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Global Epidemiology of Hepatitis C Virus Infection: New Estimates of Age-Specific Antibody to HCV Seroprevalence

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In efforts to inform public health decision makers, the Global Burden of Diseases, Injuries, and Risk Factors 2010 (GBD2010) Study aims to estimate the burden of disease using available parameters. This study was conducted to collect and analyze available prevalence data to be used for estimating the hepatitis C virus (HCV) burden of disease. In this systematic review, antibody to HCV (anti-HCV) seroprevalence data from 232 articles were pooled to estimate age-specific seroprevalence curves in 1990 and 2005, and to produce age-standardized prevalence estimates for each of 21 GBD regions using a model-based meta-analysis. This review finds that globally the prevalence and number of people with anti-HCV has increased from 2.3% (95% uncertainty interval [UI]: 2.1%-2.5%) to 2.8% (95% UI: 2.6%-3.1%) and >122 million to >185 million between 1990 and 2005. Central and East Asia and North Africa/Middle East are estimated to have high prevalence (>3.5%); South and Southeast Asia, sub-Saharan Africa, Andean, Central, and Southern Latin America, Caribbean, Oceania, Australasia, and Central, Eastern, and Western Europe have moderate prevalence (1.5%-3.5%); whereas Asia Pacific, Tropical Latin America, and North America have low prevalence (<1.5%). *Conclusion*: The high prevalence of global HCV infection necessitates renewed efforts in primary prevention, including vaccine development, as well as new approaches to secondary and tertiary prevention to reduce the burden of chronic liver disease and to improve survival for those who already have evidence of liver disease. (HEPATOLOGY 2013;57:1333-1342)

Hepatitis C virus (HCV) infection is a major global health issue. Previous global burden of disease estimates published by the World Health Organization (WHO) include only burden from acute HCV infection.[1] Available estimates indicate that worldwide there were 54,000 deaths and 955,000 disability adjusted life-years associated with acute HCV infection. The major burden from HCV infection comes from sequelae from chronic infection.[2] Estimates indicate that three to four million persons are newly infected each year, 170 million people are chronically infected and at risk of developing liver disease including cirrhosis and liver cancer, and 350,000 deaths occur each year due to all HCV-related causes.[2] Antibodies to HCV (anti-HCV) are a commonly available marker of HCV infection. The prevalence of anti-HCV from population-based studies is used to compare HCV infection levels globally. Historically, countries in Africa and Asia have the highest reported anti-HCV prevalence, whereas industrialized countries in North America, Western Europe, and Australia are known to have lower prevalence.[3-6] Without an effective vaccine, primary prevention against hepatitis C focuses on reducing risks of infection through safe injections and blood safety. With new and promising drugs recently available and more in the pipeline, hepatitis C is now considered curable in up to 70% of treated patients. Although therapy for hepatitis C can

Abbreviations: EIA, enzyme immunoassay; GBD, Global Burden of Disease Study; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; IHME, Institute of Health Metrics and Evaluation; MESH, Medical Subject Headings; NHANES, National Health and Nutrition Examination Survey; PWID, persons who use injecting drugs; UI, uncertainty interval; WHO, World Health Organization.

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be instrumental in the prevention of advanced liver disease, lack of knowledge and of skill to deliver treatment among providers, and the high costs of HCV genotyping and drugs, make access to treatment a major global problem.[7] Secondary prevention of advanced liver disease from chronic HCV infection through screening for early detection and promoting and aiding cessation of alcohol intake remain key public health strategies.[7-9] Proper planning and public health investments are necessary to ensure that preventive measures can be implemented.

To facilitate evidence-based policymaking and prudent resource allocation, it is essential to estimate the burden of HCV infection globally, regionally, and nationally. Additional epidemiological measures typically included in a generic disease model, such as incidence and excess mortality, are difficult to obtain because HCV infections are rarely clinically apparent. Limitations of available assays to distinguish acute and chronic infections[6] and poor surveillance systems worldwide for HCV infection further impede efforts to usefully quantify HCV burden. However, recent developments in modeling allow the seroprevalence of anti-HCV to be used to estimate the burden of disease for HCV infections. The Global Burden of Diseases, Injuries, and Risk Factors 2010 (GBD2010) Study is an international collaborative effort to estimate the burden of disease using available parameters.

This systematic review used the GBD Study operations guidelines, which divide the world into 21 regions based on geography and epidemiological profiles.[10] The purpose of this study was to estimate the age-specific anti-HCV seroprevalence in each of the 21 world regions in 1990 and in 2005 through a systematic review and meta-analysis of primary national data sources and articles published for peer review between 1980 and 2007. The seroprevalence was modeled using the age-averaging random effects generalized negative binomial spline model from DisMod III,[11] the latest iteration of the generic disease modeling system for model-based meta-analysis for descriptive epidemiology, developed by the Institute of Health Metrics and Evaluation (IHME) at the University of Washington. The results of this meta-analysis and the estimates produced by the models identify regions and age groups with high prevalence, and predict prevalence in areas where data are sparse or not available. The anti-HCV seroprevalence estimated in this systematic review is the first step towards modeling the global burden of disease for HCV infection.

Materials and Methods

Study Selection. Three Ovid databases, Medline, Embase, and Cinahl, were used to allow for a thorough systematic literature search. An attempt was made to include gray literature and other databases, but was abandoned when the ability to search systematically varied widely. As part of a larger body of work to estimate global prevalence for hepatitis B, C, and D, these databases were simultaneously searched for articles published over a 27-year period (1980-2007) that reported the prevalence of hepatitis B, C, and D virus infections. Medical Subject Headings (MESH) were used to search articles and freetext to search article abstracts that contained (1) a term related to hepatitis B (HBV), C, or D (HDV) or their markers of infection, and (2) a term related to prevalence, incidence, or disease burden. Due to limited resources, the results were restricted to articles in English only, which exclude 14.8% of the articles found in this search prior to deduplication, and application of selection criteria (Fig. 1).

Abstracts were screened and were required to report prevalence or incidence of hepatitis B or C. Articles were excluded if they reported prevalence from a high-risk population or if the data reported were incomplete. High-risk populations included: (1) a study population that was selected based on a risk factor for viral hepatitis, and (2) a study population that was selected based on a condition associated with hepatitis infection or risk of hepatitis transmission (e.g., persons with liver disease, persons who use injecting drugs [PWID]); (3) highly defined populations (e.g., specific small indigenous tribes, homeless people, street children); and (4) paid blood donors. Where abstracts were incomplete or missing, the full-text article was retrieved and reviewed to determine the application of inclusion and exclusion criteria.

For this analysis, only articles reporting seroprevalence of HCV were included. Articles with incomplete

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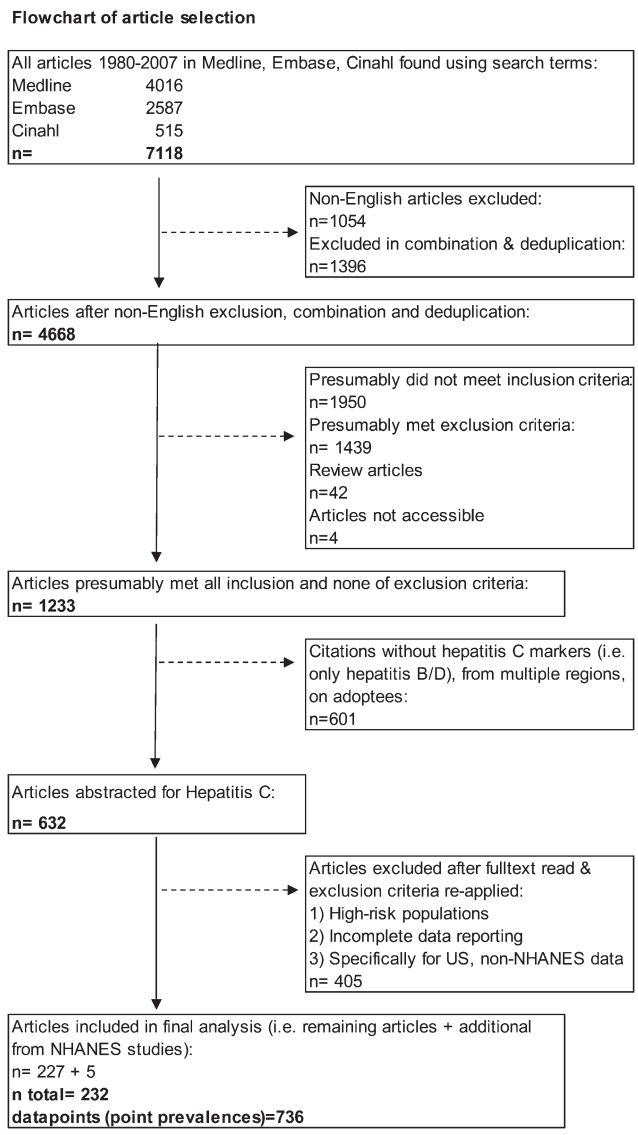

Fig. 1. Flowchart of study selection.

data include those that did not report (1) age range of samples; (2) number of persons tested; or (3) that the marker tested is anti-HCV. Articles reporting HCV seroprevalence on multiple regions or international adoptees were also excluded from this analysis, as categorization of samples from multiple regions and international adoptees into GBD regions would likely be inaccurate. As nationally representative datasets (such as the National Health and Nutrition Examination Survey [NHANES] in the United States) are believed to have superior population representativeness, the most recent estimates of anti-HCV from a primary national data source were used for countries where these were available.

The remaining articles were grouped by country. Articles were abstracted for year(s) the study was conducted, sampling strategy, marker detected and laboratory tests used, sex, ages, and number in the population tested, and numbers of positive tests. A bias indicator based on the representativeness of the study sample was assigned for each article: population-based samples were given a bias covariate of 0 and convenience samples, mostly from but not limited to voluntary or replacement blood donors and pregnant women from antenatal clinics, were given a bias covariate of 1. This bias indicator was used as a covariate to predict the overdispersion of the negative binomial distribution in the model.

World Regions. The GBD Study defined 21 regions to ensure that they were as "epidemiologically homogenous as possible so that information from detailed studies in one country can plausibly be extrapolated to other countries in the region and to create burden estimates that are useful to individual countries in planning for health sector activities."[10] Similar to previous research,[12] evidentiary support was assessed based on the average number of datapoints per country, calculated by dividing the total number of datapoints available for the region over the total number of countries within the region. The countries contributing the highest number of datapoints for their respective regions are indicated in Table 1.

Data Analysis. We conducted a meta-analysis using an age-averaging random effects generalized negative binomial spline model of age-specific prevalence. The data likelihood was modeled with a generalized negative binomial distribution, and the age pattern was modeled with a piecewise-linear spline. The age pattern was modified by country-level random effects to produce country-specific predictions, which were averaged to address age group heterogeneity. Geographic regions from GBD were analyzed hierarchically, whereby estimates in regions without sufficient data borrowed strength from similar regions (Table 2).

We used Markov Chain Monte Carlo with the adaptive Metropolis step method to fit the age-averaging negative binomial model to the data, using Python 2.7.1 and PyMC 2.0. To promote reproducible research,[13] the data and statistical analysis code are available online in Free/Libre Open Source formats at the IHME website. Age-standardization with world population age weights was applied to calculate overall prevalence estimates for each region. Total prevalence for 1990 and 2005 using world population age weights were mapped by GBD region and categorized as "High" (>3.5%), "Moderate" (1.5%-3.5%), and "Low" (<1.5%). The number of persons with anti-HCV was estimated using age-specific prevalence and IHME population data for 1990 and 2005.[14]

Table 1. Prevalence and Evidentiary Support by 21 GBD Regions

	GBD Region	Countries* & Total Population in 2005	Prevalence % (95% UI) & Numbers of Persons with Anti-HCV in 2005†	Evidentiary Support‡
1	High-income Asia Pacific	Brunei, **Japan**, South Korea, Singapore	1.4 (1.2-1.5)	Extensive
		>180 million	>2.4 million	
2	Central Asia	Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, **Mongolia**, Tajikistan, Turkmenistan, Uzbekistan	3.8 (3.0-4.5)	Very Limited
		>77 million	>2.9 million	
3	East Asia	**China**, Hong Kong, Macau, North Korea, Taiwan	3.7 (3.1-4.5)	Extensive
		>1,351 million	>50 million	
4	South Asia	Afghanistan, Bangladesh, Bhutan, India, Nepal, **Pakistan**	3.4 (2.6-4.4)	Moderate
		>1,520 million	>50 million	
5	Southeast Asia	Cocos Islands, Christmas Island, Indonesia, Cambodia, Laos, Sri Lanka, Maldives, Myanmar, Mauritius, Malaysia, Philippines, Réunion, Seychelles, **Thailand**, Timor Leste, Vietnam	2.0 (1.7-2.3)	Moderate
		>577 million	>11 million	
6	Australasia	**Australia**, New Zealand	2.7 (2.2-3.2)	Moderate
		>24 million	>0.6 million	
7	Caribbean	Aruba, Anguilla, Netherlands Antilles, Antigua and Barbuda, Bahamas, Saint Barthelemy, Belize, Bermuda, Barbados, Cuba, Cayman Islands, Dominica, Dominican Republic, Guadeloupe, Grenada, French Guiana, Guyana, **Haiti, Jamaica**, Saint Kitts and Nevis, Saint Lucia, Saint Martin, Montserrat, Martinique, Puerto Rico, Suriname, Turks and Caicos Islands, Trinidad and Tobago, Saint Vincent and the Grenadines, British Virgin Islands, US Virgin Islands	2.1 (1.6-2.6)	Very Limited
		> 42 million	>0.7 million	
8	Central Europe	Albania, **Bulgaria**, Bosnia and Herzegovina, Czechoslovakia, Czech, Croatia, Hungary, Macedonia, Montenegro, Poland, Romania, Serbia and Montenegro, Serbia, Slovakia, Slovenia, Yugoslavia	2.4 (2.0-2.8)	Moderate
		>119 million	>2.9 million	
9	Eastern Europe	Belarus, Estonia, Lithuania, Latvia, Moldova, **Russia**, USSR, Ukraine	2.9 (2.3-3.5)	Limited
		>212 million	>6.2 million	
10	Western Europe	Aland Islands, Andorra, Austria, Belgium, Belgium-Luxembourg, Switzerland, Cyprus, Germany, Denmark, Spain, Finland, France, Faeroe Islands, UK, Guernsey, Gibraltar, Greece, Greenland, Isle of Man, Ireland, Iceland, Israel, **Italy**, Jersey, Liechtenstein, Luxembourg, Monaco, Malta, Netherlands, Norway, Portugal, Svalbard and Jan Mayen, San Marino, Sweden, Vatican City, Akrotiri and Dhekelia, Channel Islands	2.4 (2.2-2.7)	Extensive
		>409 million	>10 million	
11	Andean Latin America	Peru, Ecuador, Bolivia	2.0 (1.4-2.7)	Very Limited
		>50 million	>1.0 million	
12	Central Latin America	Colombia, Costa_Rica, Guatemala, Honduras, Mexico, Nicaragua, **Panama**, El Salvador, Venezuela	1.6 (1.3-1.9)	Moderate
		>216 million	>3.4 million	
13	Southern Latin America	**Argentina**, Chile, Uruguay, Falkland Island	1.6 (1.1-2.2)	Moderate
		>58 million	>0.9 million	
14	Tropical Latin America	**Brazil**, Paraguay	1.2 (1.0-1.4)	Extensive
		>193 million	>2.3 million	
15	North Africa/Middle East	United Arab Emirates, Bahrain, Algeria, **Egypt**, Western Sahara, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Occupied Palestinian Territory, Qatar, Saudi Arabia, Syria, Tunisia, Turkey, Yemen	3.6 (3.2-4.1)	Moderate
		>420 million	>15 million	
16	High-income North America	**United States**, Canada, Saint Pierre & Miquelon	1.3 (1.1-1.6)	Extensive
		>337 million	>4.4 million	
17	Oceania	American Samoa, Cook Islands, Fiji, Micronesia, Guam, Kiribati, Marshall Islands, Northern Marianas, New Caledonia, Norfolk Island, Niue, Nauru, Pitcairn Islands, Palau, Papua New Guinea, French Polynesia, **Solomon Islands**, Tokelau, Tonga, Tuvalu, Vanuatu, Wallis and Futuna, Samoa	2.6 (2.1-3.1)	Moderate
		>8 million	>0.2 million	
18	Central Sub-Saharan Africa	Angola, **Central Africa**, Congo democratic, Congo, Gabon, Equatorial Guinea	2.3 (1.6-3.1)	Very Limited
		>87 million	>1.9 million	

Table 1. (Continued)

	GBD Region	Countries* & Total Population in 2005	Prevalence % (95% UI) & Numbers of Persons with Anti-HCV in 2005†	Evidentiary Support‡
19	East Sub-Saharan Africa	Burundi, Comoros, Djibouti, Eritrea, **Ethiopia**, Ethiopia PDR, Kenya, Madagascar, Mozambique, Malawi, Mayotte, Rwanda, Sudan, Somalia, Tanzania, Uganda, Zambia	2.0 (1.6-2.4)	Moderate
		>317 million	>6.1 million	
20	South Sub-Saharan Africa	Botswana, Lesotho, Namibia, Swaziland, South Africa, **Zimbabwe**	2.1 (1.7-2.5)	Moderate
		>68 million	>1.4 million	
21	West Sub-Saharan Africa	Benin, Burkina Faso, Cote d'Ivoire, Cameroon, Cape Verde, Ghana, Guinea,The Gambia, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, **Nigeria**, Senegal, Saint Helena, Sierra Leone, Sao Tome and Principe, Chad, Togo	2.8 (2.4-3.3)	Moderate
		>303 million	>8.4 million	
	WORLD (1990)	*>5.3 billion*	*2.3(2.1-2.5)* *>122 million*	
	WORLD (2005)	*>6.5 billion*	*2.8(2.6-3.1)* *>184 million*	

*Countries contributing highest number of datapoints for a region are highlighted in bold.

†Overall prevalence and numbers of people with anti-HCV estimated by applying age-specific prevalence to IHME age-specific population data 2005.

‡Extensive: Average of ≥5 datapoints per country; Moderate: Average of 2-4 datapoints per country; Limited: Average of 1 datapoint per country; Very Limited: Average of <1 datapoint per country.

Posterior predictive checks (an in-sample test of goodness-of-fit) identified 65 outliers, and all studies that included any of these outliers were reexamined to confirm that they met eligibility criteria for the systematic review. Twelve studies (29 outliers) were dropped from the model after thorough review of these studies showed that they were conducted in areas "known to be highly endemic for HCV"[15-18] or in populations known to have a high prevalence of markers of liver disease but missed exclusion. The final model included 736 datapoints (including 36 outliers) from 232 articles with complete data reporting that met inclusion and did not meet exclusion criteria (Fig. 1).

Results

Table 1 lists the countries and total population in 2005, total prevalence with 95% uncertainty interval

Table 2. Method of Clustering for Regions in Fitting Model

Method of Fitting	Regions	Expectations
Regions fit with empirical Bayes hierarchical model Years ≤ 1997 used for 1990 fit Years ≥ 1997 used for 2005 fit No sex effect in empirical prior phase	High income North America Western Europe	1. Changing incidence over time: Birth cohort effect in US in 1970-80, West Europe due to increased injection drug use in a particular time period 2. No large differences in prevalence between sex
Regions fit with empirical Bayes hierarchical model Years ≤ 1997 used for 1990 fit Years ≥ 1997 used for 2005 fit No sex effect in empirical prior phase	Eastern Europe East Asia South Asia Southeast Asia Australasia Oceania East Sub-Saharan Africa High income Asia Pacific Central Europe Central Asia North Africa/Middle East	1. Stable incidence over time 2. No large differences in prevalence between sex
Regions fit with empirical Bayes hierarchical model Years ≤ 1997 used for 1990 fit Years ≥ 1997 used for 2005 fit No sex effect in empirical prior phase	Latin America & Caribbean region: Caribbean, Tropical, Andean, Central and Southern Latin America Sub-Saharan Africa region: Central, Southern, and West Sub-Saharan Africa	1. Stable incidence over time 2. No large differences in prevalence between sex 3. Epidemiologically similar (Belongs to the same super-region) 4. Common age pattern due to sparse data in some regions

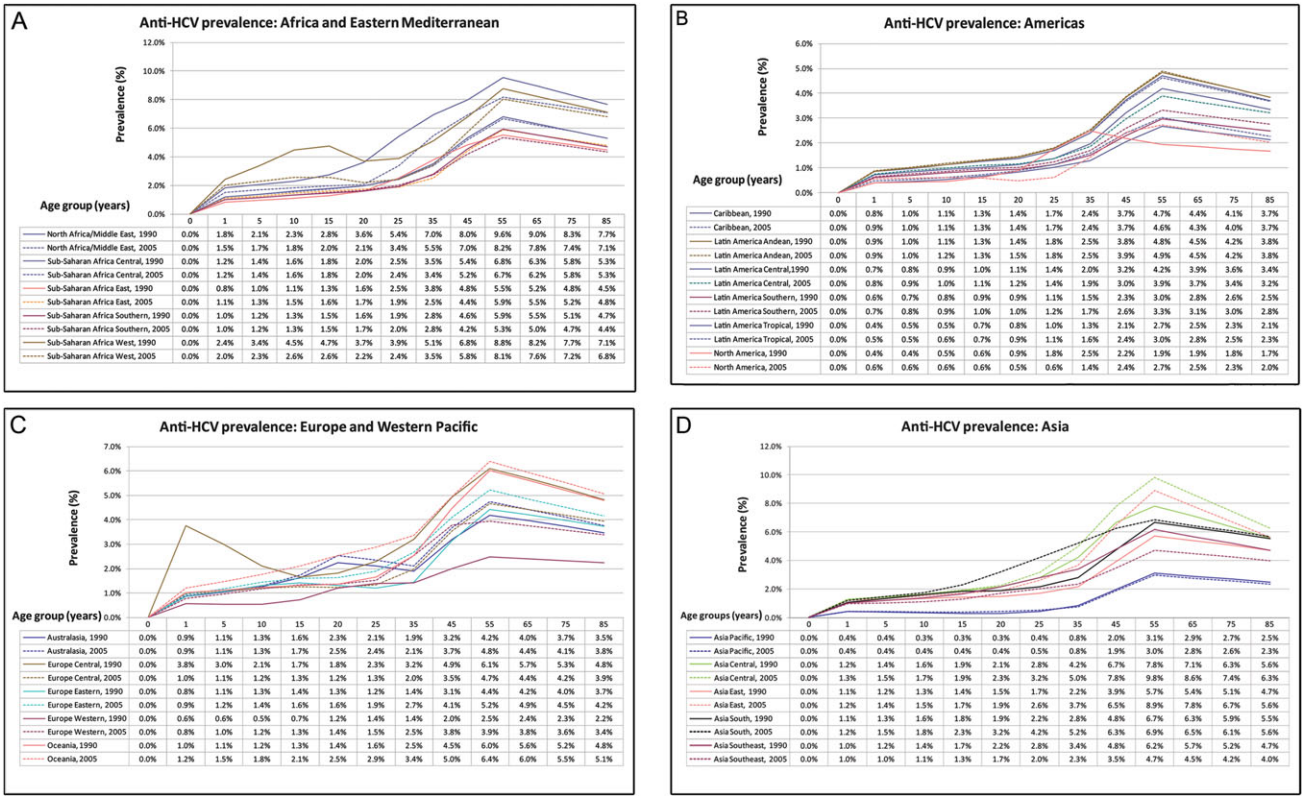

Fig. 2. Graph and table of anti-HCV seroprevalence estimates by age group, GBD region, in 1990 and 2005 in (A) Africa and the Eastern Mediterranean, (B) Americas, (C) Europe and Western Pacific, (D) Asia.

(UI) and number of persons with anti-HCV in 2005, and evidentiary support for each GBD Study region.

Sub-Saharan Africa. The prevalence pattern across age is similar in East, Central, and Southern sub-Saharan Africa, with the latter two having considerably lower prevalence compared to other sub-Saharan African regions. Prevalence increases with increasing age until peak prevalence of 5.3%-6.7% reached at 55-64 years in 2005. This peak is followed by a slight decrease in prevalence reaching 4.4%-5.3% in 85 years and above. In West sub-Saharan African the curves have two peaks; first at 15-19 years reaching 4.7% and 2.6%, and second at 55-64 years reaching 8.8% and 8.1% in 1990 and 2005, respectively. Differences in prevalence across age and total prevalence between 1990 and 2005 for sub-Saharan Africa are not significant, except in the West region, where total prevalence decreased from 4.0% (95% UI: 3.4-4.5%) in 1990 to 2.8% (95% UI: 2.4%-3.3%) in 2005 (Fig. 2; Table 1).

Americas. Data from North America show an increase of prevalence as a function of age followed by a gradual decrease after peak prevalence is reached. The age group with peak prevalence shifted from 35-44 years in 1990 (P: 2.5%, 95% UI: 1.6%-3.7%) to 55-64 years in 2005 (P: 2.7%, 95% UI: 2.0%-3.7%). This review estimates North America as having a total prevalence of 1.3% (95% UI: 0.9%-1.9%), which is similar but higher than the 2005 estimate of 1.1% for the U.S. alone.[19] A pattern of increasing prevalence across age was observed in Latin America and the Caribbean. In these regions the population peak prevalence was reached at 55-64 years in 1990 and 2005. In 2005, Andean Latin America had the highest peak prevalence (P: 4.9%, 95% UI: 2.9%-7.9%) followed by the Caribbean (P: 4.6%, 95% UI: 2.9%-7.0%), Central Latin America (P: 3.9%, 95% UI: 2.6%-5.8%), Southern Latin America (P: 3.3%, 95% UI: 1.9%-5.8%), and Tropical Latin America (P: 3.0%, 95% UI: 2.1%-4.4%). Total prevalence did not differ significantly between 1990 and 2005 in all regions (Fig. 2; Table 1).

Eastern Mediterranean. Total prevalence in North Africa/Middle East decreased from 4.2% (95% UI: 2.8%-6.2%) in 1990 to 3.7% (95% UI: 2.6%-5.1%) in 2005, although this decrease is not significant. The seroprevalence pattern across age in this region shows a slightly higher peak prevalence in 1990 (P: 9.6%, 95% UI: 6.7%-13.4%) compared with peak prevalence in 2005 (P: 8.2%, 95% UI: 6.1%-10.7%) at age 55-64 years, which declines thereafter (Fig. 2; Table 1).

Europe. In European regions, seroprevalence generally increases with age, whereby peak prevalence occurs in 55-64-year-olds and declines thereafter. In Western Europe, peak prevalence increases from 2.5% (95% UI: 1.8%-3.3%) in 1990 to 3.9% (95% UI: 2.9%-5.3%) in 2005. Eastern Europe is estimated to have the highest peak prevalence at 5.2% (95% UI: 3.4%-7.7%), followed by Central Europe with prevalence of 4.7% (95% UI: 3.2%-6.7%). Unlike in 2005, an early peak in ages 1-4 years (P: 3.8%, 95% UI: 2.3%-6.1%) is also seen in Central Europe in 1990. In Western Europe, total prevalence increased from 1.5% (95% UI: 1.4%-1.8%) in 1990 to 2.4% (95% UI: 2.2%-2.7%) in 2005 (Fig. 2; Table 1).

Asia. In 2005, and similarly in 1990, prevalence rises across age and peaks at age 55-64 in Central Asia (P: 9.8%, 95% UI: 6.4%-14.6%), East Asia (P: 8.9%, 95% UI: 6.1%-12.5%), South Asia (P: 6.9%, 95% UI: 3.9%-11.2%), Southeast Asia (P: 4.7%, 95% UI: 3.3%-6.4%), and Asia Pacific (P: 3.0%, 95% UI: 2.3%-3.9%) before plateauing. Total prevalence in Asia is highest in the Central region in 1990 (P: 3.1%, 95% UI: 2.6%-3.7%) and in 2005 (P: 3.8%, 95% UI: 3.0%-4.5%). Total prevalence in East Asia increases from 2.2% (95% UI: 1.8%-2.7%) in 1990 to 3.7% (95% UI: 3.1%-4.5%) in 2005, whereas changes in other regions were not significant (Fig. 2; Table 1).

Western Pacific. In 1990 and 2005, the pattern of seroprevalence across age in Australasia exhibit a rapid increase in prevalence, peaking first in ages 20-24 years (P: 2.5%, 95% UI: 1.6%-4.0%) and later in ages 55-64 years (P: 4.8%, 95% UI: 3.2%-6.9%), and gradually declines. In Oceania, the prevalence gradually increases and peaks in ages 55-64 (P: 6.4%, 95% UI: 4.4%-9.3%) and gradually declines. Total prevalence in both regions increased between 1990 and 2005, although this was not statistically significant (Fig. 2; Table 1).

Discussion

This study shows that the number of persons with anti-HCV in the world has increased from an estimated 122 million (P: 2.3%, 95% UI: 2.1%-2.5%) in 1990 to an estimated 184 million (P: 2.8%, 95% UI: 2.6%-3.1%) in 2005. However, given the cross-sectional nature of prevalence data, this global rise in prevalence and changes observed in East Asia, Western Europe, and West sub-Saharan Africa may reflect changes in compositional data or global shifts in age patterns rather than changes in disease epidemiology. Our analysis identifies Central and East Asia and North Africa/Middle East as regions with high prevalence; South and Southeast Asia, Andean, Central, and Southern Latin America, Australasia, Caribbean, Oceania, and Central, Eastern, and Western Europe, and sub-Saharan Africa as regions with moderate prevalence; and Asia Pacific, Tropical Latin America, and North America as regions with low prevalence in 2005 (Fig. 3). The regions with the highest estimated numbers of people with anti-HCV are South Asia (>50 million), East Asia (>50 million), North Africa / Middle East (>15 million), Southeast Asia (>11 million), and Western Europe (>10 million). However, anti-HCV is a sign of previous and current infection that does not differentiate acute from chronic infections. Further, there are a number of caveats and limitations to interpretation of the results of this study.

First, the published estimates are generally conservative, as exclusion criteria resulted in the elimination of many high-prevalence groups that are expected to increase total anti-HCV prevalence. These groups include paid blood donors who, due to the strong association between PWID and HCV transmission, were excluded, despite mixed views in the literature concerning their motivations and profile.[20,21] Even nationally representative data such as from NHANES U.S. exclude institutionalized persons, as their inclusion would likely inflate estimates of the general population. Second, this study analyzed published data only from English-language studies, available in Medline, Embase, and Cinahl. Regional databases and gray literature were not used. These limitations are expected to be restrictive for some regions, but are not expected to compromise the model as a whole or invalidate the findings in regions with a reasonable amount of peer-reviewed English publications.

Third, publication bias and heterogeneity of data also need to be considered. Regional estimates reflect prevalence of countries with the most published data without necessarily reflecting the prevalence of countries with the largest population size. In the case of South Asia, the high prevalence of anti-HCV was driven primarily by data from Pakistan; in Asia Pacific most data were from Japan; whereas the Central sub-Saharan Africa region was represented only by the Central African Republic. Within the country, the sample population may also be more defined than the general population. For example, many articles from Japan were found to publish prevalence from hyperendemic areas. Although these studies were excluded from analysis, publications from Japan seem to be heavily populated with studies conducted in

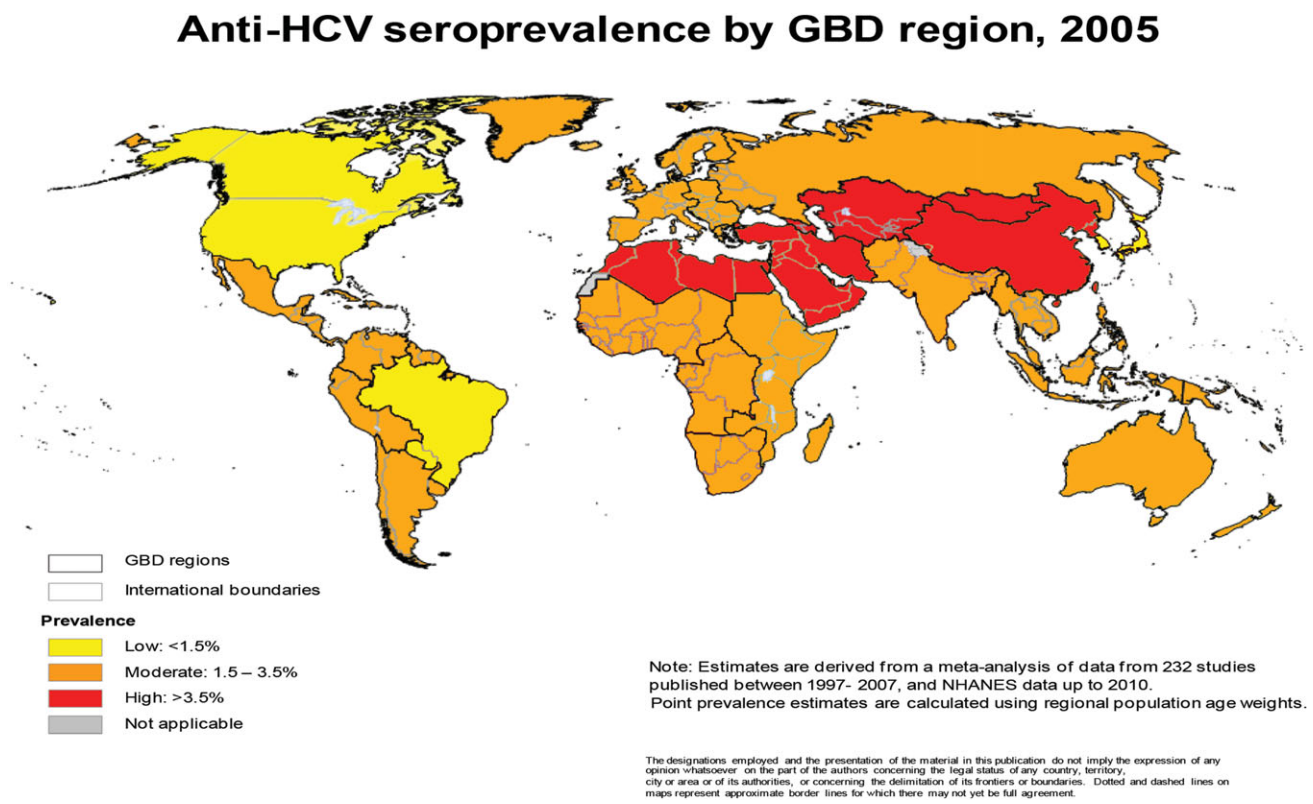

Fig. 3. Map of estimated anti-HCV seroprevalence by GBD region, 2005. Note: Includes data published up to 2007 in peer review and U.S. NHANES data up to 2010.

high-prevalence settings. Conversely, lower-income countries known to have high seroprevalence may seem to have lower estimates because published studies mainly sample urban affluent populations. Furthermore, it must be noted that seroprevalence data are generally derived from adult and older age samples, and may not be representative samples in regions with majority younger populations. These limitations in the literature underscore the challenge of estimating global prevalence in the absence of nationally representative age-specific databases such as the NHANES U.S.

Fourth, methodological limitations also apply. False positivity rates, although not a concern in enzyme immunoassay (EIA) testing for adults, is relatively high in children, particularly in first-generation test kits, and this may be among the reasons behind the high prevalence seen in children age 1-4 years old in Central Europe in 1990.[22,23] Type of diagnostic test and quality of test kits were not considered, because information on the test used were at times not included in the description of methods, which makes it difficult to appropriate bias indicators in instances where this information was not present. To exclude studies without details on the testing kit would further shrink the amount of studies that could be included, and furthermore it was expected that any influence of poor testing quality would be covered by the uncertainty interval surrounding the point estimates.

Finally, for regions with less data, borrowing strength from other regions may have hidden patterns of transmission between years and sex amid the pooled data. Although the data may be analyzed correctly using the hierarchical model, the problem with meta-analysis being used to make causal inferences has been highlighted, i.e., the studies included are observational and "group-level correlations may be mistakenly attributed to individual-level causes."[24,25]

Three distinct epidemiological profiles of HCV transmission have been described and can be used as a basis for interpreting the age-specific seroprevalence curves in this meta-analysis. In the first transmission type, prevalence is low among younger persons, and then rises steadily or sharply through middle age. After peak prevalence is reached, the seroprevalence declines in older ages. The peak prevalence seen in type 1 transmission is commonly referred to as the "cohort effect." In type 2 transmission, prevalence is low in younger populations but increases dramatically and is sustained in older populations as a reflection of a past high risk of infection that is no longer present. Type 3 transmission is seen in areas where there was a higher risk of infection in the distant past yet a high risk of

infection remains; prevalence is relatively high in all age groups, and increases steadily with age.[26] Age-group of peak prevalence varies by region, and is expected to also vary by country depending on local epidemiology of HCV transmission. For example, in the U.S. cohort effects were seen that were specific to infection stemming from injection drug use in the 1970s.[27] Areas with type 1 transmission such as North America exhibit signs of the aging cohort in prevalence, i.e., a shift in age group with highest risk of HCV-sequelae between 1990 and 2005. Regions such as East Asia and Southern Latin America, without previously hypothesized cohort effects, also show signs of type 1 transmission; this suggests that these regions may have their own cohort effects that are not as well understood or characterized. Further attention should be given to documenting the transmission patterns in different countries, particularly those that have high prevalence (such as Pakistan in South Asia), in order to inform future estimation efforts.

The total prevalence estimates in this study are higher compared to those of previous anti-HCV estimates[2] and some prominent findings in prevalence patterns of some regions require further discussion. In Australasia, the estimated peak prevalence at ages 20-24 years may reflect the high incidence of HCV among PWID reported recently.[28,29] Contrary to the literature describing Australia as having very low prevalence and type 1 transmission, our findings may be due to fewer datapoints beyond age 40, resulting in borrowing of strength and more influence from younger ages with higher prevalence for the Australasian region. Mother-to-infant transmission is the commonest route of HCV infection in children, with a vertical transmission rate of 5%.[30] In West sub-Saharan Africa, the relatively high prevalence in young children may reflect the overlapping human immunodeficiency virus (HIV) epidemic and HIV-HCV coinfection in sub-Saharan Africa, which is known to increase the risk of vertical transmission of HCV and requires further investigation.[31] Finally, despite the fact that Central Asia is estimated to have the highest total prevalence based on very limited data, the high prevalence of immigrants from Uzbekistan (31%) in a study of former Soviet Union immigrants in New York suggests the plausibility of these estimates.[32]

In conclusion, this analysis highlights the age group with the highest probability for sequelae, i.e., the group with peak prevalence that deserves attention for screening and treatment in each region. Further, it sets the stage for modeling the current and future global burden of HCV-related disease based on seroprevalence and natural history that 5%-20% will go on to develop cirrhosis over a period of 20-30 years and 1%-5% will die from the consequences of chronic infection.[33-35] This study also identifies challenges in producing useful "global" and even "regional" estimates for hepatitis C. Due to markedly different epidemiology from country to country (as seen in anti-HCV prevalence between Egypt and the rest of North Africa/Middle East) and some unavoidable inadequacies in meta-analysis, new generic modeling tools like DisMod III need additional customization for infectious diseases with varied and changing epidemiology.

To accomplish the GBD goal of estimating the burden of all diseases, it is first essential to improve primary data collection through establishment of nationally representative or population-based sampling sources and accessible databases (including non-English and gray literature). For hepatitis C specifically, the burden of disease that is currently being estimated using the data presented in this study is hoped to further inform and empower advocates and policymakers to accelerate progress in global prevention and treatment of HCV infections. The fact that global anti-HCV prevalence is increasing requires a global response for renewed efforts in primary prevention, including vaccine development, as well as new approaches to secondary and tertiary prevention to reduce the burden of chronic liver disease and to improve survival of those who already have evidence of liver disease.

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Author Contributions

K.M.H. Conducted data analysis and prepared the article; S.W. designed the study, supervised the study, and edited the article; J.G. Designed and led systematic

search of articles and edited the article; A.F. Conducted data analysis and edited the article; all authors have read and approved the final article.

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