Global Burden of Disease (GBD) for Hepatitis C

The Global Burden of Hepatitis C Working Group

Hepatitis C virus (HCV) infection is now a global public health issue. However, the global burden of disease attributable to HCV infection is unknown. The objectives of this WHO informal consultation included the following: (1) defining a strategy to estimate the global burden of disease (GBD) associated with HCV infection in terms of morbidity and mortality, (2) describing the natural history of HCV infection in terms of morbidity and mortality, and (3) identifying areas for which more research is needed. The GBD project is an attempt to examine all causes of morbidity and mortality using an approach common to all conditions. The World Health Organization (WHO) already has estimated the burden of disease associated with hepatitis B virus (HBV) infection and is now about to conduct the same analysis for HCV infection. A review has been conducted to estimate the prevalence of HCV infection by age, gender, and region. These figures can be used to estimate incidence, although there are a number of areas of uncertainty. Combined with natural history parameters, incidence estimates could be used to estimate the future burden due to current infections. However, the present model is not validated and requires calibration before it can be used. A consensus was reached over the strategies to be used to (1) estimate the current burden due to past infections and (2) estimate the future burden due to current infections. Provisional expert consensus was reached over natural history parameters and cofactors that influence them. However, systematic literature reviews and meta-analysis are preferable for obtaining estimates to be included in models. Areas deserving future research include (1) obtaining a better estimate of HCV infection prevalence by age groups, (2) characterizing the various morbidity states associated with HCV infection and their disability weights, (3) understanding the long-term natural history of HCV infection beyond 20 years after infection, and (4) estimating the prevalence (and numbers of) of HCV infection among the drug-using population worldwide. A working group was created to address unmet needs and to assist the WHO in estimating the GBD associated with HCV infection.

Keywords: *Hepatitis C virus; global burden of disease; World Health Organization; morbidity; mortality; GBD project*

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MODELING HEPATITIS C GLOBAL BURDEN OF DISEASE

A Global Perspective on Hepatitis C

Hepatitis C has become an issue of global importance. It is not only of concern to industrialized countries. In Egypt, for example, the impact of hepatitis C virus (HCV) infection exceeds that of HIV. This World Health Organization (WHO) informal consultation on the global burden of disease (GBD) caused by HCV infection was organized for two reasons:

- The WHO needs burden of disease estimates to make policy decisions.
- The world is concerned with hepatitis C and is eager for proper guidance.

In the past, the WHO estimated the prevalence of HCV infection worldwide and published the results in

the *Weekly Epidemiological Record*. However, these estimates need to be revised. In addition, preliminary, unpublished estimations of the global burden of disease have been made but need improvement.

This meeting has addressed three key areas:

1. the strategy to estimate the global burden of morbidity and mortality associated with HCV infection;
2. the natural history of HCV infection, including "healthy individuals," morbidity, and mortality; and
3. the areas for which more research is needed.

About the Global Burden of Disease

Rationale of the GBD Project

National and international health policies should be based on accurate and meaningful health information. However, much of the information collated cannot be directly translated into policy. Health data from routine statistics or epidemiological studies are often fragmented, frequently concentrate on fatal health outcomes, and may only be partially available. Studies that investigate particular conditions may exaggerate claims on mortality. This is largely a reflection of comorbidity, in which several coexisting pathologies contribute to and compete for the cause of death. Moreover, traditional statistics use a variety of different measures, which do not permit direct comparisons of the cost-effectiveness of different interventions. The GBD project addresses these problems using a single metric, the disability-adjusted life year (DALY).

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DALY is the measure used to quantify the health gap. It combines years of life lost (YLLs) and years lived with disability (YLDs) for varying degrees of severity; time itself becomes the common metric for death and disability. Years of life lost are weighted according to age (because a year of life lost does not have the same value at all ages) and discounted by 3% per year. Considering weighting and discounting, the value of an early death is reduced to approximately 75% of its original value in 10 years. GBD does not take into account the fact that life expectancy may increase over time in the future. There is not enough evidence to modify that in future projections. Japan, the country with the longest life expectancy, is being used.

GBD estimates age-specific death rates by sex using a variety of sources of data on mortality (vital registration,* surveys,† and epidemiological studies). From these, life tables can be derived using standard methods. The number of deaths abstracted from the life tables provides a "mortality envelope," which serves to limit the total number of deaths from all specific causes. GBD uses a grading system to estimate data quality and conducts uncertainty analyses to reflect this quantitatively.

Goals

The goals of the GBD project are to

- decouple evidence from advocacy,
- use both fatal and nonfatal measures of health outcomes, and
- use a single metric to estimate burden and cost-effectiveness.

Objectives

The objectives of the GBD project are to

- estimate mortality by age, sex, and regions for 130 causes of deaths and their sequelae;
- estimate other epidemiological parameters;
- evaluate risk factors; and
- project burden of disease into the future.

Classification of Outcomes

For the purpose of GBD, health outcomes are classified as follows:

1. communicable, maternal, perinatal, and nutritional diseases;

* The quality of vital registration varies from region to region. This quality is high in established market economies and the former socialist republics of Eastern Europe but low in many other places. However, the trend is toward improvement.

† Including Demographic and Health (DHS) surveys.

2. noncommunicable diseases; and
3. injuries.

This classification is used to prevent diseases from being counted twice.

Currently, hepatitis C virus infection is only counted as "acute and chronic hepatitis" (in group 1) as the data have not yet been made available to divide the chronic outcomes (hepatocellular carcinoma and chronic liver disease that are in group 2) into various causes (e.g., hepatitis B virus [HBV] infection, HCV infection, alcohol, and others). This could be revised if data are made available. However, the model ultimately needs to be built up from both ends and report on incidence and prevalence using the natural history model.

Modeling Hepatitis B from the WHO's Point of View

Methods Used

One of the main input parameters of the hepatitis B model is the prevalence of chronic infection. This decision was made because (1) no estimates of incidence were available, and (2) the majority of the burden of disease attributable to HBV infection occurs during adulthood as a consequence of chronic infection acquired early in life. Mortality and morbidity from hepatocellular carcinoma and cirrhosis were estimated among patients chronically infected (HBsAg positive). Age- and gender-specific mortality rates among chronically infected patients that were derived from Gambian studies were applied to the prevalence of HBsAg in the population by age, sex, and region. The Gambian project generated good-quality data based on extensive surveillance. The Taiwan province of China generated very similar estimates. In addition to the burden estimates for mortality associated with chronic infection, additional work is ongoing to estimate the burden associated with chronic morbidity and acute HBV infection.

Results

The GBD hepatitis B model estimates that, in 2000, there were approximately 360 million persons with chronic HBV infection, nearly 5.7 million cases of HBV-related clinical disease, and just over half a million of HBV-related deaths. This represents current burden due to past infections that should be differentiated from future burden due to current infections. Accounting for background "competing" mortality is important in the case of HBV and other chronic infections because after infection, death and disability occur later in life. This is particularly important in sub-Saharan Africa as the background HIV-related mortality is high (Figure 1) and will be increasingly important in Asia. In the absence of HIV infection, expected chronic HBV death rates in Botswana would approach that of Singapore.

In terms of mortality, hepatocellular carcinoma and cirrhosis dominate. In terms of morbidity, acute hepatitis dominates. However, this does not take into account chronic active hepatitis, and therefore morbidity may have been underestimated. The characterization of chronic morbidity in terms of annual episode incidence, duration, and level of disability is planned for the near future. The impact of cofactors of hepatocellular carcinoma, including aflatoxin, alcohol, and other viral hepatitis infection, has not been investigated but should be addressed using case control methodologies. However, it is unclear whether a better reflection of these factors would substantially improve disease burden estimates. Rather, expanding the geographical scope of research into HBV's attributable fraction in cirrhosis and hepatocellular carcinoma is likely to be more productive given the lack of information in this area.

Modeling Hepatitis B in Switzerland

In Switzerland, the global burden of HBV infection was estimated to help guide decisions in the area of immunization. In contrast to the prevalence-based approach used for the WHO global model, a decision tree approach was used based on experience with the model developed for the United States by the Centers of Disease Control and Prevention (CDC). This model could

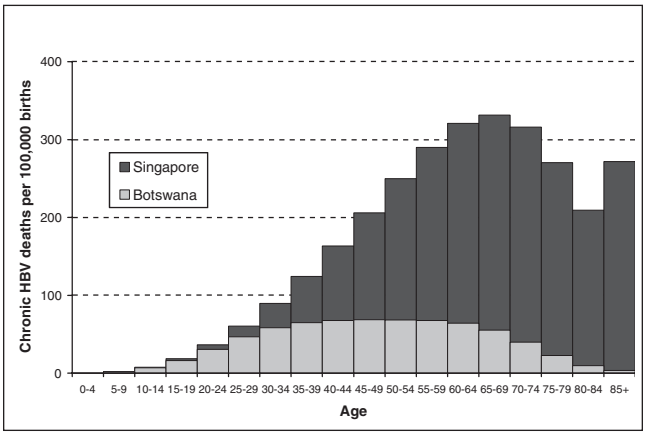

Figure 1. Background mortality does matter: Expected chronic hepatitis B virus (HBV) deaths in the 2000 birth cohort in Botswana and Singapore in the absence of hepatitis B vaccination. From Gay NJ, Edmunds WJ, Bah E, Nelson CB: Estimating the global burden of hepatitis B. *Geneva, Swizerland: World Health Organization, Department of Vaccines and Biologicals, 2001.*

be applied to hepatitis C. However, (1) data are not yet available, (2) background mortality has not been considered, and (3) DALYs have not been calculated. Besides Switzerland, the model may have been used in Liechtenstein and by private economists. For use in Asia, the model would have to be updated to take into account mutants and perinatal infection.

Global Prevalence of HCV Infection

Objective

The objective of the study was to estimate the prevalence of HCV infection by age, gender, and region and to update the estimate previously generated by WHO.

Methods

A literature search was carried out using Medline and other sources. The results of studies that included patients whose risk of HCV infection was thought to be similar to the general population were incorporated in a database. Studies were considered regardless of whether supplemental testing was conducted. Both English and non-English publications were considered. Surveys done since the late 1980s were assumed to be representative of the year 2000. First, country-specific studies were reviewed to obtain an overall estimate where possible, placing greater weight on community surveys and studies including supplemental testing. Second, gender- and age-specific prevalences were estimated. Countries lacking data were associated with other countries on the basis of epidemiologic similarities. Regional estimates were derived by weighting the country-specific estimates by overall population.

Results

Data from more than 300 studies representing all of the regions were considered in deriving estimates of the prevalence of HCV infection. Overall preliminary results suggest that the prevalence of HCV infection is approximately 2.2% worldwide. While the individual estimates from the different regions have undergone some change, the overall picture is still similar, with the WHO African region and the WHO Eastern Mediterranean region having the highest prevalence of HCV infection (Figure 2). Future work will focus on uncertainty analysis.

Discussion

Approximately one-quarter of the studies used represented community surveys, while one-third represented blood donors. No single approach was used to adjust these estimates as the mode of recruitment of blood donors differs tremendously depending on the region. However, none of the regional estimates relied exclusively on studies conducted among blood donors. In selected industrialized countries, another approach has been previously used to (1) estimate the size of the population in high-risk groups (e.g., injection drug users), (2) estimate the prevalence of HCV infection among these high-risk groups, and (3) compile these estimates to adjust the estimated prevalence in the general population. For example, this approach was considered useful in Switzerland, where community-based studies did not capture injection drug users. While this approach could work in industrialized countries where community-based studies may underestimate prevalence by not including injection drug users, it may not be useful in developing countries where unsafe medical injections are a main risk factor of infection. However, because there are emerging outbreaks of injection drug use in a number of developing and transitional countries, a mechanism to include this factor into a sensitivity analysis should be identified. The Evidence and Information for Policy (EIP) WHO cluster has estimates of the number of injection drug users by region. These figures could be used to adjust the HCV infection prevalence estimates in certain areas. Ideally, data should include estimates of both current and prior injection drug use. In the United States, for instance, most of the prevalent HCV infections were associated with former rather than current injection drug use.

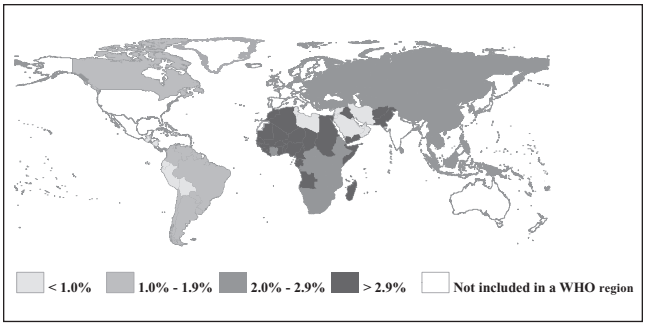

Figure 2. Estimated prevalence of hepatitis C virus (HCV) infection by region (preliminary).

Modeling the Incidence of HCV Infection

Difficulties in Estimating HCV infection Incidence

Precise estimation of the incidence of HCV infection is not possible given available data. Because direct mea-

surement of incidence is difficult, there are few published studies in which this has been attempted. Estimation of incidence from available prevalence data is the most practical approach for estimating incidence on a global scale, although results are sensitive to assumptions, particularly those regarding past trends in incidence. In addition, age-specific estimation of incidence is not possible because of the paucity of precise, age-specific data.

Impact of Past Trends on Incidence

The incidence of HCV infection is probably a function not only of age but also of time. Following the Second World War, there was an increase of use of injections, blood products, and injection drug use. However, in the past 10 years, in some industrialized countries, the incidence of new infections has decreased, presumably reflecting a decrease in percutaneous exposures. These temporal trends need to be taken into account when estimating incidence from prevalence.

Other important sources of uncertainty in the incidence model include the rate at which seropositive individuals lose detectable antibody (seroreversion) and whether persons with HCV infection have higher underlying mortality rates. The first of these, seroreversion, will cause the model to underestimate incidence if not taken into account. The second, differential mortality rates, will have the same effect. To take these issues into account, one should estimate survival functions for each of the birth cohorts that make up today's population, as well as for the subpopulation of people infected with HCV, which is not practical. There is evidence, for example, that injection drug users have higher mortality rates than their non-drug-using counterparts. In the model proposed for this project, background mortality is assumed to be the same for infected and noninfected people.

Unresolved Issues

Key unresolved issues include the following:

1. Using or not using a seroreversion rate. A 1% seroreversion rate per year may be too high. There was a 7% loss of antibodies after 25 years in a transfusion study.[1] Seroreversion may happen among nonviremic patients during the first 10 years after infection. If seroreversion does occur, then the prevalence in the population underestimates the proportion of the population ever infected.
2. Deciding on incidence trends.
3. Deciding on age-specific incidence estimates.

Natural History of HCV Infection

Revisiting the Natural History of HCV Infection

A decision tree can summarize the natural history of hepatitis C. However, an agreement needs to be reached regarding the parameters to use. A systematic review of natural history studies was conducted and published in 2001.[2] Risk of cirrhosis varied according to the type of recruitment (highest for blood transfusion and liver centers, lowest for blood donors and community studies). Overall, it was suggested that for persons who acquire HCV infection in young adulthood, less than 10% are estimated to develop cirrhosis within 20 years. While higher estimates have been used in the past in many published models, the lower estimates probably reflect reality better at a population level and should be preferred. In essence, the model is homogeneous and averages the influence of cofactors.

Uncertainties beyond 20 Years

While natural history is reasonably known for up to 20 years, we need assumptions to go beyond that point. The assumption made was linearity of progression. Linearity may be the safest assumption to date in the absence of specific data. That the disease could accelerate was hypothesized in the studies published by Poynard et al.[3] However, this interesting hypothesis was based on cross-sectional data, and there are no data to test it. Uncertainty about the long-term prognosis could be addressed using a number of approaches, including (1) population-based vital statistics data matched with incidence that we believed may have occurred in the past and (2) registry of infections based on notification of chronic cases matched with cancer registries.

The outcome of most discussions about the natural history of HCV infection is summarized later in "B. Natural History of HCV Infection, Including Morbidity and Mortality" (see p. 26).

Using DISMOD for Hepatitis C Global Burden of Disease

The DISMOD computer software was created because (1) variables are observed with different degrees of reliability (mortality > prevalence > incidence), (2) data come from different sources, and (3) other disease characteristics may be stable across populations and thus be useful for the estimation of missing parameters.

DISMOD can be used to compute incidence on the basis of prevalence, check internal consistency or estimates, or change age groups.

Limitations of DISMOD for HCV Infection

DISMOD works best for chronic diseases (e.g., asthma). It is less adapted for infectious disease such as hepatitis C because HCV infection does not produce disability in itself. It is the complication (i.e., cirrhosis) that does.

Using DISMOD for HCV Burden of Disease

We decided to use two computer software programs—DISMOD to obtain incidence and the "HCV Natural History Programme," a "homemade" MS-Access-based application—for the remainder of the modeling. The HCV natural history program includes a natural history model that is based on the parameters proposed by Dore et al[4] (up to the stage of cirrhosis) and the parameters proposed by Sagmeister et al[5] (after cirrhosis). These figures can be plugged into incidence estimates.

Results

Preliminary runs of the model suggest that 1% of cirrhosis prevalence in 2000 worldwide is caused by HCV infection. This is obviously a gross underestimation since the prevalence of HCV infection among patients with cirrhosis is much higher. We need to identify the cause of this discrepancy. Options include the following:

- Revise incidence trend scenarios. Because the incidence estimates were based on prevalence and because the incidence may have declined, thereby increasing the duration of infection, this trend scenario could have influenced the results and may explain the underestimation.
- Test the "acceleration" natural history scenario in the model.
- Calibrate the model on the basis of the fraction of chronic liver disease and hepatocellular carcinoma attributable to HCV infection in epidemiological studies.
- Introduce cofactors. However, there are few data to estimate the proportion of infected people in each cofactor category. A possibility would be to try a 100% cofactor-present case scenario as a starting point.

Models are more sophisticated in the postcirrhosis phase, but it is the pre-cirrhosis phase that is most important and that is subject to the highest source of uncertainty.

Natural History of Hepatitis C in Japan

The incidence of posttransfusion acute hepatitis C decreased in Japan in the early 1990s. However, the overall incidence of acute HCV infection has been stable, accounting for about 8% to 9% of acute hepatitis cases. Among patients dying from hepatitis C, 82% of deaths are caused by hepatocellular carcinoma. The average age of diagnosis for hepatocellular carcinoma is 62 years.[6] Persons transfused in their 20s do not develop hepatocellular carcinoma before the age of 60. Factors associated with the development of hepatocellular carcinoma include initial age (older or younger than 50 years on diagnosis), stage of fibrosis, inflammation activity, and interferon treatment. Gender is not associated with risk. Among Japanese patients with hepatocellular carcinoma associated with HCV infection, 80% have cirrhosis. The incidence of hepatocellular carcinoma from all causes increased from less than 10,000 in 1958 to more than 30,000 in 1994, with the highest increase of incidence among persons between 60 and 69 years of age. The Japanese data differ from the experience in the rest of the world.[1,7,8] This could suggest that ethnicity is a cofactor that explains the high rate of hepatocellular carcinoma among Japanese. However, there could be other factors of importance, including environmental ones.

DISCUSSIONS ON PARAMETRIC DECISIONS

A. Strategy to Estimate the Global Burden of Morbidity and Mortality Associated with HCV Infection

Two different issues need to be distinguished: the burden of disease in 2000 due to past HCV infection and the future burden of disease due to HCV infections contracted in 2000.

The Burden of Disease in 2000 Due to Past HCV Infections

The proposed approach includes the following:

1. Obtain the overall number of deaths from chronic liver disease and hepatocellular carcinoma in 2000 from the GBD.
2. Estimate the prevalence of HCV infection among chronic liver disease and hepatocellular carcinoma in 2000 by age, gender, and region.

3. Estimate the prevalence of HCV infection in 2000 by age, gender, and GBD region.
4. Estimate the fraction of chronic liver disease and hepatocellular carcinoma attributable to HCV infection on the basis of numbers 2 and 3 and on the basis of available attributable fraction studies.
5. Add to the mortality estimate a morbidity estimate based on the assumption that before dying, each patient has an average number of years alive with decompensated cirrhosis or hepatocellular carcinoma.*

Mortality and morbidity associated with acute hepatitis are considered negligible when compared to the burden associated with the chronic outcomes.

The Future Burden of Disease Due to HCV Infections in 2000

The proposed approach includes the following:

1. Estimate the prevalence of HCV infection in 2000 by age, gender, country, and GBD region.
2. Model the incidence of HCV infection in 2000 by age, gender, country, and GBD region on the basis of prevalence.†
3. Estimate the future morbidity and mortality associated with the natural history of HCV infections acquired in 2000.
4. Include prevalence, incidence, natural history parameters, and background mortality into a DISMOD model to ensure internal consistency and estimate future mortality and morbidity in DALYs due to HCV infections in 2000.

B. Natural History of HCV Infection, Including Morbidity and Mortality

All these parameters are derived by experts using established methods:

Proportion of Infected Persons Who Develop Acute Hepatitis with Jaundice‡

Estimate	25%[9,10,§]

Proportion of Infected Persons Who Develop Chronic Infection (RNA Positive)

Estimate	75%[11]
Uncertainty	50%-85%

This value tends to be lower among younger people and higher among older people.

Proportion of Chronically Infected Persons Who Develop Cirrhosis ~20 Years after Infection

Good evidence is available to document this parameter. A number of studies suggest that this parameter is age dependent:

For persons infected younger than age 40 years	
Estimate	5%[2]
For persons infected age 40 years or older	
Estimate	20%[12]

Proportion of Chronically Infected Persons Who Develop Cirrhosis ~40 Years after Infection

In contrast to the estimate for the two first decades, little evidence is currently available to document the natural history after the first two decades. Thus, this parameter is somewhat speculative. Expert consensus suggests that this parameter is age dependent:

For persons infected younger than age 40 years	
Estimate	20%
Uncertainty	10%-30%
For persons infected age 40 years or older	
Estimate	40%
Uncertainty	30%-50%

The effect of age at infection on the disease progression beyond 20 years is unknown. Assuming a linear inference to project the risk of progression to cirrhosis after 20 years implies that only age at infection matters. Under an alternative scenario, it is possible that the fibrosis progression in someone infected younger than age 40 years could accelerate as that person ages and reaches an age group for which progression to cirrhosis after 20 years of infection is higher.

* Use progression rates from transplantation lists to cross-check/validate progression rates from the natural history model.

† Incidence estimates are not needed to estimate the current burden due to past infections that will appear in the next World Health Report. However, incidence is needed for the Global Burden of Disease (GBD) 2000 study report that will come out in 2003 and for the estimation of the future burden due to current infections.

‡ Chronic and acute hepatitis C may need to be redefined. The traditional 6-month cutoff time may be outdated.

§ The death to case ratio is close to 0%.

Annual Rate of Hepatocellular Carcinoma among Patients with Cirrhosis

Estimate	1.6%[12-15]
Uncertainty	1.5%-2.5%

Japan and the Taiwan province of China fall outside this range with a rate of > 7%.

Annual Death Rate among Patients with Hepatocellular Carcinoma

A number of studies suggest that this parameter depends on access to treatment:

In industrialized countries	
Estimate	80%[16,17]
In developing countries	
Estimate	90%

The annual mortality rate of patients with HCV in Japan is significantly lower (~10%).[8,18-20]

Annual Rate of Decompensation among Patients with Cirrhosis

Estimate	4%[12,13]

Annual Death Rate among Patients with Decompensated Cirrhosis

A number of studies suggest that this parameter depends on access to treatment:

In industrialized countries	
Estimate	15%
In developing countries	
Estimate	30%

Factors that May Affect the Natural History of HCV Infection

Consistently normal ALT levels. Consistently normal alanine aminotransferase (ALT) levels are associated with slower fibrosis progression.

Steatohepatitis. Limited evidence suggests that steatohepatitis may affect fibrosis progression. Steatohepatitis, rather than obesity, seems to be the important cofactor. However, one intervention study from Brisbane, Australia, suggests that reducing weight reduces fibrosis progression.[21-24]

HIV coinfection. The influence of HIV infection depends on CD4 count. The relative risk for the development of cirrhosis among HIV and HCV coinfected patients is around two.[25,26]

HBV coinfection (HBsAg). Chronic HBV/HCV coinfection (HBsAg and anti-HCV positive) is uncommon globally, although it may be emerging in China. Coinfected patients have a higher risk of hepatocellular carcinoma than those who are only infected with one virus. However, it is unclear whether this high risk reflects a combined effect of the two viruses in the absence of interaction or some synergistic effect. The anti-HBc alone/anti-HCV serological profile is common. Some evidence suggests that the presence of anti-HBc alone might increase the risk of hepatocellular carcinoma among patients with chronic HCV infection.[27]

Alcohol intake. Intake of more than 50 g alcohol/day accelerates progression to cirrhosis with a relative risk of about three.[28,29]

Therapy. Globally, the proportion of viremic patients who undergo therapy is low, industrialized countries included. In Australia, for example, less than 10,000 people have been treated, while estimates suggest that there are 170,000 people infected. At the present time, effective treatment is not administered to all patients (e.g., in correctional facilities, developing countries). In addition, the proportion of viremic patients who will clear infection under treatment is variable, although improvements have been made for all genotypes, especially for genotypes 2 and 3. Sustained virological response is associated with improvement in necro-inflammatory lesions and fibrosis, but the effect on overall survival is still unclear. Thus, the impact of therapy is unlikely to affect the natural history of HCV infection at the population level at the present time. However, this analysis should be revised if improved treatment protocols become available and better therapy coverage is achieved.

Smoking. Preliminary evidence suggests that smoking may influence the development of hepatocellular carcinoma.

Factors that Probably Do Not Affect the Natural History of HCV Infection

Viral load. Evidence suggests that in general, viral load does not influence disease severity or progression.

Genotypes. Most studies suggest that in general, genotypes do not influence disease severity or progression.

C. Areas that Need Further Research

To better estimate the global burden associated with HCV infection, more research is needed in the following areas.

Estimates of HCV Prevalence

The quality and coverage of population-based estimates of HCV prevalence should be improved. The two critical elements for survey quality are (1) use of a representative sample and (2) use of accurate diagnostic tests. Because age-specific estimates of prevalence are important to estimate incidence trends and burden of disease, these surveys should attempt to estimate the prevalence of infection according to age. Stratification by gender should also be done.

Morbidity

Morbidity associated with chronic liver disease must be better characterized so that disability weights can be applied. This will allow a more precise estimation of DALYs. In that respect, the histological lesion of cirrhosis must be differentiated from (1) the disease that results from decompensated cirrhosis and (2) chronic hepatitis and/or chronic infection. The Australian system could be used as a basis for classifying health states of chronic hepatitis and its consequences (see Table I). In industrialized countries, knowledge of one's infection status is a major determinant of altered quality of life due to the uncertain progression of the disease and the increased anxiety caused by this uncertainty. Treatment may also need to be addressed. GBD needs a qualitative description of the range of potential symptoms, from severe to mild, that a patient may experience in one of the health states rather than a quantified estimate of disability. These figures will be useful to hepatitis B burden, too. Extrahepatic manifestations of HCV infection will not be addressed as they are uncommon (although the association between HCV infection and non-Hodgkin lymphoma needs confirmation by further studies to define the presence or absence of a causal relationship).

Natural History Parameters

Natural history parameters should be estimated using a systematic literature review and meta-analyses. In addition, research needs to better describe (1) the risk of fibrosis progression beyond 20 years, (2) the risk of fibrosis progression in developing countries, (3) spontaneous clearance of hepatitis C virus infection, and (4) the patients who do or do not progress to cirrhosis (e.g., normal aminotransferase levels, gender, ethnicity,* obesity, toxins, environmental factors).

Table I Health States Used for Hepatitis C Virus Infection by the National Centre in HIV Epidemiology and Clinical Research of Australia

Mild, chronic hepatitis, undiagnosed
Mild, chronic hepatitis, diagnosed
Moderate, chronic hepatitis, undiagnosed
Moderate, chronic hepatitis, diagnosed
Compensated cirrhosis, undiagnosed
Compensated cirrhosis, diagnosed
Liver failure
Hepatocellular carcinoma

HCV Infection among Injection Drug Users

The prevalence of HCV infection should also be estimated when estimating the size of the population of injection drug users and the prevalence of HIV infection among them.

CONCLUSIONS

The WHO needs burden of disease estimates to make policy decisions. A working group was created to address unmet needs and assist the WHO in estimating the global burden of disease associated with HCV infection. This meeting has addressed the strategy that will be used to estimate the global burden of morbidity and mortality associated with HCV infection and has tried to define the parameters that will be used for the natural history of HCV infection, including morbidity and mortality in the model. Areas for which more research is needed to improve modeling have also been defined.

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* In the United States, there is a difference between African Americans and Caucasians. However, there are no data regarding Africans living in Africa. Genotype could be a cofactor. There is no information regarding Australian Aborigines.

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