Adult viraemic population (000)	Genotypes								
						1a	1b	1c	1 (other)	2	3	4	5	6	Mixed/ other
Oceania															
Samoa	0.2% (0.2%-0.9%)			0 (0-1)											
Sub-Saharan Africa, Central															
Central African Republic									8.6%	8.6%		82.8%			
Congo, Democratic Republic of the	4.3% (3.2%-13.7%)			110 (82-350)						3.2%		96.8%			
Congo, Republic of the		62.0%													
Gabon	11.2% (2.1%-20.7%)	90.0%	10.1% (1.9%-18.6%)	115 (22-213)	104 (19-192)				5.7%	2.4%		91.9%			
Equatorial Guinea									35.0%	1.7%	3.3%	60.0%			
Sub-Saharan Africa, East															
Ethiopia	1.3% (0.7%-5.8%)			676 (378-3128)				5.6%		33.3%		50.0%	11.1%		
Madagascar	1.2% (0.8%-1.7%)	68.0%	0.8% (0.5%-1.2%)	158 (99-227)	108 (67-154)		52.9%			47.1%					
Mozambique						27.8%	22.2%				22.2%		27.8%		
Sub-Saharan Africa, Southern															
South Africa	1.7% (1.0%-2.5%)			633 (365-923)		2.3%	22.0%		7.1%	1.2%	12.6%	12.4%	35.7%		6.7%
Zimbabwe	1.6% (1.0%-9.1%)			137 (86-782)											
Sub-Saharan Africa, West															
Benin	3.6% (3.6%-12.8%)			213 (213-756)											
Burkina Faso						3.1%	9.4%			56.3%	15.6%	3.1%			12.5%
Côte d'Ivoire	3.3% (0.8%-12.8%)			393 (95-1526)											
Cameroon	11.6% (4.3%-29.7%)			1473 (546-3770)											
Ghana									8.7%	87.0%					4.3%
Gambia, The	2.1% (1.4%-2.9%)			21 (14-29)					19.4%	58.1%	6.5%				16.1%
Guinea-Bissau									1.8%	98.2%					
Mauritania	1.9% (1.1%-10.7%)			44 (26-249)											
Nigeria	8.4% (3.9%-12.8%)	82.2%	6.9% (3.2%-10.5%)	8115 (3768-12,366)	6670 (3097-10,165)				85.0%	15.0%					
Other															
Puerto Rico	2.3% (1.3%-4.2%)			68 (39-125)		39.8%	27.1%		15.2%	12.1%	3.8%	1.8%		0.2%	

HCV prevalence in children

Anti-HCV prevalence in children (<15 years old) in the above countries was used to estimate prevalence in children by the World Bank regions (low income, lower middle income, upper middle income and high income). Insufficient data was available to determine HCV prevalence by the GBD regions. The ratio of HCV prevalence in children to adults was applied to adult HCV prevalence in countries missing prevalence among children in each World Bank region.

Regional HCV prevalence

Regional prevalence estimates were applied to countries without data to estimate the global number of anti-HCV and viraemic positive cases. GBD regional prevalence (see Supplementary Table 4 for a list of countries in each region) was estimated by summing the number of HCV infections for countries in the region (with available data) and dividing this by the sum of the total population in the same countries. No studies were available in the Caribbean region. A regional prevalence of 1.0% (0.2–1.6%)

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

Regions	Anti-HCV prevalence	Viraemic HCV prevalence	Viraemic rate	2013 population (millions)	Anti-HCV infected (millions)	Viraemic HCV infected (millions)
Asia Pacific, High Income	1.1% (0.5%-1.7%)	0.8% (0.4%-1.2%)	74%	182	2.0 (0.9-3.0)	1.5 (0.6-2.2)
Asia, Central	5.4% (3.5%-6.8%)	2.3% (1.5%-3.0%)	43%	84	4.5 (2.9-5.7)	1.9 (1.3-2.5)
Asia, East	1.2% (0.4%-1.8%)	0.7% (0.3%-1.1%)	60%	1434	16.6 (6.3-25.3)	10.0 (3.9-15.1)
Asia, South	1.1% (0.7%-1.5%)	0.9% (0.5%-1.2%)	81%	1650	18.8 (11.3-24.5)	15.2 (8.9-19.8)
Asia, Southeast	1.0% (0.8%-1.8%)	0.7% (0.5%-1.1%)	63%	635	6.6 (5.3-11.3)	4.2 (3.4-7.2)
Australaisa	1.4% (1.0%-1.5%)	1.0% (0.8%-1.1%)	75%	28	0.4 (0.3-0.4)	0.3 (0.2-0.3)
Caribbean	0.8% (0.2%-1.3%)	0.6% (0.1%-0.9%)	70%	39	0.3 (0.1-0.5)	0.2 (0.0-0.4)
Europe, Central	1.3% (1.1%-1.6%)	1.0% (0.9%-1.2%)	80%	119	1.5 (1.3-1.9)	1.2 (1.1-1.5)
Europe, Eastern	3.3% (1.6%-4.5%)	2.3% (1.1%-3.0%)	69%	207	6.8 (3.4-9.3)	4.7 (2.4-6.3)
Europe, Western	0.9% (0.7%-1.5%)	0.6% (0.5%-1.0%)	70%	425	3.7 (3.0-6.3)	2.6 (2.1-4.4)
Latin America, Andean	0.9% (0.4%-1.3%)	0.6% (0.3%-0.9%)	70%	57	0.5 (0.2-0.7)	0.4 (0.2-0.5)
Latin America, Central	1.0% (0.8%-1.4%)	0.8% (0.6%-1.1%)	75%	246	2.6 (1.9-3.5)	1.9 (1.4-2.6)
Latin America, Southern	1.2% (0.5%-2.1%)	0.9% (0.4%-1.6%)	79%	62	0.8 (0.3-1.3)	0.6 (0.2-1.0)
Latin America, Tropical	1.2% (0.9%-1.2%)	1.0% (0.7%-1.0%)	80%	207	2.5 (1.9-2.6)	2.0 (1.5-2.1)
North Africa/Middle East	3.1% (2.5%-3.9%)	2.1% (1.7%-2.6%)	66%	469	14.6 (11.9-18.2)	9.7 (7.8-12.1)
North America, High Income	1.0% (1.0%-1.9%)	0.8% (0.7%-1.4%)	76%	355	3.7 (3.4-6.7)	2.8 (2.6-5.0)
Oceania	0.1% (0.1%-0.6%)	0.1% (0.1%-0.4%)	69%	10	0.0 (0.0-0.1)	0.0 (0.0-0.0)
Sub-Saharan Africa, Central	4.2% (2.4%-9.2%)	2.6% (1.5%-5.5%)	61%	100	4.3 (2.4-9.2)	2.6 (1.5-5.5)
Sub-Saharan Africa, East	1.0% (0.6%-3.1%)	0.6% (0.4%-2.0%)	62%	385	3.9 (2.4-12.1)	2.4 (1.6-7.9)
Sub-Saharan Africa, Southern	1.3% (0.8%-2.5%)	0.9% (0.6%-1.7%)	69%	75	1.0 (0.6-1.9)	0.7 (0.4-1.3)
Sub-Saharan Africa, West	5.3% (2.9%-9.1%)	4.1% (2.3%-6.7%)	77%	367	19.3 (10.5-33.3)	14.9 (8.5-24.6)
Other	1.9% (1.0%-3.4%)	1.3% (0.7%-2.4%)	69%	27	0.5 (0.3-0.9)	0.4 (0.2-0.7)
Total	1.6% (1.3%-2.1%)	1.1% (0.9%-1.4%)	70%	7162	114.9 (91.9-148.7)	80.2 (64.4-102.9)

was used, utilizing the prevalence in Oceania and Latin America for the range.

Genotype distribution

A literature search was conducted through PubMed and EMBASE using the following search terms: "[hcv OR (hepatitis c)] AND (genotype* OR hepacivirus/genetics*[mesh])" and [hepatitis c OR hcv AND (genotyp*)]. Studies were scored according to the following scale: 1 = estimate without a formal published study or small study (n <100) in a select population; 2 = large study (n >100) in a select population; 3 = study in the general population. Studies prior to 2000 were not excluded from this analysis, but were only chosen as final estimates in two countries.

Uncertainty and sensitivity analyses were conducted using Crystal Ball®, an Excel® add-in by Oracle®. Beta-PERT distributions were used for all uncertain inputs.

Results

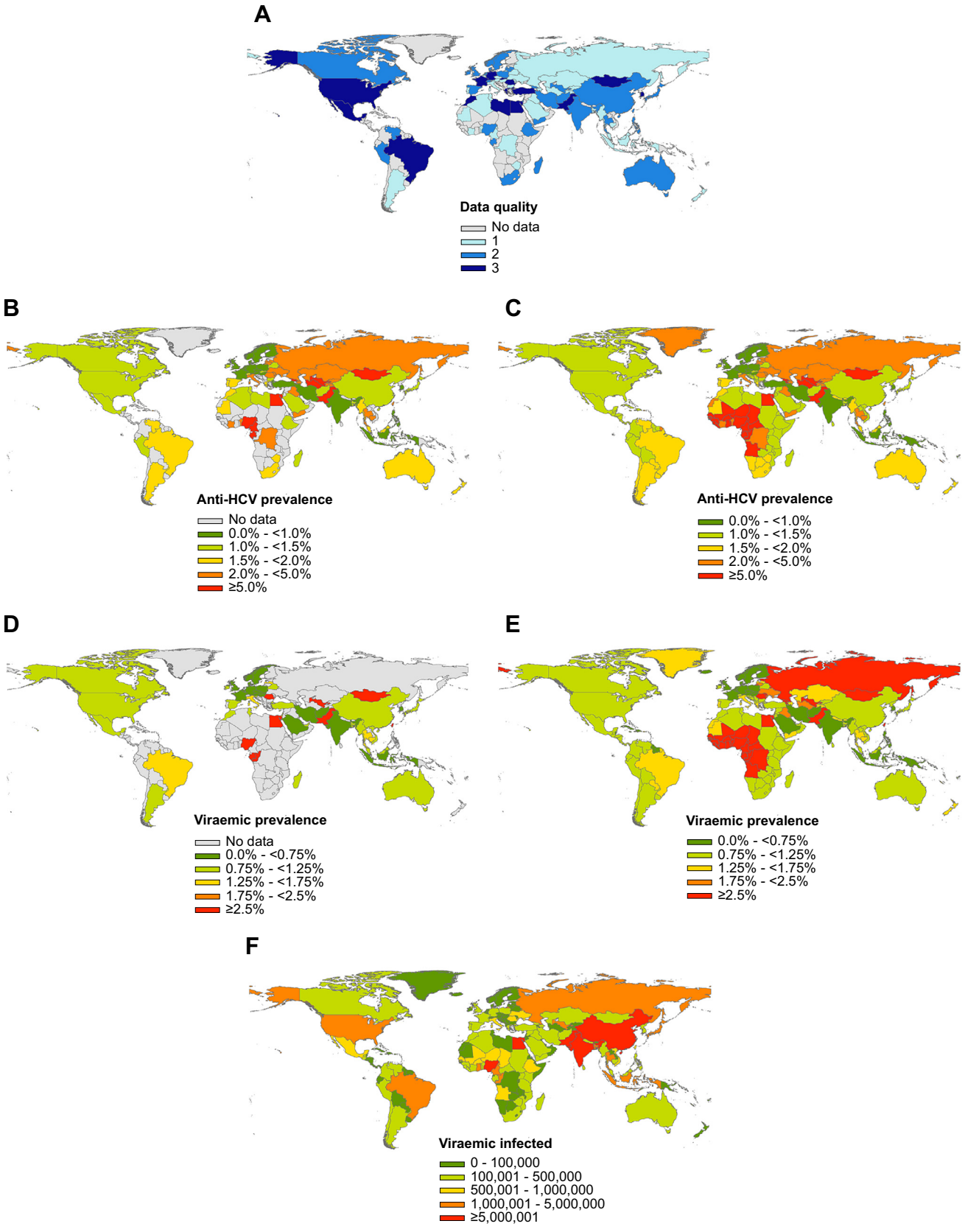
HCV prevalence

There were 23,248 studies identified through PubMed (n = 11,755) and EMBASE (n = 11,493). Following the removal of duplicates (n = 6012) and studies that did not meet inclusion criteria (n = 12,335), 4901 were selected for review and inclusion in the final analysis. Eighty-seven countries had an anti-HCV prevalence estimate that met inclusion criteria as shown in Table 1 (Supplementary Table 2 lists data sources). These countries accounted for 88% of the world's adult population and 84% of the estimated global anti-HCV population. HCV viraemic rates were available for fifty-four countries, accounting for 77% of the world's adult population and 73% of the estimated viraemic HCV population.

The ratio of HCV prevalence among children to adults was 54% in low-income countries, 28% in lower-middle-income countries, 21% in upper-middle-income countries and 4% in high-income countries. Given the high uncertainty associated with this approach, a range of 4–54% was used for all regions. An average viraemic rate of 50% (uncertainty interval of 50–75%) was applied to the infected population aged <15 years [22–25].

HCV genotype distribution

The literature search identified 17,118 studies through PubMed and EMBASE, of which 2320 were selected for review and inclusion in the final analysis. Genotype distribution was available for ninety-eight countries (as shown in Table 2 and Supplementary Table 3), which accounted for 88% of the world's adult population and 83% of the estimated anti-HCV prevalent population.


A
Data quality
No data
1
2
3
B
Anti-HCV prevalence
No data
0.0% - <1.0%
1.0% - <1.5%
1.5% - <2.0%
2.0% - <5.0%
≥5.0%
C
Anti-HCV prevalence
0.0% - <1.0%
1.0% - <1.5%
1.5% - <2.0%
2.0% - <5.0%
≥5.0%
D
Viraemic prevalence
No data
0.0% - <0.75%
0.75% - <1.25%
1.25% - <1.75%
1.75% - <2.5%
≥2.5%
E
Viraemic prevalence
0.0% - <0.75%
0.75% - <1.25%
1.25% - <1.75%
1.75% - <2.5%
≥2.5%
F
Viraemic infected
0 - 100,000
100,001 - 500,000
500,001 - 1,000,000
1,000,001 - 5,000,000
≥5,000,001

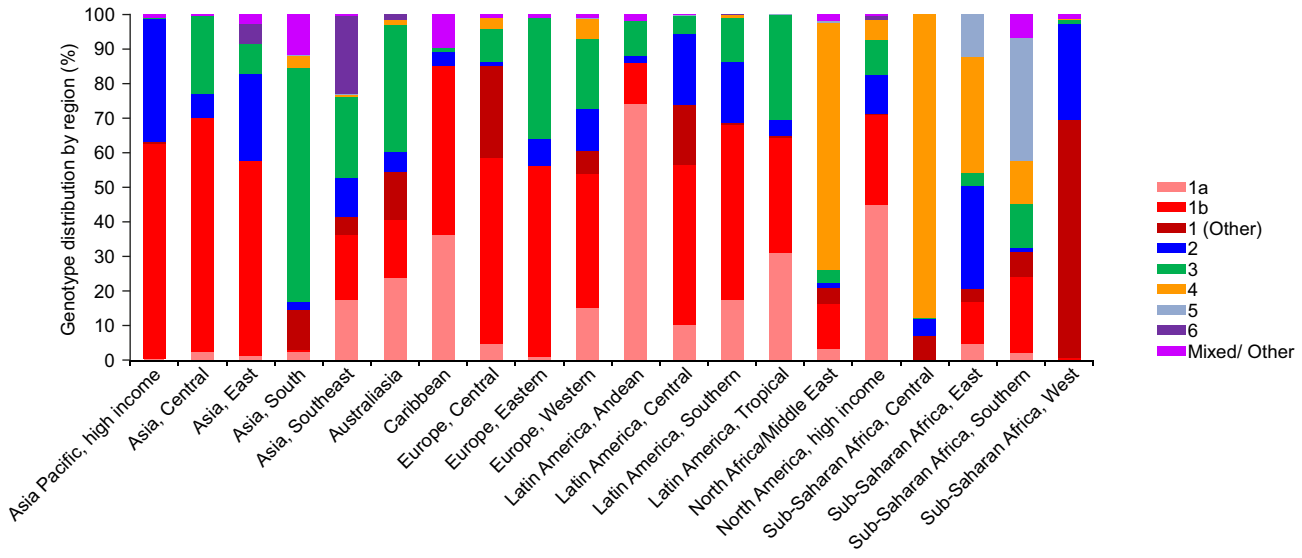


Fig. 2. Genotype distribution by region.

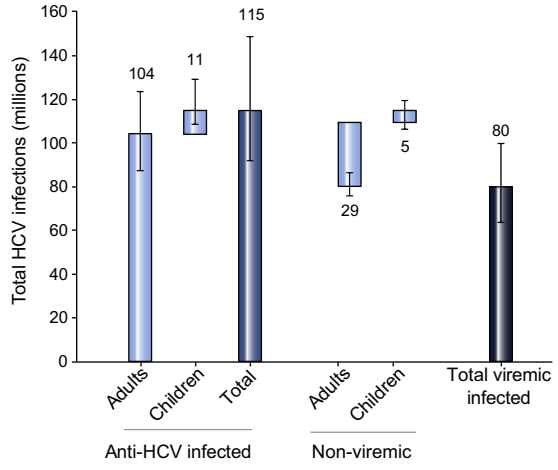


Fig. 3. The global number of HCV infections (anti-HCV and viraemic).

The evolution of the analysis is shown in Fig. 1. The quality scores of the anti-HCV studies in Fig. 1A denotes how well the reported anti-HCV prevalence could be extrapolated to the general population. The anti-HCV prevalence for countries with reported data is shown in Fig. 1B while Fig. 1C includes regional estimates for countries without reported data. The reported viraemic rates for countries with data are shown in Fig. 1D. A regional average was applied to countries without data to generate Fig. 1E (viraemic prevalence among adults for all countries). Fig. 1F summarizes the number of viraemic HCV infections (all ages), in each country. A detailed list of data sources and quality scores is presented in the Supplementary Tables 2 and 3. Anti-HCV prevalence, viraemic prevalence and genotype distribution for the countries missing studies were extrapolated from the regional estimates. Fig. 2 illustrates the genotype distribution by region.

The global prevalence of anti-HCV was estimated at 2.0% (1.7–2.3%) among adults and 1.6% (1.3–2.1%) for all ages corresponding to 104 (87–124) million and 115 (92–149) million infections, respectively. The viraemic prevalence was 1.4% (1.2–1.7%) among adults and 1.1% (0.9–1.4%) in all ages corresponding to 75 (62–89) million and 80 (64–103), respectively. Table 2 summarizes the forecasts for all ages by GBD regions while Fig. 3 shows the total number of anti-HCV and viraemic infections among adults, children and the total population.

Discussion

Total global viraemic HCV infections were estimated at 80 (64–103) million infections. Thirty-one countries accounted for 80% of total viraemic infections as shown in Fig. 4, in the order of their contribution. China, Pakistan, Nigeria, Egypt, India, and Russia together accounted for more than half of total infections. The uncertainties that account for >90% of the estimated variance of 64–103 million viraemic infections are shown in Fig. 5. The uncertainty in viraemic prevalence in Nigeria, China and Pakistan account for over 50% of the observed variance, followed by the uncertainty in ratio of HCV prevalence among children to adults. The sensitivity analysis shows that the uncertainties in prevalence estimates in African countries (Ethiopia, Cameroon and Democratic Republic of Congo) can lead to a higher estimated number of viraemic infections if the actual prevalence is closer to the upper end of our range.

In this analysis, special care was taken not to over-rely on available data but instead to focus on analysing relevant data. For example, HCV prevalence among blood donors is available in many

Fig. 1. Reported HCV prevalence and infections among adults. (A) Anti-HCV prevalence quality scores. (B) Anti-HCV prevalence – adults (reported). (C) Anti-HCV prevalence – adults (reported and estimated). (D) Viraemic prevalence – adults (with reported viraemic rate). (E) Viraemic prevalence – adults (reported and estimated). (F) Number of viraemic HCV infections – all ages.

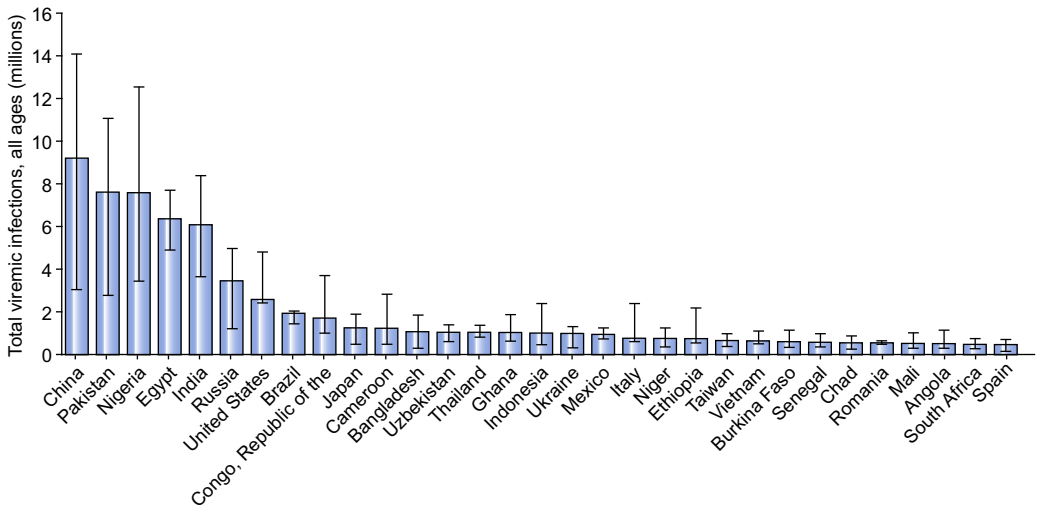


Fig. 4. Countries accounting for 80% of the total viraemic HCV infections.

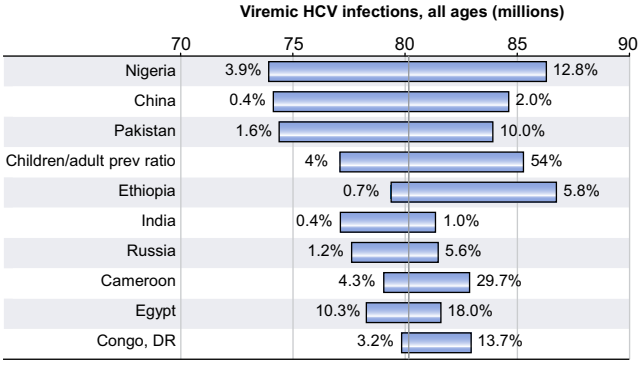


Fig. 5. Sensitivity analysis of global viraemic infections – all ages.

countries and represents an attractive data source due to the large sample size. However, this population often corresponds to healthy screened adults who are not representative of the total population. Other studies have derived a national estimate by applying a gross-up factor to HCV prevalence among blood donors [12]. All attempts to replicate national estimates in countries that reported both a national surveillance study and blood donor data were unsuccessful. In this work, HCV prevalence among blood donors was used as a low-end estimate for the uncertainty analysis.

There are also numerous studies in high-risk populations (e.g., PWIDs, haemodialysis patients, cancer patients, paid blood donors, etc.). Again, these populations were excluded, as they were not representative of HCV prevalence in the general population. Injection drug users are a major source of new infections in Europe and North America and exclusion of studies in PWIDs would suggest that we are underestimating the total number of infections. Previous publications estimated 10.0 million (6.0–15.2 million) PWIDs worldwide may be anti-HCV positive [26,27]. Some part of this population was already included in the country prevalence estimates (e.g., Australia), while the uncertainty range in other countries (e.g., US) was meant to take into account populations not captured in the base estimates. We were unable to determine the exact overlap between the reported number of HCV infections among PWIDs and the total number of infections reported here. It is possible that we are underestimating the total number of infections – at maximum by 10 million. However, the PWID population not captured in the base estimate should be within the uncertainty range presented here.

Finally, there are numerous studies reporting HCV prevalence that were published prior to 2000, which were also excluded. A number of analyses have shown that HCV prevalence has been declining in many countries [13,28–30,56,57]. This decrease was due to a number of factors – increased mortality due to the infected population aging, a reduction in the new infections due to the implementation of blood supply screening and a drop in high-risk behaviour in the early 1990s as the transmission of HIV was better understood. It is important to note that treatment has had a minimal impact on the total number of infections. With the exception of a few countries (e.g., France) [8,13], treatment and SVRs have been too low to make a large impact on HCV prevalence so far.

The total number of HCV infections reported here are lower than previous estimates [5,12,14]. As shown in Supplementary Fig. 1, most of the differences can be explained by prevalence estimates in a two regions: South Asia and East Asia. Fig. 4 highlights that the majority of HCV infections at a global level are accounted for by a few countries. India accounts for more than 75% of the population in the South Asia region and estimates for its HCV prevalence have been historically influenced by studies in the Punjab region [31]. While this region has a high HCV prevalence, it represents less than 3% of India's total population. Studies in other regions of India have shown a significantly lower HCV prevalence [32–34]. In this work, a meta-analysis was used to estimate a national average of 0.84% (0.44–1.0%) *vs.* 1.5% [5] and 3.4% (regional estimate) [14] in previous studies.

Similarly, China accounts for over 96% of the population in East Asia. There are a number of studies among commercial blood and plasma donors that showed a very high HCV prevalence [35–37]. However, paid blood donation is no longer common practice in China and studies in first time blood donors show that anti-HCV infections were less than 1% [38–40]. With a few exceptions,

prevalence studies in hospital patients [41] and rural/urban populations [42–45] all show a relatively low HCV prevalence. In this study, a meta-analysis (excluding studies in blood donors) was used to estimate a national prevalence of 1.3% (0.39–1.96%) *vs.* 2.2% [5] and 3.7% (regional estimate) [14] in previous analyses.

The present work estimates a higher prevalence in Sub-Saharan West Africa where Nigeria accounts for close to half of the region's population. As shown in Supplementary Table 2, a meta-analysis of non-blood donor studies in Nigeria resulted in an anti-HCV prevalence of 8.4% (3.9–12.8%) as compared to 2.1% [5] and 2.8% (regional estimate) [14] in previous work.

There are other minor differences between this study and previous work. One study applied the anti-HCV prevalence to the total population [5]. According to the United Nations [46], 25% of the world's population was aged <15 years in 2013. There is ample evidence that prevalence in this population is a fraction of the adult population [47–52] and a higher percentage of this population spontaneously clears the virus [22–24]. Other studies applied the HCV prevalence to the adult population ($\geqslant$15) without further adjustments for the younger ages [12].

This analysis reports the total number of viraemic infections. The average viraemic rate was estimated at 70% (all ages), although it varied between 43% in Central Asia to 81% in South Asia. Some countries that reported high anti-HCV prevalence also had a low viraemic rate. The most vivid example was a study in Poland [53], which found an anti-HCV prevalence of 1.9% with a viraemic rate of 31% (a viraemic prevalence of 0.6%). A separate study in the same country used confirmatory antibody testing and found an anti-HCV prevalence of 0.86% [54] with the same viraemic prevalence of 0.6% [unpublished data]. This example highlights the need to study viraemic infections since some historically high antibody prevalence estimates may have had a corresponding low viraemic rate.

Globally, genotype 1 (G1) accounted for 46% of all anti-HCV infections among adults making it the most common, followed by G3 (22%), G2 (13%), G4 (13%), G6 (2%), and G5 (1%). Undefined or combination genotypes accounted for 3% of the total HCV infections. Genotype 1b was the most common sub-type, accounting for 22% of all infections. However, significant regional, country and local variations existed. Infections in North America, Latin America, and Europe were predominately G1 (62–71%) with G1b accounting for 26%, 39%, and 50% of all cases respectively. North Africa and the Middle East had a large G4 population (71%), which was attributable to the high prevalence of G4 in Egypt. When Egypt was excluded, genotype 4 accounted for 34% of all infections and the genotype distribution of this region was dominated by G1 (46%). Asia was predominately G3 (39%) followed by G1 (36%), largely driven by the HCV infections in India and Pakistan. G1b accounted for 25% of all infections in this region. In Australasia, G1 dominated (53%), followed by G3 (39%). G1b was present in 16% of cases. HCV genotypes by subregions are shown in Fig. 2.

There were a number of limitations worth noting. PubMed and EMBASE do not capture all sources for non-English language studies, thus, some studies may not have been identified. Efforts were made to include non-English publications and government reports. Personal communications with local experts were also used to capture data published in sources not listed in the above databases. In addition, data was not available for all countries (as shown in Fig. 1B and D) and regional estimates had to be used for many countries. In regions where limited data was available, the regional average was highly dependent on data from very few countries and countries with a high population. For example, the Asia-Central viraemic rate estimate was based on estimates from Uzbekistan (viraemic rate of 39%) and Mongolia (viraemic rate of 70%), yet the regional estimate was heavily weighted by Uzbekistan due to its much larger population. Data from additional countries in the region would be helpful in minimizing this type of bias.

Another limitation was the availability of robust epidemiology studies at the national level. Among the eighty-seven countries with an anti-HCV prevalence estimate, only 16 (18%) received a quality score of 3. High quality studies were not limited to high-income countries. In fact, more than 50% of these studies were in low-income or upper middle-income countries. The characteristics consistent among these sources included the following: random sampling strategy in the general population, inclusion of participants from multiple cities or "regions" (e.g., districts, states, provinces, etc.) and a sample size >10,000, although a well conducted study in a small country with a sample size of >1500 could be sufficient. In addition, 75% of these studies were published after 2010 and more than 80% reported a viraemic rate. Alternatively, 36 (41%) studies received a quality score of 1. These sources were generally conducted in a select population (e.g., pregnant women, health care workers, etc.) within one setting (e.g., hospital, clinic, city, etc.). The authors acknowledge that robust studies with large sample sizes are costly and take time to complete; however, these types of studies are much more dependable for estimating the burden of HCV at a national level.

In the absence of better data, this analysis assumed that HCV prevalence remained constant from the time of the study to 2013. In fact, other studies have suggested that HCV prevalence may be declining with time in some countries [28,29,56,57]. Similarly, the viraemic rate was applied to the 2013 estimates. However, we expect that the impact of a change in viraemic rate would be small since treatment rates have remained low in most countries [8,13]. In addition, not all studies reported the age of participants. The reported prevalence was applied to the adult population; thus, we may be underestimating the true number of infections if individuals younger than 15 years old were included (a lower prevalence is typical when children are included).

There were relatively few studies that included children and several studies used a broad range (e.g., age cohort 0–20) to describe prevalence in younger populations. In this study, care was taken to use a different ratio of HCV prevalence among children to adults in different regions to provide a more accurate estimate. Our analysis found that HCV infection among children is highest in low-income countries and lowest in high-income countries, presumably due to the different risk factors for new infections (injection drug use in high-income countries *vs.* nosocomial infections in low-income countries). To examine the impact of uncertainty in this population, a wide range was used (a range 4–54% for the ratio of HCV prevalence among children to adults in all regions). The impact of this population on the global estimate appears to be small. Sensitivity analysis (Fig. 5) showed that we could be underestimating the total number of viraemic infections by 5 million if the actual rate was set to the high end of the uncertainty range for all countries/regions.

Another limitation was the way national prevalence was reported. Some studies reported the HCV prevalence in a country

based on the sampling in the study. When data was provided, an attempt was made to estimate a more refined HCV prevalence estimate by using age specific prevalence rates and the country's population by age cohort. This minimized any error due to a different age distribution in the general and studied population. However, not all countries provided age-specific prevalence rates.

In light of new therapies, many countries are examining requirements to eliminate HCV infection within their borders. The current study suggests that this task might be less daunting since recent data suggest that there are fewer HCV infections than were previously reported. For years, anti-HCV prevalence has been used as a proxy for the HCV infection rate. As cure rates, and potentially treatment rates, increase, measurement and reporting of viraemic prevalence will be required to measure and track the impact of HCV elimination strategies. A number of countries are attempting to quantify the proportion of HCV prevalence within the country due to immigration. Researchers are cautioned to use the data presented here without any adjustments. Our research (to be published) has shown that the average age among immigrants, in most countries, is approximately 30 years of age, leading to a lower HCV infection rate than estimated in the broad population in the country of origin.

The data shown here represent the most recent estimates of HCV infection and genotype distribution. The HCV prevalence estimates are generally lower than in previous work. This is alarming as it may suggest that HCV infection is more deadly than previously thought since the number of observed deaths [55] is the consequence of a lower number of viraemic infections. The prevalence and genotype estimates will need to be updated as new data become available and will likely change significantly with the adoption of highly efficacious therapies in the coming years. Previous research has shown that although the total number of infections may be declining in some countries, the disease burden of HCV is expected to increase [1,13,28,29]. The results highlight the need for more robust surveillance studies to quantify the HCV disease burden more accurately.

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Conflict of interest

EG, CE, SH, KR-S, and HR are employees of the Center for Disease Analysis and are barred from accepting any personal consulting or any other outside funding. The Center for Disease Analysis has received research funding from public and private sources (Gilead Sciences, Boehringer Ingelheim, and Abbvie), but its projects are limited to basic epidemiology and modelling research.

Authors' contributions

EG designed and led systematic search of articles, conducted data analysis, prepared and edited the article. HR supervised the study, conducted data analysis, prepared the article and edited the article. CE, SH and KR-S conducted data analysis and edited the article. All authors have read and approved the final article.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2014.07.027.

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