

The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide[☆]

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Background/Aims: End-stage liver disease accounts for one in forty deaths worldwide. Chronic infections with hepatitis B virus (HBV) and hepatitis C virus (HCV) are well-recognized risk factors for cirrhosis and liver cancer, but estimates of their contributions to worldwide disease burden have been lacking.

Methods: The prevalence of serologic markers of HBV and HCV infections among patients diagnosed with cirrhosis or hepatocellular carcinoma (HCC) was obtained from representative samples of published reports. Attributable fractions of cirrhosis and HCC due to these infections were estimated for 11 WHO-based regions.

Results: Globally, 57% of cirrhosis was attributable to either HBV (30%) or HCV (27%) and 78% of HCC was attributable to HBV (53%) or HCV (25%). Regionally, these infections usually accounted for >50% of HCC and cirrhosis. Applied to 2002 worldwide mortality estimates, these fractions represent 929,000 deaths due to chronic HBV and HCV infections, including 446,000 cirrhosis deaths (HBV: $n = 235,000$; HCV: $n = 211,000$) and 483,000 liver cancer deaths (HBV: $n = 328,000$; HCV: $n = 155,000$).

Conclusions: HBV and HCV infections account for the majority of cirrhosis and primary liver cancer throughout most of the world, highlighting the need for programs to prevent new infections and provide medical management and treatment for those already infected.

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1. Introduction

End-stage liver disease represents a major source of morbidity and mortality worldwide. The World Health

Organization (WHO) estimates that in 2002 cirrhosis and primary liver cancer caused 783,000 and 619,000 deaths, respectively, [1]. Taken together, these conditions represented approximately one of every forty deaths (2.5%) worldwide.

Among primary liver cancers occurring worldwide, hepatocellular carcinoma (HCC) represents the major histologic type and likely accounts for 70% to 85% of cases [2]. Cirrhosis precedes most cases of HCC, and may exert a promotional effect via hepatocyte regeneration [3,4]. Compared with other causes of cirrhosis, chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) is associated with a higher risk of developing HCC [3,5]. Alcohol abuse represents a leading cause of cirrhosis and is also a major contributor to

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Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; WHO, World Health Organization; GBD, Global Burden of Disease.

HCC in many parts of the world, with some evidence for a synergistic effect in the presence of HBV or HCV infection [6,7]. Other factors appear to be of regional or local importance [8,9]. For example, dietary aflatoxin exposure in parts of Africa and Asia has been associated with primary liver cancer, especially in hosts with chronic HBV infection [8].

An understanding of the relative contribution of various etiologies to disease burden is important for setting public health priorities and guiding prevention programs [10,11]. The World Health Organization's Global Burden of Disease (GBD) 2000 project aims to quantify the burden of premature morbidity and mortality from over 130 major causes [1,12]. Liver cancer and cirrhosis are included in the analysis, but with the exception of alcohol, the etiologies underlying these diseases have not been well accounted for [1,11,13]. In particular, HBV and HCV infections have been poorly characterized in previous WHO estimates since these were based primarily on the acute effects of infection and omitted the associated burdens of chronic liver disease [10,11].

The attributable fraction represents the proportion of disease occurrence that potentially would be prevented by eliminating a given risk factor. For cirrhosis, a systematic analysis of attributable fractions has been lacking altogether. For HCC, previous estimates of the attributable fractions due to HBV and HCV are available but are not comprehensive and do not correspond to the regional designations and related conventions of the current GBD project [14]. In this study, we sought to estimate the attributable fractions of cirrhosis and HCC due to HBV infections and HCV infections globally and divided according to WHO GBD-based regions.

2. Materials and methods

2.1. Regions

Regions used in this analysis were based on subdivisions of the six primary WHO regions (AFR, African; AMR, The Americas; EMR, Eastern Mediterranean; EUR, European; SEAR, South-East Asian; and WPR, Western Pacific), as defined in the GBD 2000 project [1]. Each region is designated by the three- or four-letter region code followed by a one-letter suffix, corresponding to the mortality pattern of its member countries: A = very low child, low adult mortality; B = low child, low adult mortality; C = low child, high adult mortality; D = high child, high adult mortality; and E = high child, very high adult mortality [1]. Due to the limited availability of suitable data in certain regions, we combined the African D and E regions, the American B and D regions, and the European B and C regions to obtain a total of 11 regions (Table 1).

2.2. Search strategy, selection criteria and source data

We identified published studies of the prevalence of hepatitis B surface antigen (HBsAg) and antibody to HCV (anti-HCV) among groups of patients diagnosed with HCC or cirrhosis through Medline searches and by reviewing the references of retrieved articles and pertinent review articles. Index search terms included the medical subject

heading terms "hepatitis," "cirrhosis," "liver cancer," "hepatocellular carcinoma," and "prevalence." Full-text articles were retrieved if the reviewer considered the citation potentially relevant. Language translations were obtained for selected articles, including studies published in French, Spanish, and Russian. Data were abstracted for >250 study populations using a standardized instrument and entered into a computerized database. Information abstracted included publication year, study year(s) and location(s), outcome examined (i.e., HCC or cirrhosis), HCV testing methods, total number of subjects, and numbers of subjects with positive test results. In addition to the total numbers of subjects with HBsAg or anti-HCV, the numbers that were positive for both markers (i.e., indicative of co-infection) were also ascertained.

For each region, we aimed to identify at least three studies each for HCC and cirrhosis in which: (1) patient samples were drawn since 1990; (2) the sample size consisted of at least 15 subjects per condition examined (i.e., HCC or cirrhosis); and (3) HBsAg and anti-HCV testing was performed among all study subjects. Further, when selecting studies for inclusion in our analysis, we aimed to achieve a mix of studies that avoided duplication and was representative of each region in terms of the member states' contributions to the regional population (Table 1). Preference was given to the most recent and/or nationally representative reports and to studies that employed second- and third-generation anti-HCV assays.

2.3. Estimation of attributable fractions

For a given condition and risk factor [15], the attributable fraction may be calculated as: $(\text{Prevalence of exposure among cases}) \times [(\text{Risk ratio} - 1) / (\text{Risk ratio})]$. When the risk ratio is high (>10), as is the case for the risk factors and conditions under consideration here [16–19], the right-hand side of this expression approaches unity and the prevalence of the exposure among cases approximates the attributable fraction. Study-level prevalence data were adjusted to provide estimates of the fraction of cases attributable to infection with HBV or HCV as follows. The overall prevalence of infection (number of subjects with positive test results divided by the total number of subjects) was calculated for each virus. To avoid double-counting subjects with evidence of co-infection, we assumed that the attributable fraction due to coinfection with HBV and HCV should be apportioned evenly (50:50) between the individual viruses. Therefore, the final study-level estimate for each virus was calculated as the overall prevalence minus one-half of the coinfection (i.e., HBsAg+/anti-HCV+) prevalence. We then calculated the unweighted arithmetic mean of the study-level estimates to obtain the attributable fractions for each combination of region, virus and condition. In several instances (as noted in Table 3), weighting was applied to compensate for under- or over-representation of particular studies or countries that might otherwise have skewed the regional estimate. No further adjustments were made to account for other possible co-factors (e.g., alcohol). We estimated attributable fractions at the global level by calculating weighted averages of the regional attributable fraction estimates, using the numbers of regional cirrhosis or liver cancer deaths in 2002 as the weights [1]. This was done for each of the four combinations of condition and virus (i.e., cirrhosis-HBV, cirrhosis-HCV, HCC-HBV, and HCC-HCV). Finally, we applied the HBV- and HCV-attributable fractions estimates to worldwide mortality figures to estimate the total numbers of cirrhosis and liver cancer deaths potentially associated with these infections.

3. Results

For cirrhosis, we included a total of 43 study populations (median number per region, 4; range, 2–7) in the analysis (Table 2). For HCC, the total number of study populations that contributed data to the analysis was 52 (median, 4; range, 3–10) (Table 3). Most studies were set in hospitals and were conducted during the mid- or late-1990s, after the introduction of second-generation anti-HCV assays. Typically, the

Table 1
WHO member states comprising the 11 world regions used in this study

Region ^a	Population (millions) ^b	Member states (% contribution to regional population) ^c
AFR- D/E	672	Algeria (5%), Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Côte d'Ivoire, Democratic Republic of the Congo (8%), Equatorial Guinea, Eritrea, Ethiopia (10%), Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya (5%), Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria (18%), Rwanda, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, South Africa (6%), Swaziland, Tanzania (5%), Togo, Uganda, Zambia, Zimbabwe
AMR-A	334	Canada (10%), Cuba, United States of America (87%)
AMR- B/D	519	Antigua and Barbuda, Argentina (7%), Bahamas, Barbados, Belize, Bolivia, Brazil (34%), Chile, Colombia (8%), Costa Rica, Dominica, Dominican Republic, Ecuador, El Salvador, Grenada, Guatemala, Guyana, Haiti, Honduras, Jamaica, Mexico (20%), Nicaragua, Panama, Paraguay, Peru (5%), Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, Venezuela (5%)
EMR- B	143	Bahrain, Cyprus, Iran (49%), Jordan (5%), Kuwait, Lebanon, Libya, Oman, Qatar, Saudi Arabia (16%), Syria (12%), Tunisia (7%), United Arab Emirates
EMR- D	360	Afghanistan, Djibouti, Egypt (19%), Iraq, Morocco, Pakistan (44%), Somalia, Sudan, Yemen
EUR-A	415	Andorra, Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France (14%), Germany (20%), Greece, Iceland, Ireland, Israel, Italy (14%), Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain (10%), Sweden, Switzerland, United Kingdom (14%)
EUR- B/C	463	Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Bulgaria, Estonia, Hungary, Former Yugoslav Republic of Macedonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Moldova, Poland (8%), Romania (5%), Russian Federation (32%), Slovakia, Tajikistan, Turkey (14%), Turkmenistan, Ukraine (11%), Uzbekistan (5%)
SEAR-B	298	Indonesia (73%), Sri Lanka (6%), Thailand (21%)
SEAR-D	1293	Bangladesh (10%), Bhutan, Democratic People's Republic of Korea, India (82%), Maldives, Myanmar, Nepal, Timor-Leste
WPR-A	155	Australia (12%), Brunei Darussalam, Japan (83%), New Zealand, Singapore
WPR- B	1562	Cambodia, China (84%), Cook Islands, Federated States of Micronesia, Fiji, Kiribati, Laos, Malaysia, Marshall Islands, Mongolia, Nauru, Niue, Palau, Papua New Guinea, Philippines (5%), South Korea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu, Viet Nam

^a Corresponding WHO region designations: AFR, African; AMR, The Americas; EMR, Eastern Mediterranean; EUR, Europe; SEAR, South-East Asia; WPR, Western Pacific [1].

^b World Population Prospects – the 2002 revision. New York, NY, United States Population Division.

^c Percentage shown for member states contributing at least 5% to regional population.

studies specified diagnosis via histology or imaging techniques, supplemented by consideration of biochemical markers (e.g., α -fetoprotein levels for HCC). Fewer than 10% of the included studies specified first-generation anti-HCV tests [33–36,48,58,59]; these primarily involved cirrhosis patients and reflected the limited availability of suitable studies, as was the case in EMR-B. Other regions where suitable data were lacking overall included EUR-B/C and AMR-B/D. Sample sizes among the study populations varied greatly, and several multicenter studies that involved large numbers of patients were included [31,44,66,81,85]. Notably, for HCC in China, data were obtained from a recently published meta-analysis [96]. Among the studies that provided information on gender, males predominated; this was more pronounced among the HCC subject populations which were generally comprised of 70–90% males.

The prevalence of HBV and HCV infection among cirrhosis and HCC patients varied considerably within and between regions (Tables 2 and 3). These variations tended to reflect known patterns of HBV and HCV infection endemicity [99,100]. For example, in countries where HCV infection has long been endemic, such as Japan and Egypt, there were high prevalences of HCV infection among cirrhosis and HCC patients. The same held true for China and most of the African nations in our sample regarding HBV infection. Areas such as these, where HBV infection predominated, appeared to have a younger population of HCC cases, which is thought to reflect the preponderance of infections acquired early in life (e.g., perinatal HBV transmission) [8]. Patterns of HBV and HCV co-infection were also notable. Among cirrhosis patients, evidence of co-infection with HBV and HCV was most frequently observed in EMR-D,

Table 2
Characteristics of studies that examined the prevalence of HBV and HCV infections among cirrhosis patients

Region	Country	Years ^a	No. of patients	Mean age	(% Male)	Proportions of subjects with serologic markers			Source
						HBsAg (total) (%)	anti-HCV (total) (%)	Both HBsAg and anti-HCV (%)	
AFR-D/E	Ethiopia	1992–94	156	42	75 ^d	29	36	0	[20]
	Gabon	1990–98	73	45 ^d	67 ^d	34	34	4	[21]
	Kenya	P 1995	30	40	53	27	0	0	[22]
	Mali	1998–99	53	45 ^d	65 ^d	55	25	13	[23]
	Nigeria	1993–94	18	47 ^d	84 ^d	67	0	0	[24]
	Senegal	1995	25	39	89 ^d	84	0	0	[25]
	South Africa	1991–92	77	45	73	19	23	1	[26]
AMR-A ^c	United States	1989–2000	516	54	61	7	27	2 ^c	[27]
	United States	1994–97	285	49	56	2	35	0	[28]
	United States	1994–96	39	39	80	8	51	0	[29]
	United States	1991–92	52	44	65	6	58	1	[30]
AMR-B/D	Mexico	2000–02	1486	57 ^d	49	5	37	0	[31]
	Peru	1991–92	85	57 ^d	55 ^d	12	11	2	[32]
EMR-B	Saudi Arabia	1989–90	28	56 ^d	76 ^d	46	36	7	[33]
	Saudi Arabia	1990–91	34	– ^b	–	21	44	0	[34]
	Tunisia	P 1992	23	–	–	48	30	9	[35]
	Tunisia	P 1994	168	–	–	35	45	5	[36]
EMR-D	Egypt	1992	39	–	–	36	82	23	[37]
	Egypt	1994–95	18	37	83	22	78	17 ^c	[38]
	Pakistan	1999–2000	72	52 ^d	54	24	68	10	[39]
	Pakistan	1997–2000	54	–	–	31	48	4	[40]
	Somalia	1988–90	30	34 ^d	100	50	10	3	[41]
EUR-A	Belgium	1995	141	–	63 ^d	9	24	1	[42]
	Czech Republic	1991–93	115	59	–	21	24	3	[43]
	Italy	2001	2185	62	57 ^d	13	70	3	[44]
EUR-B/C	Russia	1994–96	25	–	–	24	40	12	[45]
	Russia	1996–2000	335	–	–	22	33	4	[46]
	Turkey	1999–2002	226	57	64	37	38	1	[47]
SEAR-B	Indonesia	1990	58	–	–	33	43	16	[48]
	Indonesia	P 1994	86	50	65	28	45	1	[49]
	Thailand	P 1994	94	50 ^d	69	29	18	1	[50]
	Thailand	1997–98	65	53	57	34	23	2	[51]
SEAR-D	India	1994–95	99	43	72	16	11	2 ^c	[52]
	India	1994–95	32	42	87 ^d	31	28	9 ^c	[53]
	India	1997–99	111	47	91	25	14	4 ^c	[54]
	Nepal	1989–92	63	52	76	40	14	6 ^c	[55]
WPR-A	Japan	1991	8576	–	–	24	52	3	[56]
	Japan	1997–99	325	64	72	12	70	9 ^c	[57]
	Japan	P 1991	150	–	–	16	73	5	[58]
WPR-B	China	P2002	769	–	–	66	32	21 ^c	[59]
	Mongolia	2004	41	48	44	68	41	29 ^c	[60]
	South Korea	1995–2000	585	51	74 ^d	56	13	3	[61]
	Taiwan	1996–97	210	57 ^d	81	66	29	6	[17]

^a Years indicate the period of subject recruitment when available; “P” indicates publication year.

^b Dashes indicate data not available.

^c Co-infection not specified in report and estimated as product of HBV and HCV prevalences.

^d Estimated from available data.

^e Due to limited available data in AMR-A, we included one study [26] that used chart review rather than testing to ascertain infection status and two studies [27,28] that examined patients with chronic liver disease not limited to cirrhosis.

EUR-B/C, SEAR-D, and WPR-B. Among HCC patients, co-infection appeared most often in EMR-D, and WPR-B.

The estimated fractions of cirrhosis attributable to HBV infection ranged from 5% (AMR-A) to 57% (WPR-B) (Table 4, Fig. 1). The fractions of cirrhosis

Table 3
Characteristics of studies that examined the prevalence of HBV and HCV infections among HCC patients

Region	Country	Years ^a	No. of patients	Mean age	(%) Male	Proportions of subjects with serologic markers			Source
						HBsAg (total) (%)	anti-HCV (total) (%)	Both HBsAg and anti-HCV (%)	
AFR-D/E	Ethiopia	1992–94	68	49	75 ^d	19	47	1	[20]
	Gabon	1990–98	44	45 ^d	67 ^d	39	27	5	[21]
	Gambia	1997–2001	216	48	80	61	19	4	[62]
	Kenya	P 1995	42	33	74	36	0	0	[22]
	Mali	1998–99	38	45 ^d	65 ^d	55	26	8	[23]
	Nigeria	1995	64	52	66	59	19	11	[63]
	Nigeria	1993–94	23	47 ^d	84 ^d	61	9	0	[24]
	Senegal	1995	46	43	89 ^d	67	4	0	[25]
	South Africa	1991–92	33	48	61	45	24	0	[26]
Zimbabwe	P1997	63	50 ^d	70 ^d	41	24	3	[64]	
AMR-A ^c	United States	1993–98	216	60 ^d	65	10	31	4 ^c	[65]
	United States	1994–97	27	–	–	7	63	7	[28]
	United States	1997–99	691	–	–	20	51	5	[66]
AMR-B/D	Brazil	1992–94	287	55	78	42	27	4	[67]
	Brazil	1992–99	36	50	86	58	8	5 ^c	[68]
	Mexico	1992–2002	127	57 ^d	50	18 ^f	59 ^f	11 ^f	[69]
	Peru	1995–98	136	35	63	63	1	0	[70]
EMR-B	Iran	1999–2004	71	54 ^d	63	54	8	0	[71]
	Saudi Arabia	1995–96	118	58	81	67	12	3	[72]
	Tunisia	P 1994	31	– ^b	–	65	26	10	[36]
EMR-D	Egypt	1995–96	34	–	76	21	94	15	[73]
	Egypt	1995–96	33	55	70	15	76	11 ^c	[74]
	Pakistan	1997–2000	29	–	–	55	38	7	[40]
	Pakistan	1994–2000	41	–	–	17	32	2	[75]
	Sudan	1996–98	115	60 ^d	77	43	11	1	[76]
EUR-A ^c	Germany	1993–97	268	59	79	35	27	10	[77]
	Germany	1994–2000	118	61	80	8	18	0	[78]
	Greece	1995–98	333	–	85	63	16	3	[79]
	Italy	2001	341	–	–	16	74	3	[80,81]
	Spain	2000	64	73	66	8	75	2	[82]
	Spain	1990–94	512	55	63	15	45	7 ^c	[83]
EUR-B/C	Russia	1996–2000	37	–	–	14	3	0	[84]
	Turkey	1994–97	207	57 ^d	79	56	23	4	[85]
	Turkey	1999–2002	35	61	80	69	31	3	[47]
	Turkey	P 1996	47	57	87	70	6	0	[86]
SEAR-B	Indonesia	P 2002	47	54	77	23	43	2	[87]
	Indonesia	P 1994	39	55 ^d	87	15	44	0	[49]
	Thailand	1996–98	101	52	85	62	12	6	[88]
	Thailand	1997–98	43	57	93	56	16	7	[51]
SEAR-D	Bangladesh	1992	16	–	88	38	56	6	[89]
	India	1993–99	74	49	85	53	12	8	[90]
	India	P 2002	15	63	73	80	53	53	[87]
	Myanmar	1996–98	28	47	89	54	29	7	[91]
WPR-A	Japan	1995–2000	375	66	65	6	88	1	[92]
	Japan	1990–97	330	–	–	16	79	4	[93]
	Japan	1993–99	573	64	72	9	83	1	[94]
	Japan	P 2002	191	64	73	19	71	1	[87]
	Singapore	1990–93	55	56	82	85	20	11	[95]
WPR-B ^c	China	P 1995–2004	2697	49 ^d	–	72	22	14	[96]
	Mongolia	2004	76	58	46	88	82	72 ^c	[60]
	S Korea	1995–2000	565	54 ^d	81 ^d	73	13	1	[97]
	Taiwan	1996–97	284	55	82	67	31	9	[98]

(continued on next page)

Table 3 (continued)

- ^a Years indicate the period of subject recruitment when available; “P” indicates publication year.
^b Dashes indicate data not available.
^c Co-infection not specified in report and estimated as product of HBV and HCV prevalences.
^d Estimated from available data.
^e For AMR-A, the multicenter study [66] was weighted 85%; for EUR-A, relative weights were based on country population (Germany 43%, Italy 30%, Spain 21%, Greece 6%); for WPR-B, China was weighted 80%.
^f This study relied on chart review to determine HBV and HCV status; the prevalences shown differ from those reported [69] since we assumed 50% lower infection rates among the 56 subjects for whom etiology was unavailable relative to the 71 subjects whose status was known.

attributable to HCV infection ranged from 16% (AFR-D/E) to 62% (WPR-A). The attributable fractions of HCC due to HBV or HCV ranged from 16% (AMR-A) to 65% (WPR-B) and from 13% (EMR-B) to 66% (WPR-A), respectively. The two viruses together accounted for >50% of HCC in all of the regions; this was also true for cirrhosis in 8 of 11 regions. Globally, we estimated that approximately 57% of cirrhosis was due to either HBV (30%) or HCV (27%) (Table 4). For HCC, approximately three-quarters (78%) was attributable to HBV (53%) or HCV (25%).

When we applied the HBV- and HCV-attributable fractions we derived to 2002 worldwide mortality estimates [1], we found that approximately 929,000 deaths from cirrhosis ($n = 446,000$) and primary liver cancer ($n = 483,000$) were likely due to chronic viral hepatitis infections. HBV infection accounted for 563,000 deaths (235,000 from cirrhosis and 328,000 from liver cancer) and HCV infection accounted for 366,000 deaths (211,000 from cirrhosis and 155,000 from liver cancer).

4. Discussion

This study provides a detailed regional accounting of the underlying contributions of HBV and HCV infections to end stage liver disease worldwide and is the first

such effort to include cirrhosis. We showed that chronic viral hepatitis infections likely account for the majority of both cirrhosis and HCC globally and in nearly all regions of the world.

One of the strengths of our analysis was that it employed simple and transparent methods. Our estimates of attributable fractions were derived from reviews of published studies reporting the prevalence of HBV and HCV infections in patients with cirrhosis or HCC in all regions of the world. Alternate approaches rely on estimates of the prevalence of risk factors and corresponding relative risks in the source populations. However, errors associated with extrapolating exposure or hazard from one population to another are a major source of uncertainty in efforts to characterize international health risks [12]. Given the lack of representative data regarding HBV and HCV infection prevalences worldwide along with uncertainties in deriving region-specific risk estimates, we believe ours is the preferred approach.

Despite differences in methods, our overall findings are similar to other available global estimates. For example, estimates of infection prevalence and relative risks for HCC were used to calculate that 60% and 24% of global HCC in 1990 could be attributed to HBV and HCV respectively [14]. A recent update of this analysis for 2002 yielded HBV- and HCV-attributable fractions of 54% and 31% [101]. For cirrhosis, previous estimates have been scant; the WHO Global Burden of Disease estimates for 1990 indicate a contribution for HBV (51%), but the methods used to arrive at this estimate were not documented. Kim illustrated that, by extrapolation from the GBD figures, 17% of worldwide cirrhosis might be attributable to HCV [10]. Geographic variations in our attributable fraction estimates also appeared to be consistent overall with current knowledge of global patterns of HBV and HCV infection prevalence and estimates of HCC attributable fractions [8,99,100,102–105].

Our study was limited by its inability to account for risk factors other than HBV or HCV infections, particularly alcohol abuse. A recent analysis, performed in the context of the GBD 2000 Study, ascribed 32% and 25% of worldwide cirrhosis and HCC cases, respectively, to alcohol [13]. These figures are compatible with our global estimates which indicated 57% of cirrhosis and 78% of

Table 4
Estimates of the attributable fractions of cirrhosis and hepatocellular carcinoma due to infection with HBV and HCV, by region

Region	Attributable fractions of cirrhosis			Attributable fractions of HCC		
	HBV (%)	HCV (%)	Combined (%)	HBV (%)	HCV (%)	Combined (%)
AFR-D/E	44	16	60	47	18	65
AMR-A	5	42	47	16	48	64
AMR-B/D	8	23	31	43	21	64
EMR-B	35	36	71	59	13	72
EMR-D	27	51	78	26	47	73
EUR-A	13	38	51	18	44	62
EUR-B/C	25	34	59	51	15	66
SEAR-B	28	30	58	37	27	64
SEAR-D	26	14	40	47	28	75
WPR-A	14	62	76	25	66	91
WPR-B	57	21	78	65	18	83
World	30	27	57	53	25	78

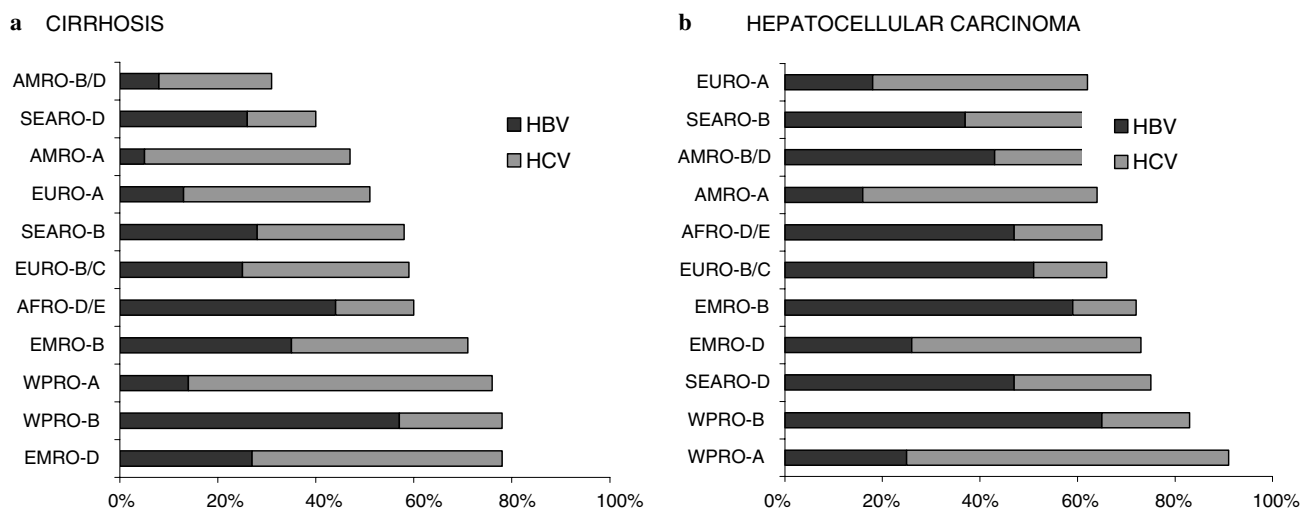


Fig. 1. Estimates of the attributable fractions of cirrhosis and hepatocellular carcinoma due to infection with HBV or HCV, by region.

HCC were attributable to HBV and HCV. Regional estimates of the alcohol-attributable fractions were also consistent with our estimates. Reported alcohol-attributable fractions were generally high where viral hepatitis-attributable fractions are low, and vice versa. It has previously been noted that alcoholic cirrhosis may predominate in areas with low prevalences of HBV and HCV infections and be associated with a high proportion of HCC cases [8]. However, co-morbidity from alcohol abuse and HBV and/or HCV infection is substantial in certain regions and future efforts to characterize the burden of end-stage liver disease should aim at a more integrated accounting of these and other risk factors.

Additional limitations in our study stem from issues related to sampling, classifying and testing liver disease patients. In general, we found that the quality and quantity of studies appropriate for our analysis was lower among cirrhosis patients relative to HCC patients, while resource poor regions tended to have fewer well-suited studies available for inclusion overall. Such regions might have less reliable diagnostic tools available to clinicians and researchers (for viral hepatitis testing and for the diagnosis of cirrhosis and HCC). Another concern relates to the fact that we utilized serologic test results exclusively to classify subjects as HBV or HCV infected, rather than considering the results of nucleic acid testing when available. This might have resulted in a degree of under-ascertainment of HBV- or HCV-related cases [103], but was necessary to assure a uniform approach.

Our findings help illustrate the great need for programs aimed at preventing HBV or HCV transmission. In 1992, WHO recommended that all countries include hepatitis B vaccine in their routine infant immunization programs. As of 2003, WHO/UNICEF estimated 42% hepatitis B vaccination coverage among the global birth

cohort [106]. Therefore, implementation of this strategy, which represents the most effective way of preventing chronic HBV infection and related end stage liver disease, is far from complete [107,108]. Other key primary prevention strategies include screening blood donors and maintaining infection control practices to prevent the transmission of healthcare-related HBV and HCV infections [105,109,110]. In countries where these activities have not been fully implemented, they should be given a high priority. In most developed countries, injection drug use and high-risk sexual behaviors represent the major risk factors for HCV infection and HBV infection, respectively, indicating the importance of related prevention efforts (e.g., reducing the numbers of new initiates to injection drug use).

The role of programs to identify, counsel, and provide medical management for the many persons already infected with HBV or HCV requires careful consideration [105,110]. Counseling that includes advice regarding avoidance of alcohol and education regarding modes of transmission can help reduce the risks for developing chronic disease or spreading infection to susceptible persons. The widespread application of therapeutic interventions also has the potential to accelerate the declines in end-stage liver disease that will eventually follow from hepatitis B vaccination and other primary prevention efforts [104,107]. Recent advances have occurred in the therapeutic management of chronic hepatitis B and chronic hepatitis C, but treatments are long and involve substantial costs and side effects [111–113]. Countries will need to consider the potential benefits of treatment while insuring that scarce healthcare resources are allocated in a manner that does not undermine primary prevention efforts [114].

The relative contributions of HBV and HCV to end-stage liver disease are subject to temporal trends and

projections of the future burdens of disease are difficult to make [11,115]. Countries lacking their own estimates of the roles of HBV or HCV as causes of liver disease might use the regional estimates presented here as a reasonable starting point for health planning, research, and educational activities. Our findings might also serve as benchmarks for testing assumptions regarding the prevalence, incidence, and natural history of HBV or HCV infections in dynamic models [11,115]. Applications such as cost-effectiveness studies [116] would aid the development of health policy by examining the balance between interventions aimed at preventing new infections or identifying and treating persons already infected.

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