The Global Burden of Viral Hepatitis 1990-2013

Jeffrey D. Stanaway, PhD,[1*] Abraham D. Flaxman, PhD,[1] Mohsen Naghavi, PhD,[1] Christina Fitzmaurice, MD,[1,2] Theo Vos, PhD,[1] Ibrahim Abubakar, PhD,[3] Laith J. Abu-Raddad, PhD, [4] Reza Assadi, PhD,[5] Neeraj Bhala, DPhil,[6,7] Benjamin Cowie, PhD,[8,9] Mohammad H. Forouzanfour, PhD,[1] Justina Groeger, MD,[10] Khayriyyah Mohd Hanafiah, PhD,[11,12] Kathryn H. Jacobsen, PhD,[13] Spencer L. James, MPH,[14] Jennifer MacLachlan, MS,[9,15] Reza Malekzadeh, MD,[16] Natasha K. Martin, DPhil,[17,18] Ali A. Mokdad, MD,[19] Ali H. Mokdad, PhD,[1] Christopher J.L. Murray, DPhil,[1] Dietrich Plass, DrPH,[20] Saleem Rana, PhD,[21,22] David B. Rein, PhD,[23] Jan Hendrik Richardus, PhD,[24] Juan Sanabria, MD,[25,26] Mete Saylan, PhD,[27] Saeid Shahraz, PhD,[28] Samuel So, MBBS,[29] Vasiliy V. Vlassov, MD,[30] Elisabete Weiderpass, PhD,[31-34] Steven T. Wiersma, MD,[35] Mustafa Younis, DrPH,[36] Chuanhua Yu, PhD,[37,38] Maysaa El Sayed Zaki, MD,[39] Graham S. Cooke, DPhil,[40*]

Affiliations

[1] Institute of Health Metrics and Evaluation, University of Washington, Seattle, USA.

[2] Division of Hematology, Department of Medicine, University of Washington, Seattle, USA.

[3] Centre for Infectious Disease Epidemiology and MRC Clinical Trials Unit, University College London, Gower Street, London WC1E 6BT, UK.

[4] Infectious Disease Epidemiology Group, Weill Cornell Medical College – Qatar, Cornell University, Qatar Foundation – Education City, Office C148, P.O. Box 24144, Doha, Qatar.

[5] Mashhad University of Medical Sciences, No. 86 Ibn-Sina St., Mashhad, Iran.

[6] Queen Elizabeth Hospital Birmingham, Metchley Way, Birmingham B15 2TH, UK .

[7] University of Otago Medical School, Riddiford Way, Wellington, New Zealand 2011.

[8] WHO Collaborating Centre for Viral Hepatitis, Victorian Infectious Diseases Reference Laboratory, 792 Elizabeth St., Melbourne, VIC 3000, Australia.

[9] Doherty Institute, University of Melbourne, 792 Elizabeth St., Melbourne, VIC 3000, Australia.

[10] Johns Hopkins Bayview Medical Center, Baltimore, MD, USA.

[11] Centre for Biomedical Research, Burnet Institute, 85 Commercial Rd., 3004 Melbourne, VIC, Australia.

[12] School of Biological Sciences, Universiti Sains Malaysia, 11800, Gelugor, Penang, Malaysia.

[13] Department of Global and Community Health, George Mason University, 4400 University Drive 5B7, Fairfax, VA, 22030, USA.

[14] Geisel School of Medicine at Dartmouth, Dartmouth College, Hanover, NH, USA.

[15] WHO Collaborating Centre for Viral Hepatitis, Victorian Infectious Diseases Reference Laboratory, 792 Elizabeth St., Melbourne, VIC 3000, Australia.

[16] Digestive Disease Research Institute, Tehran University of Medical Sciences, Kargar Shomali St., Tehran 14117, Iran.

[17] Division of Global Public Health, University of California San Diego, CA, USA.

[18] School of Social and Community Medicine, University of Bristol.

[19] Department of Surgery, University of Texas Southwestern Medical Center, 5232 Harry Hines Blvd., Dallas, TX 75390, USA.

[20] Section Exposure Assessment and Environmental Health Indicators, Federal Environmental Agency, Corrensplatz 1, D-14195, Berlin, Germany.

[21] Contech School of Public Health, 54-A, HBFC Faisal Town, Lahore 54700, Pakistan.

[22] Contech International Health Consultants, 2-G Model Town, Lahore 54700, Pakistan.

[23] NORC at the University of Chicago, Illinois, USA.

[24] Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Postbus 2040, 3000 CA Rotterdam, Netherlands.

[25] Case Western Reserve University, 10000 Euclid Ave., Cleveland, OH 44106, USA.

[26] Cancer Treatment Centers of America, RFU Chicago Medical School, 3333 Greenbay Rd., North Chicago, IL 60043, USA.

[27] Novartis Turkey, Suryapi & Akel Is Merkezi, Rüzgarlibahçe, Mah., Sehit Sinan Eroglu Cad: No. 6, Kavacik-Beykoz, TR-34805 Istanbul, Turkey.

[28] Tufts Medical Center, 800 Washington St., #63, Boston, MA 02111, USA.

[29] Asian Liver Center, Stanford University School of Medicine, 300 Pasteur Dr., Palo Alto, CA 94304, USA.

[30] National Research University Higher School of Economics, PO Box 13, Moscow, 109451 Russia.

[31] Department of Medical Epidemiology and Biostatistics, Karolinska Institute, SE-171 77 Stockholm, Sweden.

[32] Department of Research, Cancer Registry of Norway, PO Box 5313 Majorstuen, N-0304 Oslo, Norway.

[33] Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, The Arctic University of Norway, Hansine Hansens veg 18, 9019 Tromsø, Norway.

[34] Genetic Epidemiology Group, Folkhälsan Research Center, Biomedicum Helsinki Haartmaninkatu 8 (PO Box 63) FI-00014 University of Helsinki, Helsinki, Finland.

[35] U.S. Centers for Disease Control and Prevention (CDC), Plot 1577 Ggaba Road, Kampala, Uganda.

[36] Jackson State University, PO Box 17037, Jackson, MS 39217, USA.

[37] Department of Epidemiology and Biostatistics, School of Public Health, Wuhan University, 185 Donghu Rd., Wuhan, Hubei, China 430071.

[38] Global Health Institute, Wuhan University, Wuchang, Wuhan, China 430072.

[39] Mansoura Faculty of Medicine, 60 Elgomhoria St., Mansoura, Egypt 35516.

[40] Division of Infectious Diseases, Imperial College, London, UK.

***corresponding authors** g.cooke@imperial.ac.uk Division of infectious Diseases, Imperial College, London W2 1NY +44 207 594 3903 and stanaway@uw.edu Institute of Health Metrics and Evaluation, 2301 Fifth Ave., Suite 600, Seattle, WA 98121, USA

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Abstract

Background:
With recent improvements in vaccines and treatments against viral hepatitis, a better understanding of the burden of viral hepatitis is needed to inform global intervention strategies. We present estimates from the Global Burden of Disease (GBD) Study of morbidity and mortality for acute viral hepatitis, and for cirrhosis and liver cancer due to viral hepatitis by age, sex and country for 1990 through 2013.

Methods:
Mortality was estimated using natural history models for acute hepatitis and GBD's cause-of-death ensemble model for cirrhosis and liver cancer. We estimated disease prevalence, and liver cancer and cirrhosis aetiologies via meta-regression. 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, viral hepatitis deaths increased from 0·90 million (95% uncertainty interval 0·86 – 0·94) to 1·45 million (1·38–1·54); YLLs increased 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 7th leading cause of death globally.

Interpretation:
Viral hepatitis is a leading cause of death and disability worldwide. Unlike most communicable diseases, between 1990 and 2013, viral hepatitis has increased in terms of both absolute burden and its relative rank.

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Background

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

Effective vaccinations for HAV and HBV have been available for over two decades, and a hepatitis E vaccine was recently licensed in China, but is not widely available.[6] More recently there have been major improvements in antiviral therapies for HBV and HCV. 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, though it is too early to have long term follow up data.[7,8] Together, these advances overcome many of the barriers to control and treatment in lower income countries and are set to be important components of a new global strategy to combat viral hepatitis.[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 time points 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]

GBD estimates the burden resulting from acute sequelae of hepatitis A, B, C and E, and chronic sequela (i.e. cirrhosis and liver cancer) of hepatitis B and C. Still, the total impact of viral hepatitis is not clearly recognised within previous GBD reports as estimates for acute disease, cirrhosis and liver cancer are categorised in separate parts of the GBD schedule of diseases and injuries.[11] Building on estimates for individual sequelae, we 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 impacts lower 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 A.10 for details of decomposition methods).

Seroprevalence models

We obtained anti-HAV IgG, Hepatitis B surface antigen (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 (http://ghdx.healthdata.org/). Age/sex/country/year-specific estimates for seroprevalence of HBsAg, anti-HCV, and anti-HEV were developed using the meta-regression tool, DisMod-MR, described elsewhere.[12] Briefly, DisMod-MR produces consistent estimates of disease incidence, prevalence, remission, and mortality using a compartmental offset log-normal non-linear mixed effects model, with hierarchical random effects on geography. The models for HBsAg, anti-HCV, and anti-HEV 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 modeling conditions for which prevalence approaches 100%. Thus, given 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 based on IgG anti-HAV seroprevalence. Specifically, we used a binomial generalized 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 (LDI) 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 rate and the estimated duration of acute infection (Appendix A.2), based on expert opinion and published literature, using a duration of four weeks for HAV and HEV, and six weeks for HBV and HCV.[14–16] Since only a subset of individuals with acute infection are actually symptomatic, and since antibody presence does not necessarily indicate a disease state that causes any disability, we divided these acute infections between 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] increasing from 1% at birth to 33% among adults for HBV,[17] and increasing from less than 1% at birth to 60% among adults for HEV (Appendix A.4).[1] For HCV, we assumed that 25% of acute infections would be symptomatic.[14,15,18]

Mortality models

Age/sex/country/year-specific estimates of cause-specific mortality were developed for cirrhosis, liver cancer, and acute viral hepatitis (including HAV, HBV, HCV and HEV) using the GBD 2013 cause-of-death ensemble model (CODEm), and fit using data on 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 5,952 site-years of mortality data, with 2,144 site-years of data for cirrhosis, 1,635 for hepatitis, and 2,173 for liver cancer. Candidate covariates for the CODEm model were selected based on expert judgement and literature review, and included seroprevalence of HAV, HBsAg, HCV, and HEV from the DisMod-MR models (described above), alcohol consumption, educational attainment, health system access, and lagged-smoothed GDP per capita, among others (Appendix A.7). Virus specific mortality data for acute hepatitis were too limited for direct modelling in CODEm. 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 CODEm tool; second, we developed separate natural history models for each subtype in which we estimated mortality as the product of incidence and case fatality. Estimates of case fatality for acute hepatitis were derived by pooling estimates from published literature and were 0·024% (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] HEV deaths were estimated following the approach described by Rein et al[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/country/year (Appendix A.5). 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 models

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

Cirrhosis and liver cancer due to hepatitis

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 etiologies among those with cirrhosis or liver cancer and, using DisMod-MR, developed etiological proportion models for each of the four etiologies for cirrhosis and liver cancer. Within each country/year/age/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 etiological proportion estimates to derive etiology-specific mortality and prevalence (Appendix A.8).[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] The two studies conducted surveys in Bangladesh, Hungary, Indonesia, Italy, the Netherlands, Peru, Sweden, Tanzania, and the USA, plus an open-access web survey to obtain supplementary data.[25] For acute hepatitis, we divided symptomatic cases between three generic acute infectious disease health states: mild, moderate and severe, with disability weights of 0·006, 0·051 and 0·133 respectively.[26] The disability weight for cirrhosis was 0·178. To calculate disability due to liver cancer, the overall prevalence was divided between four sequelae: diagnosis and primary treatment, controlled phase, metastatic phase,

and terminal phase with disability weights 0·288, 0·049, 0·451 and 0·540, respectively (Appendix A.6).

Aggregated Ranking

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

Results

Between 1990 and 2013, deaths due to viral hepatitis increased by 63% (95% uncertainty interval (UI) 52 – 75%), from 0·89 million (95% UI 0·86 – 0·94) to 1·45 million (95% UI 1·38 – 1·54); YLLs due to viral hepatitis increased 34% (95% UI 24 – 46%), from 31·0 million (29·6 – 32·6) to 41·6 million (39·1 – 44·7); YLDs increased 34% (95% UI 29 – 40%), from 0·65 million (0·45 – 0·89) to 0·87 million (0·61 – 1·18); and DALYs increased 34% (95% UI 24 – 46%) from 31·7 million (30·2 – 33·3) to 42·5 million (39·9 – 45·6). Conversely, when trends were decomposed to remove the effect of demographic trends (i.e. changing population sizes and age structures) we see that the underlying age-specific rates are declining: age-specific YLL rates have declined 20% (8 – 30%), YLD rates have declined 13% (8 – 18%), and DALY rates have declined 20% (8 – 30%)(Figure 2). No significant trend was detected in age-standardized mortality rates. Increases in absolute mortality and disability appear, therefore, to be driven primarily by demographic changes, most notably population growth (Table S4).

Together, viral hepatitis deaths from acute infection, cirrhosis and liver cancer were the 10th leading cause of death, globally, in 1990 (95% UI 10 – 12) and 7th leading cause in 2013 (95% UI 7 – 8)(Figure 1 and Table S5). This increase in rank is in contrast to other major communicable diseases such as diarrheal disease, malaria and tuberculosis which fell over the same time period (Figure 1). In 1990 viral hepatitis ranked 22nd (95% UI 20 – 25) amongst leading causes of DALYs and 18th in 2013 (95% UI 16 – 20) (Figure S3).

The greatest numbers of viral hepatitis deaths and DALYs are seen in the East and South Asia regions with 0·46 million deaths (95% UI 0·41 – 0·51) and 0·29 million deaths (95% UI 0·25 – 0·34) respectively (Table 2). The greatest mortality rates are seen in Oceania, West Africa and Central Asia (Figure 3, Table S8).

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

S6). This has not changed significantly since 1990 when they accounted for 92% (95% UI 90 – 94%) and 84% (95% UI 80 – 88%) respectively. Of the 96% of viral-hepatitis mortality resulting from HBV and HCV in 2013, the two viruses accounted for nearly equal amounts, contributing 47% (95% UI 45 – 49) and 48% (95% UI 46 – 50), respectively. The majority of mortality is driven by liver cancer and cirrhosis due to HBV and HCV, with the majority of both liver cancer and cirrhosis attributed to HCV (Table S7). The relative burden of disease for HBV and HCV varies between and within geographic regions. Broadly, a greater proportion of mortality in Europe, Middle East, The Americas and North Africa is attributed to HCV compared to HBV, whilst in Sub-Saharan Africa and most of Asia, the converse is true (Figure 3, Table S10). Most mortality attributed to HAV and HEV is within Sub-Saharan Africa and Asia. The proportion of deaths due to HAV, HBV and HEV have declined, whilst the proportion due to HCV has increased since 1990 (Table S6).

We explored the relationship between the burden of viral hepatitis and economic status (stratified by low, low-middle (LMIC), upper middle (UMIC) and high income countries according to World Bank Classification 2014 (Figure 5, Table S12). In 2013, the number of deaths attributed to viral hepatitis was somewhat lower in low/LMIC countries with 0·61 million deaths (0·57 – 0·67) compared to 0·84 million deaths in UMIC/high-income countries (0·79 – 0·90). 42% of viral hepatitis deaths were found in low and low-middle income countries. DALYs attributed to viral hepatitis were similar in low/LMIC and UMIC/high-income (20·7 million [19·0 – 23·1] compared to 21·7 million [20·1 – 23·1]) with 49% of DALYs contributed by lower income countries. However, age standardised rates of both death and DALYs were higher in low/low middle income countries in each time period (supplemental Figure 10). Viral hepatitis has consistently been ranked as a leading cause of mortality in UMIC, but a relative rise in mortality in LMIC compared to UMIC (Figure 5) has been associated with a narrowing in the rankings by 2013 (Table S13).

Discussion

To our knowledge, this 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 globally, and causes at least as many deaths annually as either tuberculosis, HIV/AIDS or malaria. HBV and HCV account for 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 2016-2021.[9]

Between 1990 and 2013, the relative importance of mortality and DALYs due to viral hepatitis has risen. This contrasts with other major infectious diseases (including diarrhoeal disease, tuberculosis and malaria) whose fall in relative rankings reflects the global transition towards non-communicable diseases. Absolute numbers of deaths and DALYs attributed to viral hepatitis have risen substantially during the period (63% and 34% respectively). However, when we decompose trends a more interesting and complex picture emerges (Figure 2). HAV is the only 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 a function of vaccination and improvements in water supply and sanitation. Age-specific rates of DALYs have declined for HBV, likely due to 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 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, likely due to improvements in water supply and sanitation; these improvements have been largely counted by population growth, yielding statistically insignificant declines in DALYs for HEV.

The most notable limitations of this analysis stem from sparse data. A limited number of large-scale population seroprevalence surveys has been carried out for viral hepatitis. Where no data were available estimates were based on regional extrapolations and covariates, potentially minimizing 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 as limited data exist to inform the aetiology models: 124 data points from 66 unique sources inform the models of the proportion of cirrhosis due to hepatitis; and 294 data points from 108 unique sources inform the models of the proportion of liver cancer due to hepatitis. These models, therefore, rely heavily on covariates and space-time extrapolation, and highlight the need for more longitudinal studies and better ascertainment of hepatocellular carcinoma (as opposed to other liver cancers), and their aetiologies. It is now well recognised that seroprevalence data can often overestimate the number of individuals with active chronic infection and a lack of specific markers for acute HCV infection can lead to misclassification of chronic HCV infection as acute.

Of note, we assigned no disability to chronic HBV or HCV between acute infection and end-stage disease. Evidence suggests that, even in the absence of cirrhosis or liver cancer, individuals with chronic HCV may have significant morbidity, particularly neuropsychiatric symptoms.[27] Similar data on the morbidity of mild-moderate disease are lacking from many parts of the world, but disability due to HCV is likely to be underestimated here as is also the potential impact of viral hepatitides (particularly HCV) on non-liver related mortality.[28]

Viral hepatitis is unusual amongst leading communicable diseases as the distribution of morbidity is evenly divided between higher and lower income settings. Both HBV and HCV have benefited from biomedical advances that have delivered efficacious vaccines and treatments that could be delivered at scale, but it is too early to say whether treatment scale up will be able to control transmission. However, in contrast to HIV, TB and malaria, mechanisms to fund these interventions in the poorest countries are largely lacking except for individuals also infected with HIV. The relatively 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 viral hepatitis and allow effective responses in low and low-middle income countries.

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Figure Legends

Figure 1: Top 15 leading causes of mortality with trends 1990-2013. Red lines connect causes with increasing ranks, blue lines connect those with decreasing ranks, and grey lines connect causes with stable ranks.

Figure 2: Decomposed drivers of global changes in hepatitis DALYs between 1990 and 2013, by virus and for all hepatitis combined. Green bars show the percent change in DALYs due to population growth, dark grey bars show the effect of changes in population age structures, red bars show the effect of changes in age-specific DALY rates, and the light grey bars show the overall percent change in DALYs between 1990 and 2013 (with 95% uncertainty intervals).

Figure 3: Map of viral hepatitis related age-standardized mortality rate, by GBD region. Overlaid pie charts indicate each subtype's contribution to the total hepatitis mortality (size of circles proportionate to regions hepatitis-attributable mortality rate).

Figure 4: Age-standardized DALY rates attributable to (a) Hepatitis A, (b) Hepatitis B, (c) Hepatitis C, and (d) Hepatitis E by country, 2013.

Figure 5: Burden of viral hepatitis stratified by income group. Left panel shows deaths (in thousands) by time period. Right panel shows DALYs (in millions).

Authors' contributions
The manuscript was drafted by JDS, ADF, NKM and GSC, all other authors provided critical feedback and edits to finalize the manuscript. The analysis was designed by JDS, ADF, NKM and GSC. Systematic review and statistical analysis was performed by JDS, ADF, SJ, AAM, MHF, KMH, JG, STW, and DBR. All other authors provided data, reviewed results, provided guidance on methodology, and reviewed the manuscript.

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Conflicts of Interest
GC has been an investigator on trials of HCV therapy sponsored by Boeringher-Ingelheim, Gilead, Merck and Bristol-Myers Squibb. GC has acted in an advisory role to Merck, Boeringher-Ingelheim, Gilead, Janssen and WHO in relation to viral hepatitis and clinical trials unrelated to this work. NKM has received research grants from Gilead unrelated to this work and has received honoraria from AbbVie, Gilead, and Jannsen. JDS has received research grants from Merck unrelated to this work.

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Ethics committee approval
There were no human subjects involved in this research.