# The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013

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## Summary

**Background** **With recent improvements in vaccines and treatments against viral hepatitis, an improved understanding of the burden of viral hepatitis is needed to inform global intervention strategies. We used data from the Global Burden of Disease (GBD) Study to estimate morbidity and mortality for acute viral hepatitis, and for cirrhosis and liver cancer caused by viral hepatitis, by age, sex, and country from 1990 to 2013.**

**Methods** **We estimated mortality using natural history models for acute hepatitis infections and GBD's cause-of-death ensemble model for cirrhosis and liver cancer. We used meta-regression to estimate total cirrhosis and total liver cancer prevalence, as well as the proportion of cirrhosis and liver cancer attributable to each cause. We then estimated cause-specific prevalence as the product of the total prevalence and the proportion attributable to a specific cause. Disability-adjusted life-years (DALYs) were calculated as the sum of years of life lost (YLLs) and years lived with disability (YLDs).**

**Findings** **Between 1990 and 2013, global viral hepatitis deaths increased from 0·89 million (95% uncertainty interval [UI] 0·86–0·94) to 1·45 million (1·38–1·54); YLLs from 31·0 million (29·6–32·6) to 41·6 million (39·1–44·7); YLDs from 0·65 million (0·45–0·89) to 0·87 million (0·61–1·18); and DALYs from 31·7 million (30·2–33·3) to 42·5 million (39·9–45·6). In 2013, viral hepatitis was the seventh (95% UI seventh to eighth) leading cause of death worldwide, compared with tenth (tenth to 12th) in 1990.**

**Interpretation** **Viral hepatitis is a leading cause of death and disability worldwide. Unlike most communicable diseases, the absolute burden and relative rank of viral hepatitis increased between 1990 and 2013. The enormous health loss attributable to viral hepatitis, and the availability of effective vaccines and treatments, suggests an important opportunity to improve public health.**

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## Introduction

Infectious viral hepatitis is an important challenge to health worldwide. Hepatitis A virus (HAV) and hepatitis E virus (HEV) are endemic in many low-income countries.[1,2] They usually cause self-limiting hepatitis but occasionally lead to fulminant liver failure and, in rare cases of immunosuppression, chronic HEV infection. Hepatitis B virus (HBV) and hepatitis C virus (HCV) also cause acute illness but more commonly lead to progressive liver fibrosis, cirrhosis, and an increased risk of liver cancer (specifically hepatocellular carcinoma).[3–5]

Effective vaccines for HAV and HBV have been available for more than two decades, and an HEV vaccine was licensed in China in 2011, but is not widely available.[6] More recently, major improvements in antiviral therapies for HBV and HCV have been made. In the absence of a vaccine, progress in HCV treatment has been particularly important. New short-course oral treatments can achieve cure in most patients, including those previously considered difficult to treat, although long-term follow-up data are not yet available.[7,8] Together, these advances overcome many barriers to the control and treatment of viral hepatitis in low-income countries and are set to be important components of a new global health strategy.[9] However, a better understanding of the burden of disease is required to guide these efforts.

The Global Burden of Disease (GBD) Study is a systematic effort to estimate health loss due to diseases, injuries, and risk factors by age, sex, and geography for timepoints from 1990 to 2013. It is the most comprehensive effort to estimate causes of mortality and morbidity, and their relative importance. GBD quantifies health loss using disability-adjusted life-years (DALYs), a summary metric combining premature death and non-fatal health outcomes.[10] The GBD Study estimated the burden resulting from the acute sequelae of HAV, HBV, HCV, and HEV infections, and the chronic sequelae (ie, cirrhosis and liver cancer) of HBV and HCV infections. Still, the total burden of viral hepatitis was not clearly recognised in previous GBD reports because estimates for acute disease, cirrhosis, and liver cancer were categorised in separate parts of the GBD schedule of diseases and injuries.[11]

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## Research in context

### Evidence before this study

On Oct 5, 2015, we searched PubMed for ""Hepatitis, Viral, Human"[Mesh] AND (burden OR DALY OR QALY OR HALE OR YLL OR YLD)", with no restrictions on language or date of publication, and found 1445 publications. We excluded any studies that did not report original estimates of the frequency or burden of disease related to hepatitis A, B, C, or E infection, any studies that were restricted to special subpopulations (eg, injection drug users and people living with HIV), and any studies that did not produce estimates for an area larger than a country. 20 articles met our search criteria: two studies of hepatitis A virus seroprevalence; three studies of hepatitis B virus (HBV) seroprevalence; 12 studies of hepatitis C virus (HCV) that reported estimates of seroprevalence, prevalence of viraemia, incidence, or mortality; one study of hepatitis E virus (HEV) incidence and mortality; one study reporting estimates of cirrhosis and liver cancer due to HBV and HCV; and one study of liver cancer due to HBV and HCV. We found no studies that reported original estimates of the total burden of viral hepatitis, and no studies reporting global estimates of a comprehensive health gap metric (ie, disability-adjusted life-years or quality-adjusted life-years) for any of the four hepatitis viruses.

### Added value of this study

We used data from the Global Burden of Disease (GBD) Study to estimate morbidity and mortality for acute viral hepatitis, and for cirrhosis and liver cancer due to HBV and HCV, by age group, sex, and country from 1990 to 2013. Although sequela-specific hepatitis burden estimates have been published previously, our study is the first formal attempt to estimate the total burden of viral hepatitis, using systematic data gathering and robust statistical methods, and the trends in that burden over time. To our knowledge, this study is the first to explore the drivers of change in the burden of hepatitis and the effect of hepatitis in different country income levels. The effect of viral hepatitis has not been clearly recognised in previous GBD reports because estimates for acute disease, cirrhosis, and liver cancer have been reported separately. This paper is the first to place the burden of viral hepatitis in the context of overall global health.

### Implications of all the available evidence

Our results show that viral hepatitis is one of the leading causes of death and disability worldwide, and causes at least as many deaths annually as tuberculosis, AIDS, or malaria. By contrast with most other communicable diseases, hepatitis has risen in importance since the first GBD Study in 1990. As WHO launches a major new effort to tackle viral hepatitis, these data are of crucial importance to global health policy.

Building on estimates for the individual sequelae, we aimed to estimate the global burden of disease due to viral hepatitis, investigate the changes in disease burden between 1990 and 2013, and explore the extent to which disease burden affects low-income and lower-middle-income countries.

## Methods

### Overall approach

We estimated mortality and morbidity due to acute viral hepatitis for the four most important viruses—HAV, HBV, HCV, and HEV—and the mortality and morbidity due to cirrhosis and liver cancer secondary to HBV and HCV. We aggregated burden from these hepatitis-attributable causes and decomposed trends to assess changes resulting from changing demographics versus changing age-specific rates (see appendix p 8 for details of decomposition methods).

### Prevalence modelling (acute infection)

We obtained anti-HAV IgG, HBsAg, anti-HCV IgG, and anti-HEV IgG seroprevalence data through reviews of published and grey literature, and searches of surveys indexed in the Global Health Data Exchange. We estimated the seroprevalence of HBsAg, anti-HCV IgG, and anti-HEV IgG—specific to age group, sex, country, and year—using the meta-regression tool, DisMod-MR.[12] Briefly, DisMod-MR produces consistent estimates of disease incidence, prevalence, remission, and mortality with a compartmental offset log-normal non-linear mixed-effects model, with hierarchical random effects on geography. The models for HBsAg, anti-HCV IgG, and anti-HEV IgG seroprevalence included a study-level covariate to adjust data from studies of blood donors for a systematic bias towards lower estimates.[6] The model for HEV seroprevalence also included the proportion of the population with access to improved sanitation facilities and the proportion of the population living in the classic monsoon belt as predictive covariates. As a log-normal model, DisMod performs poorly when modelling conditions for which prevalence approaches 100%. Thus, in view of the ubiquity of HAV infection and the reasonably stable force of infection among susceptible people across age groups, we used a catalytic binomial model to estimate the force of HAV infection on the basis of anti-HAV IgG seroprevalence. Specifically, we used a binomial generalised linear model with a complementary log–log link, an offset term for log-age, and a predictive covariate derived from principal components analysis of lag-distributed income and the proportion of the population with access to improved water.[13]

We estimated the prevalence of acute infection as the product of the population incidence and the estimated duration of acute infection (appendix p 2), which was 4 weeks for HAV and HEV infections, and 6 weeks for

HBV and HCV infections on the basis of expert opinion and published work.[14–16] Because only a subset of individuals with acute infection are symptomatic and antibody presence does not necessarily indicate a disease state that causes any disability, we divided these acute infections into asymptomatic and symptomatic states. We used published age-specific estimates of the probability of symptomatic infection, increasing from 1% at birth to 85% among adults for HAV,[13] from 1% at birth to 33% among adults for HBV,[17] and from less than 1% at birth to 60% among adults for HEV (appendix p 3).[1] For HCV, we assumed that 25% of acute infections would be symptomatic.[14,15,18]

### Mortality modelling

We estimated cause-specific mortality—by age group, sex, country, and year—for cirrhosis, liver cancer, and acute viral hepatitis (including HAV, HBV, HCV, and HEV) using the GBD 2013 cause-of-death ensemble model, and fitted these estimates using data for all-cause mortality and cause-specific mortality that were compiled from vital registration, verbal autopsy, cancer registry, and mortality surveillance sources.[19] In total, there were 5952 site-years of mortality data, with 2144 site-years of data for cirrhosis, 1635 for hepatitis, and 2173 for liver cancer. Candidate covariates for the cause-of-death ensemble model were selected on the basis of expert judgment and literature review, and included seroprevalence of anti-HAV, HBsAg, anti-HCV, and anti-HEV from the DisMod-MR models, alcohol consumption, educational attainment, health system access, and lagged-smoothed gross domestic product per person, among other factors (appendix pp 5–7). Virus-specific mortality data for acute hepatitis were too limited to use directly in the cause-of-death ensemble model. We therefore used a two-step nested-model approach for acute hepatitis: first, we modelled the joint mortality from all acute hepatitis using cause-specific mortality data in the cause-of-death ensemble model; second, we developed separate natural history models for each virus, in which we estimated mortality as the product of incidence and case fatality. We derived estimates of case fatality for acute hepatitis by pooling estimates from published literature—0·024% (95% uncertainty interval [UI] 0·0058–0·054) for HAV,[20–22] 0·42% (0·25–0·64) for HBV,[20,22] and 0·12% (0·025–0·29) for HCV.[20,22] We estimated HEV deaths using the approach described by Rein and colleagues,[1] in which we assumed a higher case fatality for pregnant women (3·9%, 1·9–8·0) than for other groups (0·38%, 0·16–0·57), and applied these two values in proportions defined by the proportion of women estimated to be pregnant in each age group, country, and year (appendix p 4). Finally, the estimates of viral hepatitis deaths by subtype were scaled using the GBD 2013 CoDCorrect process[19] to sum to the total viral hepatitis envelope, and the estimates of deaths by all causes were scaled to sum to the total mortality envelope.

### Prevalence modelling (cirrhosis and liver cancer)

We used DisMod-MR to estimate the prevalence of decompensated cirrhosis using data derived primarily from hospital discharge data, and cause-specific cirrhosis mortality estimates produced as described previously. For liver cancer, we modelled mortality-to-incidence ratios by country, year, age, and sex. We estimated incidence by dividing estimated mortality by the estimated mortality-to-incidence ratio. Moreover, we used mortality-to-incidence ratios to predict liver cancer survival, assuming that high ratios correspond to poor access to care and poor survival, and that low ratios correspond to good access to care and good survival. Finally, we estimated prevalence as a function of incidence and survival.[23]

For both cirrhosis and liver cancer, we estimated the proportion of cases and deaths due to HBV, HCV, alcohol, and other causes (including autoimmune disease). We identified studies that reported the prevalence of these four causes among those with cirrhosis or liver cancer

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| | Deaths, thousands | YLLs, thousands | YLDs, thousands | DALYs, thousands |
|---|---|---|---|---|
| 1990 | 895 (855–937) | 31 038 (29 617–32 577) | 653 (450–892) | 31 691 (30 212–33 287) |
| 1995 | 1028 (989–1065) | 34 437 (33 145–35 837) | 697 (485–958) | 35 134 (33 816–36 524) |
| 2000 | 1149 (1111–1192) | 36 648 (35 347–38 178) | 755 (530–1038) | 37 404 (36 040–38 986) |
| 2005 | 1263 (1218–1318) | 38 648 (37 139–40 590) | 806 (566–1091) | 39 455 (37 893–41 435) |
| 2010 | 1377 (1323–1462) | 40 277 (38 433–43 333) | 859 (604–1154) | 41 137 (39 210–44 238) |
| 2013 | 1454 (1377–1539) | 41 580 (39 149–44 657) | 874 (612–1181) | 42 454 (39 927–45 580) |
| Percent change between 1990 and 2013 | 63% (52–75) | 34% (24–46) | 34% (29–40) | 34% (24–46) |

Data in parentheses are 95% uncertainty intervals. YLLs=years of life lost. YLDs=years living with disability. DALYs=disability-adjusted life-years.

***Table 1:*** **Deaths, YLLs, YLDs, and DALYs attributable to viral hepatitis, by year**

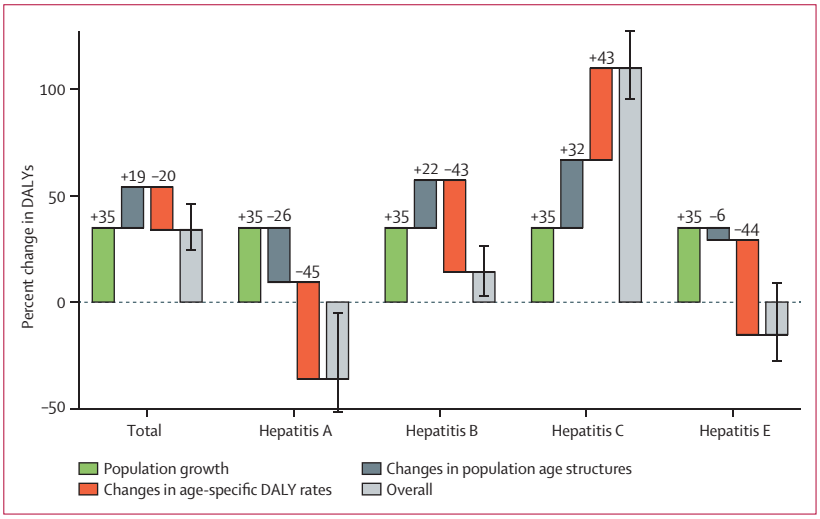


***Figure 1:*** **Decomposed drivers of global changes in DALYs attributable to viral hepatitis between 1990 and 2013, by virus and for all hepatitis viruses combined**

Error bars represent 95% uncertainty intervals. DALYs=disability-adjusted life-years.

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See Online for appendix

For the **Global Health Data Exchange** see http://ghdx.healthdata.org

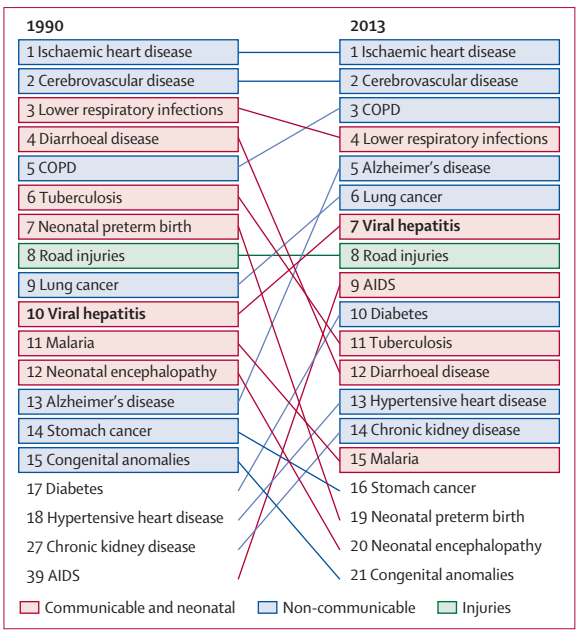


***Figure 2:*** **Leading causes of mortality and trends, 1990–2013**
COPD=chronic obstructive pulmonary disease.

and, using DisMod-MR, developed aetiological proportion models for each of the four causes of cirrhosis and liver cancer. Within each country, year, age group, and sex, we rescaled these proportions to ensure that they summed to 100%. We then multiplied our estimates of cirrhosis and liver cancer mortality and prevalence by the corresponding aetiological proportion estimates to derive cause-specific mortality and prevalence (appendix p 7).[23]

### Disability weights

Disability weights quantify the severity of a health state on a scale of zero (complete health or no disability) to one (complete disability, equivalent to death). Disability weights for GBD 2013 were derived from a pooled analysis of data from the GBD 2010 Disability Weights Measurement Study[24] and the more recent European Disability Weights Measurement Study.[25] In these two studies, researchers conducted surveys in Bangladesh, Hungary, Indonesia, Italy, the Netherlands, Peru, Sweden, Tanzania, and the USA, and an open-access web survey to obtain supplementary data.[25] For acute hepatitis, we divided symptomatic cases into three generic acute infectious disease health states: mild (disability weight 0·006), moderate (0·051), and severe (0·133).[26] The disability weight for cirrhosis was 0·178. To calculate disability due to liver cancer, the overall prevalence was divided into four sequelae: diagnosis and primary treatment (disability weight 0·288), controlled phase (0·049), metastatic phase (0·451), and terminal phase (0·540; appendix p 5).

### Aggregated ranking

GBD causes are organised within a hierarchy. Level 1 organises causes into three broad categories: communicable, maternal, neonatal, and nutritional diseases; non-communicable diseases; and injuries. Level 2 subdivides the level 1 categories into 21 groups of related conditions (eg, cancer, cirrhosis). Level 3 subdivides the level 2 groups into 163 conditions or narrow categories of conditions (eg, liver cancer, cirrhosis due to HBV, acute hepatitis); where relevant, level 3 causes may be further subdivided, and there are 119 level 4 causes (eg, liver cancer due to HBV, acute HAV). When determining the relative ranks of causes, causes within the same level of the hierarchy should be compared. Although no aggregate hepatitis group exists within the GBD hierarchy, we treated our aggregated hepatitis estimates as if they belonged to a level 3 cause, the same level as the total acute hepatitis category.[19,26]

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Between 1990 and 2013, the number of deaths worldwide attributable to viral hepatitis increased by 63% (95% UI 52–75), YLLs due to viral hepatitis increased by 34% (24–46), YLDs increased by 34% (29–40), and DALYs increased by 34% (24–46; table 1). However, when these trends were decomposed to remove the effect of demographic trends (ie, changing population sizes and age structures), the underlying age-specific rates declined between 1990 and 2013: YLL rates declined by 20% (8–30), YLD rates declined by 13% (8–18), and DALY rates declined by 20% (8–30; figure 1). No significant trend was detected in age-specific mortality rates (–4%, –14 to 8). Therefore, increases in absolute mortality and disability seem to be driven primarily by demographic changes—most notably, population growth (appendix p 10).

Together, viral hepatitis deaths from acute infection, cirrhosis, and liver cancer were the tenth (95% UI tenth to 12th) leading cause of death worldwide in 1990 and seventh (seventh to eighth) leading cause in 2013 (figure 2; appendix p 11). By contrast, the ranking of other major communicable diseases—eg, diarrhoeal disease, malaria, and tuberculosis—fell over the same time period (figure 2). Viral hepatitis ranked 22nd (95% UI 20th to 25th) among leading causes of DALYs in 1990 and 18th (16th to 20th) in 2013 (appendix p 10).

In 2013, the greatest numbers of deaths and DALYs attributable to viral hepatitis were seen in east Asia and south Asia (table 2). The greatest mortality rates were seen in Oceania, western sub-Saharan Africa, and central Asia (figure 3; appendix p 13).

When combined, HBV and HCV accounted for 96% (95% UI 94–97) of viral hepatitis-related mortality and 91% (88–93) of viral hepatitis-related DALYs in 2013

| | Deaths, thousands | YLLs, thousands | YLDs, thousands | DALYs, thousands |
|---|---|---|---|---|
| High-income Asia Pacific | 77·2 (66·8–94·1) | 1403·0 (1189·1–1767·3) | 25·0 (17·7–34·3) | 1428·0 (1211·5–1795·5) |
| Central Asia | 23·2 (21·4–25·7) | 735·7 (674·8–818·3) | 15·1 (10·6–20·5) | 750·9 (689·9–832·5) |
| East Asia | 459·7 (405·4–508·1) | 12 402·1 (10 880·7–13 856·1) | 254·9 (179·2–341·7) | 12 657·0 (11 125·1–14 139·3) |
| South Asia | 289·7 (253·4–341·5) | 10 570·3 (9 171·0–12 773·4) | 180·6 (124·4–247·7) | 10 750·9 (9336·4–12 979·3) |
| Southeast Asia | 134·4 (118·6–152·0) | 3841·7 (3338·0–4438·8) | 76·3 (53·5–103·6) | 3918·0 (3416·4–4513·1) |
| Australasia | 2·7 (2·2–3·2) | 58·8 (49·3–67·4) | 2·0 (1·4–2·8) | 60·8 (51·2–69·7) |
| Caribbean | 4·9 (4·5–5·6) | 117·9 (105·7–133·9) | 3·2 (2·2–4·4) | 121·1 (108·8–136·7) |
| Central Europe | 22·8 (20·7–24·4) | 564·6 (510·9–605·5) | 14·9 (10·5–20·2) | 579·5 (523·4–622·2) |
| Eastern Europe | 43·5 (39·0–49·6) | 1331·6 (1182·1–1530·1) | 27·4 (19·1–37·3) | 1359·0 (1207·9–1556·9) |
| Western Europe | 77·2 (69·4–84·1) | 1529·9 (1380·9–1667·6) | 40·3 (28·8–54·2) | 1570·1 (1414·2–1715·0) |
| Andean Latin America | 8·0 (6·9–9·2) | 194·8 (164·9–226·5) | 3·8 (2·6–5·3) | 198·7 (168·1–230·4) |
| Central Latin America | 32·9 (31·5–34·5) | 825·6 (784·7–869·3) | 19·0 (13·3–26·0) | 844·6 (803·1–889·7) |
| Southern Latin America | 8·8 (7·8–9·8) | 203·5 (176·2–230·2) | 4·4 (3·0–6·0) | 207·8 (180·3–235·0) |
| Tropical Latin America | 22·4 (18·5–26·8) | 605·7 (500·7–733·5) | 13·8 (9·4–18·9) | 619·5 (514·7–744·4) |
| North Africa and Middle East | 93·6 (86·2–101·8) | 2403·7 (2198·1–2645·8) | 56·4 (39·2–77·0) | 2460·2 (2251·0–2700·9) |
| High-income North America | 48·6 (40·4–57·9) | 1201·5 (1001·5–1443·0) | 26·4 (18·3–35·7) | 1227·9 (1025·2–1468·5) |
| Oceania | 2·9 (1·9–4·3) | 112·0 (72·0–168·5) | 1·4 (1·0–2·0) | 113·4 (73·2–169·9) |
| Central sub-Saharan Africa | 10·9 (9·2–12·8) | 376·0 (310·9–449·5) | 11·7 (7·9–16·0) | 387·7 (320·4–460·3) |
| Eastern sub-Saharan Africa | 31·0 (28·4–33·7) | 1023·8 (920·6–1124·8) | 39·2 (26·9–54·3) | 1063·0 (958·1–1163·9) |
| Southern sub-Saharan Africa | 4·8 (4·2–5·4) | 145·7 (126·3–167·2) | 6·9 (4·7–9·6) | 152·6 (133·1–174·6) |
| Western sub-Saharan Africa | 55·1 (48·5–62·1) | 1932·5 (1680·4–2205·3) | 51·1 (34·9–70·5) | 1983·6 (1728·7–2250·5) |

Data in parentheses are 95% uncertainty intervals. YLLs=years of life lost. YLDs=years living with disability. DALYs=disability-adjusted life-years.

***Table 2:*** **Deaths, YLLs, YLDs, and DALYs attributable to viral hepatitis in 2013, by region**

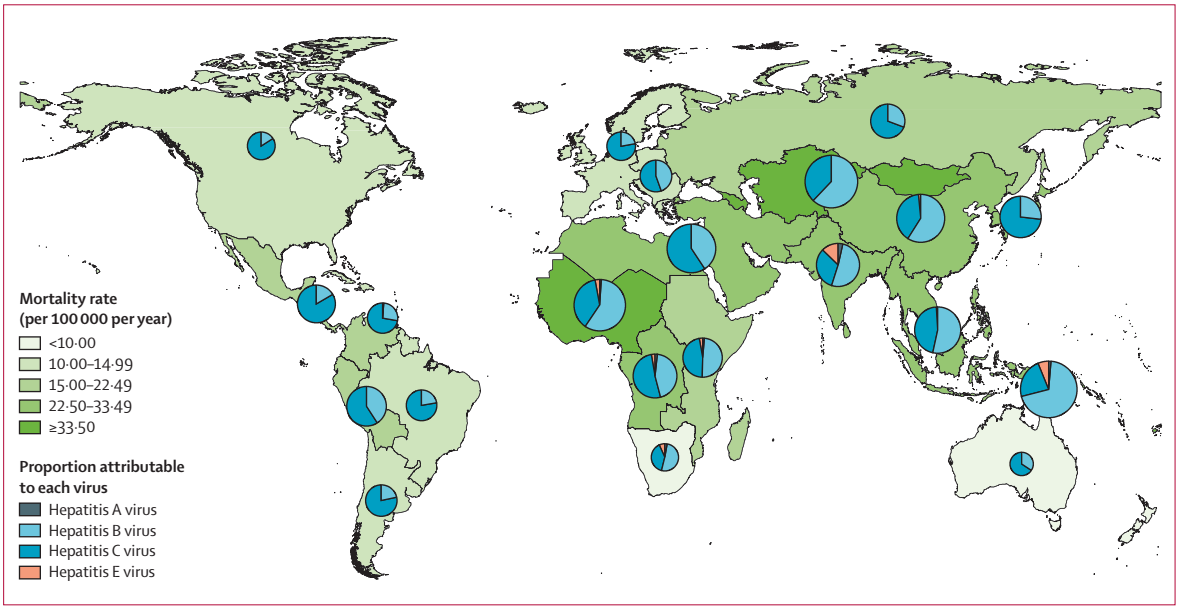


***Figure 3:*** **Map of viral hepatitis-related, age-standardised mortality rate, by GBD region**
Overlaid pie charts indicate each virus type's contribution to the total hepatitis-related mortality; the size of the pie charts are proportional to the region's hepatitis-attributable mortality rate. GBD=Global Burden of Disease.

(appendix p 11). This finding has not changed significantly since 1990, when they accounted for 92% (90–94) of mortality and 84% (80–88) of DALYs. Of the 96% of viral hepatitis-related mortality resulting from HBV and HCV in 2013, the two viruses accounted for nearly equal amounts (HBV 47% [45–49] *vs* HCV 48% [46–50]). Most mortality is attributable to liver cancer and cirrhosis due to HBV and HCV (appendix p 12). The relative burden of disease for HBV and HCV varies between and within geographical regions (figure 4).

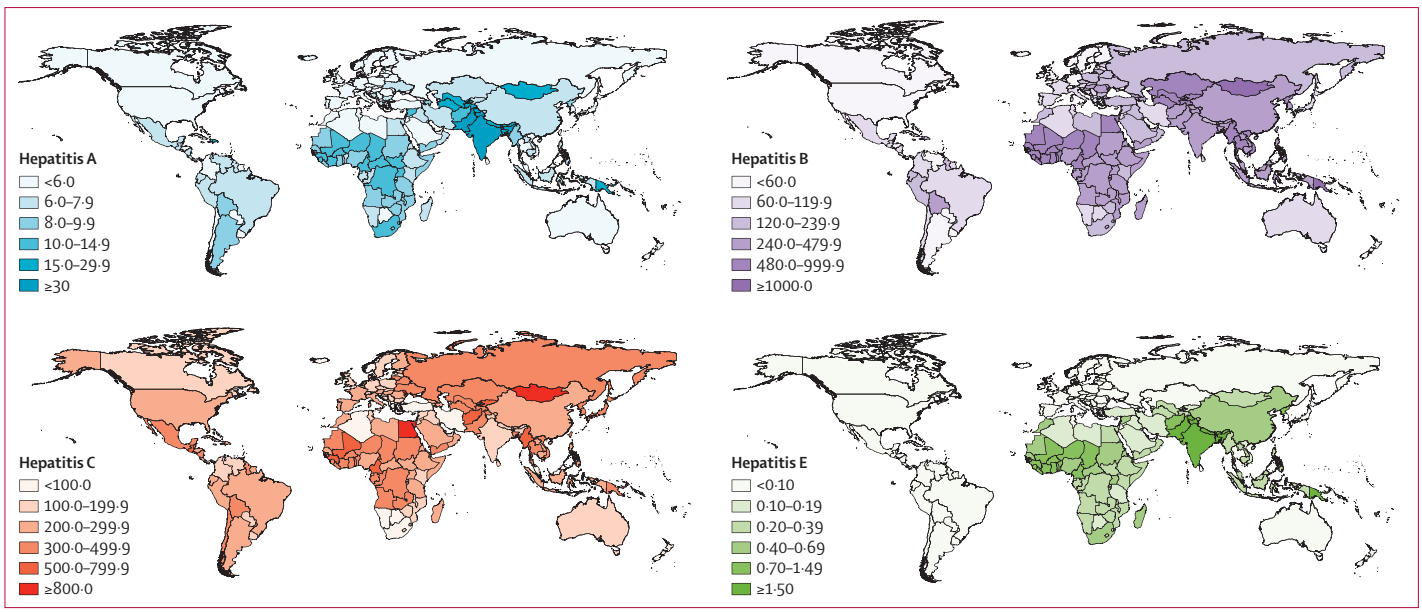


*Figure 4:* **Age-standardised disability-adjusted life-year rates (per 100 000 per year) attributable to hepatitis A, B, C, and E viruses in 2013, by country**

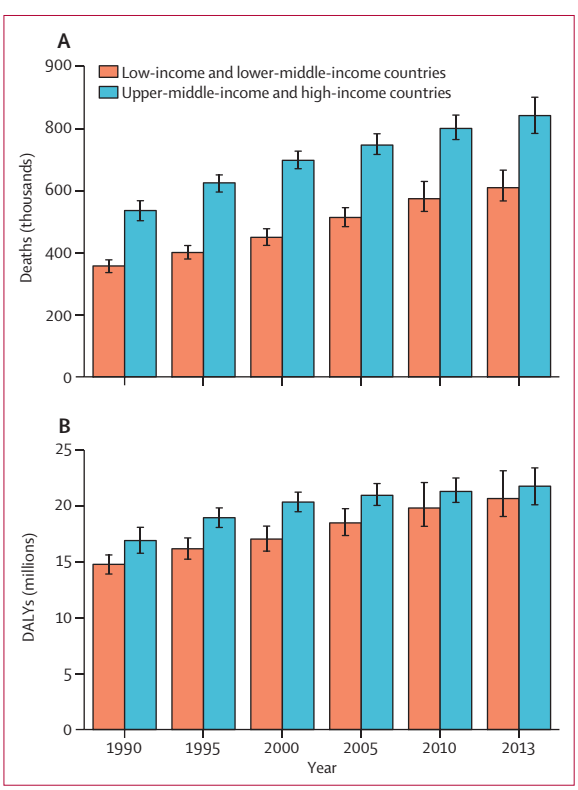


*Figure 5:* **Burden of viral hepatitis, stratified by economic status**
(A) Annual deaths and (B) DALYs of viral hepatitis. Error bars indicate 95% uncertainty intervals. DALYs=disability-adjusted life-years.

Broadly, a greater proportion of mortality in Europe, the Middle East, the Americas, and north Africa is attributed to HCV than to HBV, whereas in sub-Saharan Africa and most of Asia, the converse is true (figure 3; appendix pp 14–15). Most mortality attributed to HAV and HEV is in sub-Saharan Africa and Asia. The proportion of deaths due to HAV, HBV, and HEV has declined, whereas the proportion due to HCV has increased since 1990 (appendix p 11).

We explored the relation between the burden of viral hepatitis and economic status, stratified by low-income, lower-middle-income, upper-middle-income, and high-income countries according to World Bank Classification 2014 (figure 5; appendix p 20). In 2013, the number of deaths attributed to viral hepatitis was lower in low-income and lower-middle-income countries (0·61 million deaths, 95% UI 0·57–0·67) than in upper-middle-income and high-income countries (0·84 million deaths, 0·79–0·90). 42% (95% UI 40–45) of viral hepatitis deaths were found in low-income and lower-middle-income countries. DALYs attributed to viral hepatitis were similar in low-income and lower-middle-income countries (20·7 million, 95% UI 19·0–23·1) and in upper-middle-income and high-income countries (21·7 million, 20·1–23·1), with 49% of DALYs contributed by low-income and lower-middle-income countries. However, age-standardised rates of both death and DALYs were higher in low-income and lower-middle-income countries in each time period (appendix p 12). Viral hepatitis has consistently been ranked as a leading cause of mortality in upper-middle-income countries, but a rise in mortality in lower-middle-income countries relative to that in upper-middle-income countries (figure 5) has been associated with a narrowing in the rankings of leading cause of death by 2013 (appendix p 21).

## Discussion

To our knowledge, this study is the first attempt to formally estimate the burden of viral hepatitis using systematic data gathering and robust statistical methods. Our results show that viral hepatitis is one of the leading causes of death and disability worldwide, and causes at least as many deaths annually as tuberculosis, AIDS, or malaria. HBV and HCV account for more than 90% of viral hepatitis-related deaths and disability, and are the focus of renewed international efforts to combat viral hepatitis, including the proposed Global Strategy for 2016–21.[9]

Between 1990 and 2013, the relative importance of mortality and DALYs due to viral hepatitis has risen. This finding is by contrast with other major infectious diseases (including diarrhoeal disease, tuberculosis, and malaria); their fall in relative rankings reflects the global transition towards non-communicable diseases. Absolute numbers of deaths attributed to viral hepatitis have risen substantially by 63% and DALYs by 34% during 1990–2013. However, when we decomposed the trends, a more interesting and complex picture emerged (figure 1). HAV is the only hepatitis virus for which DALYs have declined significantly between 1990 and 2013. Some of this decline has been driven by changing population age structures, but most is due to declines in age-specific rates, most likely as a result of vaccination and improvements in water supply and sanitation. Age-specific DALY rates have declined for HBV, probably because of the effect of vaccination; however, demographic changes have countered these improvements and yielded an overall increase in DALYs. HCV is the only virus for which an increase in age-specific rates has been observed; combined with increases due to both population growth and changing age structures, DALYs for HCV have more than doubled since 1990. Finally, age-specific rates of DALYs for HEV have declined, probably because of improvements in water supply and sanitation; these improvements have been largely countered by population growth, yielding insignificant declines in DALYs for HEV.

The most notable limitations of this analysis stem from sparse data. Few large-scale population surveys of viral hepatitis seroprevalence have been done. Where no data were available, estimates were based on regional extrapolations and covariates, potentially minimising spatial heterogeneity and differences in epidemics. Whether these data gaps yield underestimation or overestimation is unclear. Similarly, establishing the proportion of cirrhosis and liver cancer due to HBV and HCV is challenging, because low amounts of data exist to inform the aetiology models: 124 datapoints from 66 unique sources for the models of the proportion of cirrhosis due to hepatitis, and 294 datapoints from 108 unique sources for the models of the proportion of liver cancer due to hepatitis. Therefore, these models rely heavily on covariates and space–time extrapolation, highlighting the need for more longitudinal studies and better ascertainment of hepatocellular carcinoma (as opposed to other liver cancers) and their causes. It is now well recognised that seroprevalence data can often overestimate the number of individuals with active chronic infection and that the absence of specific markers for acute HCV infection can lead to misclassification of chronic HCV infection as acute.

Of note, we assigned no disability due to chronic HBV or HCV between acute infection and end-stage disease. Even in the absence of cirrhosis or liver cancer, individuals with chronic HCV might have substantial morbidity, particularly neuropsychiatric symptoms.[27] Similar data for the morbidity of mild-to-moderate disease are not available from many parts of the world, but disability due to HCV is likely to be underestimated in our study, as is the potential effect of viral hepatitis (particularly HCV) on non-liver-related mortality.[28]

Viral hepatitis is unusual among leading communicable diseases because the distribution of morbidity is evenly divided between high-income and low-income settings. Biomedical advances have led to efficacious vaccines and treatments for HBV and HCV that could be delivered at scale, but it is too early to say whether treatment scale-up will be able to control transmission. However, by contrast with tuberculosis, HIV/AIDS, and malaria, mechanisms to fund these interventions in the poorest countries are largely non-existent, except for individuals who are also infected with HIV. The small proportion of global health funding targeted at viral hepatitis is disproportionate to its importance as a major cause of death and disability.[29] Our results suggest that an evolution in funding structures is required to accommodate the burden of viral hepatitis and allow effective responses in low-income and lower-middle-income countries.

#### Contributors

JDS, ADF, NKM, and GSC drafted the report and designed the analysis. JDS, ADF, SLJ, AAM, MHF, KMH, JG, STW, and DBR did the systematic review and statistical analysis. All other authors provided data, reviewed results, provided guidance on the method, reviewed the report, and provided critical feedback on the report.

#### Declaration of interests

GSC has been an investigator on trials of hepatitis C virus therapy sponsored by Boehringer Ingelheim, Gilead, Merck, and Bristol-Myers Squibb, and has acted in an advisory role to Merck, Boehringer Ingelheim, Gilead, Janssen, and WHO in relation to viral hepatitis and clinical trials unrelated to this work. NKM reports research grants from Gilead unrelated to this work and honoraria from AbbVie, Gilead, and Jannsen. JDS reports research grants from Merck unrelated to this work. All other authors declare no competing interests.

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**References**

1 Rein DB, Stevens GA, Theaker J, Wittenborn JS, Wiersma ST. The global burden of hepatitis E virus genotypes 1 and 2 in 2005. *Hepatology* 2012; **55:** 988–97.

2 Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. *Vaccine* 2010; **28:** 6653–57.

3 Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. *Vaccine* 2012; **30:** 2212–19.

4 Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology* 2013; **57:** 1333–42.

5 Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet* 2015; **386:** 1546–55.

6 Zhu F-C, Zhang J, Zhang X-F, et al. Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-controlled, phase 3 trial. *Lancet* 2010; **376:** 895–902.

7 Poordad F, Lawitz E, Kowdley KV, et al. Exploratory study of oral combination antiviral therapy for hepatitis C. *N Engl J Med* 2013; **368:** 45–53.

8 Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013; **368:** 1878–87.

9 WHO. Draft global health sector strategy on viral hepatitis, 2016–2021—the first of its kind. Geneva: World Health Organization, 2015. http://www.who.int/hepatitis/strategy2016-2021/Draft_global_health_sector_strategy_viral_hepatitis_13nov.pdf (accessed June 21, 2016).

10 Murray CJL, Ezzati M, Flaxman AD, et al. GBD 2010: design, definitions, and metrics. *Lancet* 2012; **380:** 2063–66.

11 Cooke GS, Lemoine M, Thursz M, et al. Viral hepatitis and the Global Burden of Disease: a need to regroup. *J Viral Hepat* 2013; **20:** 600–01.

12 Flaxman A, Vos T, Murray C, eds. An integrative metaregression framework for descriptive epidemiology. Seattle: University of Washington Press, 2015.

13 Armstrong GL, Bell BP. Hepatitis A virus infections in the United States: model-based estimates and implications for childhood immunization. *Pediatrics* 2002; **109:** 839–45.

14 Orland JR, Wright TL, Cooper S. Acute hepatitis C. *Hepatology* 2001; **33:** 321–27.

15 Hoofnagle JH. Hepatitis C: the clinical spectrum of disease. *Hepatology* 1997; **26:** 15S–20S.

16 Kamar N, Dalton HR, Abravanel F, Izopet J. Hepatitis E virus infection. *Clin Microbiol Rev* 2014; **27:** 116–38.

17 McMahon BJ, Alward WL, Hall DB, et al. Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. *J Infect Dis* 1985; **151:** 599–603.

18 Seeff LB. Natural history of hepatitis C. *Hepatology* 1997; **26:** 21S–28S.

19 GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; **385:** 117–71.

20 Bianco E, Stroffolini T, Spada E, et al. Case fatality rate of acute viral hepatitis in Italy: 1995–2000. An update. *Dig Liver Dis* 2003; **35:** 404–08.

21 Rein DB, Hicks KA, Wirth KE, et al. Cost-effectiveness of routine childhood vaccination for hepatitis A in the United States. *Pediatrics* 2007; **119:** e12–21.

22 Stroffolini T, Ragni P, Moiraghi A, et al. Case fatality rate of acute hepatitis in Italy: results from a 10 year surveillance. *Scand J Infect Dis* 1997; **29:** 87–89.

23 Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Dicker D, et al. The global burden of cancer 2013. *JAMA Oncol* 2015; **1:** 505–27.

24 Salomon JA. New disability weights for the global burden of disease. *Bull World Health Organ* 2010; **88:** 879.

25 Haagsma JA, Maertens de Noordhout C, Polinder S, et al. Assessing disability weights based on the responses of 30,660 people from four European countries. *Popul Health Metr* 2015; **13:** 10.

26 Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; **386:** 743–800.

27 Wright M, Grieve R, Roberts J, Main J, Thomas HC, UK Mild Hepatitis C Trial Investigators. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. *Health Technol Assess* 2006; **10:** 1–113, iii.

28 Simmons B, Saleem J, Heath K, Cooke GS, Hill A. Long-term treatment outcomes of patients infected with hepatitis C virus: a systematic review and meta-analysis of the survival benefit of achieving a sustained virological response. *Clin Infect Dis* 2015; **61:** 730–40.

29 Institute for Health Metrics and Evaluation. Financing global health 2013: transition in an age of austerity. http://www.healthdata.org/policy-report/financing-global-health-2013-transition-age-austerity (accessed Oct 12, 2015).