Global epidemiology of hepatitis C virus infection

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Hepatitis C virus (HCV) is a major cause of liver disease worldwide and a potential cause of substantial morbidity and mortality in the future. The complexity and uncertainty related to the geographic distribution of HCV infection and chronic hepatitis C, determination of its associated risk factors, and evaluation of cofactors that accelerate its progression, underscore the difficulties in global prevention and control of HCV. Because there is no vaccine and no post-exposure prophylaxis for HCV, the focus of primary prevention efforts should be safer blood supply in the developing world, safe injection practices in health care and other settings, and decreasing the number of people who initiate injection drug use.

Introduction
Since its discovery in 1989, hepatitis C virus (HCV) has been recognised as a major cause of chronic liver disease worldwide. The most recent WHO estimate of the prevalence of HCV infection is 2%, representing 123 million people. HCV is the leading cause of liver transplantation in developed countries, and the most common chronic bloodborne infection in the USA.

Prevalence
Most descriptions of global HCV epidemiology rely heavily upon HCV seroprevalence studies. These studies are typically cross-sectional in design and are done in select populations—eg, blood donors or patients with chronic liver disease—which are not representative of the community or region in which they reside. Population-based studies representative of an entire community are far more useful, but this kind of study is not feasible in most parts of the world.

Nonetheless, for several years WHO has reported data on the worldwide prevalence of HCV infection, based on both published studies and submitted data (figure). Although HCV is endemic worldwide, there is a large degree of geographic variability in its distribution. Countries with the highest reported prevalence rates are located in Africa and Asia; areas with lower prevalence include the industrialised nations in North America, northern and western Europe, and Australia. Populous nations in the developed world with relatively low rates of HCV seroprevalence include Germany (0–6%),1 Canada (0–8%),1 France (1–1%),1 and Australia (1–1%).15,16 Low, but slightly higher seroprevalence rates have been reported in the USA (1–8%),1 Japan (1.5–2–3%),1,16 and Italy (2–2%).11

There is a wide range of prevalence estimates among developing countries, and generally less data available to validate assumptions about the burden of disease than in the developed world. This range in prevalence is reflected in reviewing the estimates from developing countries that are among the world’s most populous nations (table).17 China, whose citizens account for one-fifth of the world’s population, has a reported seroprevalence of 3–2%.18 In India, which holds an additional one-fifth of the world’s population, one community-based survey reported an overall rate of 0.9%.19 Indonesia’s rate is 2.1%, but is based on serosurveys of voluntary blood donors.14 More thorough data exist on the seroprevalence in Pakistan, where most reported rates range between 2.4% and 6.5%.16,18–20 Egypt, with an estimated population of 73 million,21 has the highest reported seroprevalence rate, 22%.

Incidence and trends in HCV infection
Although HCV infection has both acute and chronic forms, most of the morbidity associated with infection is realised through the development of chronic liver disease in a subset of infected people years after initial acquisition of the infection. Thus, a major determinant of the future burden of disease is the past and present incidence of infection.22 However, establishing the incidence of HCV infection is difficult because most infections are initially asymptomatic and available assays do not distinguish acute from chronic or resolved infection. Acute disease reporting systems can underestimate the incidence of HCV infection even in countries with well-established surveillance systems.24

Because the direct measurement of HCV infection incidence is impractical, researchers have relied upon mathematical models to infer trends in incidence. These undertakings have occurred primarily in developed countries where population-based age-specific seroprevalence data are available, and rely on the assumption that current prevalence reflects the cumulative risk of acquiring infection.

In the USA, the Centers for Disease Control and Prevention (CDC) has modelled trends in HCV incidence using age-specific reported cases of acute disease and data from a cross-sectional national survey done from 1988 to 1994 that provided nationally representative seroprevalence estimates.23 This model revealed a period of low incidence (0–44 per 100 000) before 1965, a transitional period of increasing incidence between 1965 and 1980, and a period of high incidence in the 1980s (100–200 per 100 000).25 A model of HCV burden in France, which used death rates from hepatocellular carcinoma in addition to cross-sectional seroprevalence studies to estimate past incidence, showed a similar trend of increasing incidence through the 1980s.26

An alternate approach to modelling disease burden in Australia showed a steady increase in new HCV
infections in that country from 1961 to 2001. By contrast, the incidence of HCV infection in the USA dropped sharply and steadily through the 1990s, based on data from the CDC’s Sentinel Counties Study. The rate of new HCV infections also declined in Italy in the 1990s according to analysis of acute disease reporting data. Differences in 1990s incidence trends notwithstanding, all published models predict that the incidence of HCV-related sequelae will rise in their respective countries in the coming decades.

Disease transmission patterns

The risk factors most frequently cited as accounting for the bulk of HCV transmission worldwide are blood transfusions from unscreened donors, injection drug use, unsafe therapeutic injections, and other health-care-related procedures. Most developed countries have accumulated evidence that the predominant source of new HCV infections within their borders over the past few decades is injection drug use. In the developing world, unsafe therapeutic injections and transfusions are likely to be the major modes of transmission, especially in countries where age-specific seroprevalence rates suggest ongoing increased risk of HCV infection. In developed countries with high seroprevalence in older age groups, unsafe therapeutic injections probably had a substantial role in HCV transmission 30–50 years ago, and may persist as an important cause of transmission in isolated, hyperendemic areas.

Injection drug use

Injection drug use is the primary mode of transmission for HCV infection in the developed world. In countries such as the USA and Australia, where the highest seroprevalence is among middle-aged people, injection drug use has been the dominant mode of transmission for more than 30 years, and accounts for 68% and 80% of current infections, respectively. The prevalence of HCV infection among long-term injection drug users is high—64–94% among those with a duration of injecting of 6 years or more. HCV infection is thought to occur rapidly after initiating injecting behaviour, based on a seroprevalence of 65% observed in the late 1980s among injection drug users with less than 1 year of injecting. More recent studies among young injection drug users with 5 years or fewer of injecting have reported HCV seroprevalence rates of 20–46%. Fewer sharing partners are necessary to sustain HCV transmission than are necessary for other bloodborne viruses, and indirect drug sharing and preparation practices—eg, backloading (injecting with a syringe filled with drugs that were first mixed or measured in someone else’s syringe), and sharing cotton, cooker (containers used to mix and heat drugs),

Figure: Estimated prevalence of HCV infection by WHO region
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and rinse water—have been associated with HCV transmission.46 Several European countries have also identified injection drug use as the dominant risk factor for HCV infection within their borders. In Norway, 67% of prevalent cases of HCV infection reported a history of injection drug use.41 In Italy, injection drug use was the most commonly reported risk factor among incident cases of acute hepatitis C from 1994 to 1996, and was reported by 60% of patients aged 15–24 years.42 In England and Wales, injection drug use was the most commonly reported risk factor for people with positive antibody to HCV (anti-HCV) results tested at seven public-health laboratories over a 3 month period in 1997.43 Among anti-HCV-positive voluntary blood donors in France, the most commonly reported risk factor for HCV infection was injection drug use.44 Very little data exist regarding the prevalence of injection drug use and its contribution to HCV transmission in the developing world.

Unsafe therapeutic injections

In the developed world, the relative contribution of health-care-related transmission of HCV infection to overall HCV infection transmission is difficult to quantify, but likely small, despite numerous recent outbreaks stemming from lapses in aseptic techniques and infection control practices.45–48 However, in many developing countries, supplies of sterile syringes may be inadequate or non-existent, non-professionals often give injections outside the medical setting, and injections are often given to deliver medications that could otherwise be delivered by the oral route.49 In this environment people may receive multiple contaminated injections over the course of a lifetime, incurring a substantial cumulative risk of HCV infection.

Contaminated injection equipment appears to be the major risk factor for HCV infection in several countries, including several of the most populous nations in the world. In Egypt, the country with the highest reported seroprevalence in the world, transmission has been attributed to contaminated glass syringes used in nationwide schistosomiasis treatment campaigns from 1960 to 1987.50 In India, seroprevalence of HCV infection among patients receiving multiple injections to treat kala-azar was 31·1%—well above the seroprevalence among hospitalised and community controls.51 Two 2003 studies among populations in different regions of India found substantial associations between prevalent HCV infection and frequent visits to “freelance” or unlicensed practitioners of medicine, as well as a history of therapeutic injections using reusable syringes.15,52 Similarly, a case control study in a community in Pakistan found that HCV-infected cases were more likely to report five or more injections per year from a health-care provider in the past 10 years than were controls.53 In Taiwan, a study involving consecutive anti-HCV-positive patients at a medical practice in a rural agricultural community showed that anti-HCV-positive patients were substantially more likely to report receiving frequent medical injections (six injections per year for the past 2 years) and visiting “freelance” practitioners (vs doctors, pharmacists, and non-medical staff under physician supervision) than were consecutive anti-HCV-negative patient controls from the same practice.54 Therapeutic injections were similarly associated with HCV infection in prevalence studies among both paediatric and elderly Taiwanese populations.55,56

Prompted by evidence for ongoing transmission of HCV and other bloodborne viruses via unsafe therapeutic injection practices, WHO has coordinated the Safe Injection Global Network (SIGN), a coalition of governments, international health agencies, corporations, and individuals that advocate for safer injection practices worldwide.57 WHO has sponsored assessments of injection practices in countries suspected of having excessive health-care-related transmission of bloodborne viruses.15 WHO models estimate that unsafe injections accounted for 2 million new HCV infections in 2000.58 As part of the 2000 update of WHO’s global burden of disease study,19 WHO and collaborating epidemiologists estimated the global burden of disease attributable to contaminated injections in the health-care setting.60 They found the highest reported rates of needle reuse in the middle east, southeast Asia, and the western Pacific. In most countries in these areas, studies with the power to examine potential associations between needle reuse and prevalent HCV infection have not been done.

Blood transfusion

Blood transfusion is a highly effective means of transmitting HCV infection. In most of the developed world, numerous measures over the past four decades have resulted in progressive reductions in the risk of transfusion-transmitted HCV infection. These measures include adoption of an all-volunteer donor system, screening of blood donations with surrogate laboratory tests for liver disease (eg, alanine aminotransferase), screening of potential donors based upon answers to questions related to HIV risk factors, anti-HCV testing, and HCV nucleic acid testing. Blood is now so safe in

<table>
<thead>
<tr>
<th>Country</th>
<th>Estimated 2004 total population (millions)</th>
<th>Estimated HCV seroprevalence (%)</th>
<th>Population studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>1300</td>
<td>3·2</td>
<td>Nationally representative sample (n=68 000)</td>
</tr>
<tr>
<td>India</td>
<td>1087</td>
<td>0·9</td>
<td>Community-based, West Bengal (n=4 1579)</td>
</tr>
<tr>
<td>USA</td>
<td>294</td>
<td>1·1</td>
<td>Nationally representative sample (n=21 214)</td>
</tr>
<tr>
<td>Indonesia</td>
<td>219</td>
<td>2·1</td>
<td>Volunteer blood donors (n=7572)</td>
</tr>
<tr>
<td>Brazil</td>
<td>179</td>
<td>1·3</td>
<td>Volunteer blood donors (n=46 414)</td>
</tr>
<tr>
<td>Pakistan</td>
<td>159</td>
<td>4·0</td>
<td>Volunteer blood donors (n=103 858)</td>
</tr>
</tbody>
</table>

Table: Reported HCV infection prevalence in the six most populous nations in the world
many developed countries that classic methods to measure risk are no longer sensitive enough to provide meaningful estimates or document transfusion-related transmission events.65

The largest reductions in the incidence of transfusion-transmitted HCV infection have coincided with adoption of an all-volunteer donor system. In the USA, a more than threefold drop in the incidence of post-transfusion non-A, non-B hepatitis was observed in one veterans’ hospital after the proportion of paid donor blood used for transfusions was reduced from 91% to 4%.66 Because most blood donations in the developing world do not come from voluntary, non-remunerated donors,64,65 transfusion is probably a major source of HCV transmission throughout the developing world, much as it was in the developed world decades ago. The obstacles to creation of a nationwide system of all-volunteer blood donors in the developing world are complex and vary widely. The widespread use of paid donor blood in China has been ascribed to cultural beliefs incompatible with blood donation and inadequate efforts to recruit volunteer blood donors.65 In India, some observers have suggested that problems with regulatory oversight of the nation’s blood transfusion service led to insufficient use of volunteer-donated blood.66 In Kenya, government hospitals outside Nairobi are responsible for their own blood donor recruitment, blood collection, and testing; budget shortfalls commonly lead to the use of family/replacement donors.67 A study of blood banking practices in countries throughout North and South America suggested a correlation between per capita gross national product (GNP) and percentage of blood donations coming from voluntary, non-remunerated donors. Of 28 countries with per capita GNP less than US$5000, only Cuba had greater than 90% of its blood donations from voluntary, non-remunerated donors.68

Most countries in the developing world do not screen blood donations for the presence of HCV. WHO’s Global Database on Blood Safety estimates that 43% of donated blood in the developing world is not screened adequately for transfusion-transmitted infections, including HCV.64 A review of transfusion safety in 12 Latin American countries found that half screened all blood products for HCV.64 In India, HCV screening of blood products is mandated by law but not usually done due to financial constraints.64 In New Delhi, among 182 anti-HCV-negative hospitalised patients studied prospectively following a blood transfusion, HCV infection developed in 5–4%.65 In Ghana, one in 2578 donations is estimated to contain HCV.71

Other sources of HCV transmission

Transmission of HCV infection through occupational, perinatal, and sexual exposures occurs with much less efficiency compared with transmission through large or repeated percutaneous exposures. Thus, occupational, perinatal, and sexual transmission are unlikely to be major sources of new HCV infections, regardless of the population or geographic area. Occupational transmission of HCV infection is largely confined to health-care workers who have sustained a contaminated needlestick injury, and observed attack rates under these circumstances are as low as 0.3%.61,72,73 Acquisition of HCV infection through perinatal transmission is estimated to occur in 2.7–8.4% of infants born to HCV-infected mothers, and a higher proportion of infants born to HIV/HCV coinfected mothers.74–77 Sex with an infected partner and with multiple partners have been identified as risk factors for HCV transmission,78 but sexual transmission of HCV is far less efficient than that of other sexually transmitted viruses. Among people in long-term monogamous relationships in particular, the risk of sexual transmission of HCV is extremely low.79,80 There are no published data sufficient to show whether specific sexually transmitted coinfections or particular sexual practices increase the likelihood of sexual transmission of HCV.

Because of the wide variety of human activities that involve the potential for percutaneous exposure to blood or blood-derived body fluids, there are many biologically plausible modes of transmission besides those with clearly demonstrated epidemiological associations with infection. These modes of transmission include cosmetic procedures and religious or cultural practices such as tattooing, body-piercing, commercial barbering, ritual scarification, circumcision, acupuncture, and cupping.82,83 A community-based cross-sectional prevalence study among blood donors in the UK and Australia found significant associations between anti-HCV seropositivity and a history of tattooing (p<0.00001), but not with ear piercing or acupuncture.84 A community-based cross-sectional seroprevalence study in Taiwan found a significant association with acupuncture (p<0.05), but not with tattooing.85

Epidemiology of disease-accelerating cofactors among HCV-infected people

Several cofactors have been associated with accelerated progression of hepatic fibrosis among those infected with HCV, or with increased incidence of HCV-related complications of chronic liver disease and hepatocellular carcinoma (HCC). These cofactors are male sex, older age at acquisition of HCV infection, obesity, HIV coinfection, hepatitis B virus (HBV) coinfection, and alcohol consumption. Because the future burden of
HCV-related complications may be altered substantially by the relative presence or absence of these cofactors among HCV-infected people, those cofactors that are modifiable through public-health prevention programmes—ie, HIV, HBV, and alcohol consumption—are of particular interest.

**HIV coinfection**

The accumulated evidence suggests that HCV behaves like an opportunistic infection in people with HIV infection. In observations made before the widespread introduction of highly active antiretroviral therapy (HAART) in the developed world, HIV coinfection was associated with accelerated progression of liver disease and decreased survival among HCV-infected individuals.15–47 There is less consensus regarding the effect of HCV on the natural history of HIV infection. Some studies have concluded that HCV accelerates clinical progression of HIV infection,43,45 while a recent study among an urban US HIV-infected population found that the presence of HCV coinfection did not increase the risk of death, accelerate the development of AIDS, or alter the immunological response to HAART.39

Although use of HAART in coinfected patients does not typically reduce the HCV viral load, it has been shown in an observational study among primarily haemophiliac HIV-positive patients to decrease mortality from HCV-related chronic liver disease.37 This finding is supported by observed delays in the progression of liver fibrosis among coinfected patients on HAART compared with untreated coinfected patients.32 Despite HAART’s beneficial effects on coinfected patients, chronic liver disease has emerged as a major cause of mortality among HIV-infected patients on HAART.31–35 HCV infection has also been identified as a risk factor for drug-related hepatotoxicity among HIV-infected patients on HAART—an important consideration while antiretrovirals are made available in the developing world.36,37

Population-based data on the prevalence of HIV/HCV coinfection are largely unavailable. Based on seroprevalence data from large clinical trials involving geographically diverse groups of HIV-positive adults, estimates of the prevalence of coinfection in HIV-infected people in the USA and Europe have ranged from 16% to 33%.48,49 In HIV-positive cohorts with a single predominant risk factor for acquiring HIV, the proportion coinfected with HCV depends largely on the primary HIV risk factor. For example, in studies of HIV-positive haemophiliacs, almost all are coinfected with HCV.100,101 Among HIV-positive people with a history of injection drug use, the proportion coinfected is almost as large. Observations among urban injection drug users found coinfection prevalence rates of 84% and 88%.102,103 Among HIV-positive men in developed countries whose primary HIV risk factor is sex with other men, published HCV seroprevalence rates are much lower (3·7–6·6%).104,105

In the developing world, there are less data on which to base estimates of the prevalence of HIV/HCV coinfection. In these settings, injection drug use is a less common behaviour, and heterosexual transmission is responsible for most new HIV cases. Because the understanding of sexual transmission of HCV is incomplete, estimating HIV/HCV seroprevalence in the developing world based upon the major risk factor for HIV transmission is problematic. There are few HCV seroprevalence studies among HIV-positive people who acquired HIV through heterosexual sex, especially in developing world settings. There is also a paucity of data regarding the risk of HCV coinfection in HIV-positive people whose primary HIV risk factor is exposure to contaminated injection equipment. An investigation of an outbreak of HIV infection in a paediatric population in Libya linked to contaminated injection equipment reported that 47% of HIV-positive patients were coinfected with HCV, suggesting that HIV/HCV coinfection caused by unsafe therapeutic injections may be a problem where these practices are common.105

**HBV coinfection**

The proportion of HCV-infected people who also have chronic HBV infection will have an impact on the overall burden of chronic liver disease. HCV and HBV coinfection in chronic hepatitis patients has been associated with clinically and histologically more severe liver disease than that of chronic hepatitis patients with HCV infection alone.106 A meta-analysis found HBV/HCV coinfection to be more strongly associated with HCC than either infection alone, suggesting a synergistic effect between the two viruses in the carcinogenic process of HCC.107

Like HIV/HCV coinfection, population-based seroprevalence data on HBV/HCV coinfection is largely unavailable, and most published observations are among high-risk groups—eg, chronic liver disease patients and injection drug users. In a New Zealand study of the causes of chronic liver disease in its population, 10% of hepatitis B surface antigen (HBsAg) positive patients were also anti-HCV positive.108 7% of HBsAg-positive patients recruited at liver disease clinics in Italy were anti-HCV positive.109 In the Gambia, where HBV is highly endemic, 3·8% of HCC patients were HBsAg positive.110 A population-based survey among people living in an urban area in Pakistan found that 0·6% were both anti-HCV positive and HBsAg positive.29 Among residents of communities in southern Taiwan, 2% were both HBsAg positive and anti-HCV positive.111

**Alcohol consumption**

High levels of alcohol intake have been associated with an accelerated course of chronic hepatitis C. Patients who drink more than 50 g of alcohol each day—an amount that is equivalent to approximately four or five alcoholic drinks (330 mL of beer, 120 mL of wine, or...
40 mL of liquor)—have an increased rate of progression of liver fibrosis.\textsuperscript{112} Multiple studies have confirmed this finding, as well as shown associations between heavy alcohol consumption and increased rates of cirrhosis and risk of death in chronic hepatitis C patients.\textsuperscript{113} The proportion of HCV-infected individuals enrolled in clinical trials or transfusion look-back studies who consume at least 30 g/day of alcohol is 11–23%,\textsuperscript{112,114,115} but there are few data on alcohol consumption among the wider population of HCV-infected people in the developed world. The rate of alcohol consumption among HCV-infected people in the developing world has not been well-studied; however, observations of worldwide alcohol consumption rates suggest that detrimental patterns of alcohol consumption are generally on the rise in these areas.\textsuperscript{116}

**Chronic liver disease and HCC**

The importance of the current and potential burden of HCV-related complications is evident in recent trends in the proportion of chronic liver disease mortality and HCC attributable to HCV infection. In the USA, mortality due to chronic liver disease fell in the 1980s,\textsuperscript{117} but the decline was not sustained after 1994, largely because of increases in HCV-related deaths.\textsuperscript{118}

HCV infection is implicated in the rising incidence of HCC in many developed countries, including Japan, Spain, France, and Italy, where the proportion attributable to HCV ranges from 50% to 70%.\textsuperscript{119–121} The potential contribution of HCV to morbidity from HCC is particularly evident in countries with a high prevalence of HCV in older age groups. In Japan, where the peak prevalence of HCV infection is in the 60–70 year age group,\textsuperscript{122} HCV-related HCC incidence has more than tripled over the past four decades and HCV infection accounts for as much as 90% of all reported HCC.\textsuperscript{120,123} In a study of the clinical characteristics of Asian patients with HCC, 71% of Japanese patients were anti-HCV positive, compared with 42% and 11% of Indonesian and Chinese HCC patients, respectively.\textsuperscript{124} HCC incidence in the USA rose steadily during the late 1980s and 1990s,\textsuperscript{111} but it is not clear yet whether this rise in HCC incidence is attributable to HCV, or whether countries with peak HCV seroprevalence among middle-aged people—eg, in the USA and Australia—will face an increase in HCV-related HCC similar to Japan as their infected populations age.

**Availability of treatment**

Interferon-based therapy for HCV infection, introduced even before the discovery of HCV in 1989,\textsuperscript{128} is an important potential component of secondary prevention of morbidity and mortality from HCV infection. Although post-exposure prophylactic administration of interferon-based therapy is not yet justified by any data, treatment of newly acquired HCV infection has been used with sustained response rates of 80–98%.\textsuperscript{127–130} One must interpret these results with caution, given that the subjects of these studies were mostly symptomatic infections, and therefore not representative of most newly infected people. Chronic hepatitis C occurs in 60–85% of newly infected people,\textsuperscript{129} and the relation of the presence of symptoms at initial infection to the development of chronic infection has not been well-established. Combination regimens of pegylated interferons and ribavirin, introduced in 2001, induce a sustained response in 42–82% of patients with chronic hepatitis C, depending on genotype.\textsuperscript{132,133} There are early indications that interferon-based regimens improve the prognosis of chronic hepatitis C patients who respond to therapy,\textsuperscript{134} and more definitive demonstration of their ability to reduce HCV-related mortality is expected based on the correlation of sustained viral response to therapy and improvements in liver histology.\textsuperscript{135}

In countries where primary prevention of HCV infection has been addressed through implementation of safe transfusion and injection practices, secondary prevention of morbidity and mortality from HCV infection through provision of interferon-based therapy to infected people is a logical public-health imperative. The price of current regimens, however, is high—US$25 000 for a typical 48-week course of therapy for HCV genotype 1 infection.\textsuperscript{136} Given the exponential rise in HCV-related liver disease over the next 10–20 years predicted by mathematical models, an obvious concern of health policymakers and planners is whether treatment regimens can be made affordable to most HCV-infected people. One recent economic analysis projects $10·7 billion in direct medical expenditures in the USA for HCV-related disease from 2010 to 2019, based in part on an estimated twofold rise in annual HCV-related liver deaths in the USA during these years, compared with 1991.\textsuperscript{139} However, on the basis of health-care costs for hepatitis C in recent years, costs in the next decade may exceed these projections. Estimates of US hepatitis C-related health-care costs in 1998 alone approached $1 billion, including $530 million for antiviral medication, $24 million for physician services, and $125–500 million for inpatient hospitalisations.\textsuperscript{138} A steep rise in health-care expenditures is also predicted in Australia, based on a projected tripling of the incidence of HCV-related liver failure and HCC by the year 2020.\textsuperscript{5,118} Similar forecasts for Switzerland, Ireland, and Canada have also been published.\textsuperscript{5,140,141}

**Conclusions**

The underpinning of any effort to prevent and control hepatitis C is accurate epidemiological data. The epidemiology of HCV infection in the developing world has not been well-characterised, and resources necessary for high-quality studies of the seroprevalence and the major modes of HCV transmission in these countries should be made available.
The risk factors most frequently cited as accounting for the bulk of HCV transmission worldwide are blood transfusions, injection drug use, and unsafe therapeutic injections. Injection drug use is generally considered to be the predominant source of new HCV infections in developed countries, while unsafe therapeutic injections and transfusions are likely to be the major modes of transmission in the developing world based on limited data from these areas. Because transmission of HCV infection through occupational, perinatal, and sexual exposures occurs with much less efficiency compared with transmission through large or repeated percutaneous exposures, these exposures are unlikely to be major sources of new HCV infections, regardless of the population or geographic area.

The prevalence of cofactors known to accelerate the progression of chronic hepatitis C among HCV-infected people, particularly HIV coinfection, HBV coinfection, and alcohol consumption, is likely to have a large impact on the overall burden of HCV-related disease. Data from the developed world suggest that HIV coinfection and alcohol consumption are common among HCV-infected people. The epidemiology of these cofactors among HCV-infected people in the developing world has not been well-defined, and would be an important area of future research.

Most of the burden of HCV infection is realised through the development of chronic liver disease and HCC in a subset of infected people decades after initial acquisition of the infection. HCV infection has already been implicated in the rising incidence of HCC and chronic liver disease in several developed countries, and many others have projected a steady rise in the incidence of HCV-related complications in the coming decades. In the developing world, the future burden of HCV infection is more difficult to predict. Short life expectancies in many countries seem to suggest that most HCV-infected people will die before the onset of HCV-related complications. Nonetheless, the HCV-infected population may grow so large in highly endemic areas that HCV-related complications are an important public-health problem, even though they occur in only a fraction of infected people.

Because there is no vaccine and no post-exposure prophylaxis for HCV, the focus of primary prevention efforts should be safer blood supply in the developing world, safe injection practices in health care and other settings, and decreasing the number of people who initiate injection drug use. In these ways HCV prevention may form valuable alliances with HIV and HBV prevention programmes. Screening and testing of blood donors and virus inactivation of plasma-derived products have been shown to be extremely successful in preventing new infections, and resources need to be identified to expand these practices to poorer countries. WHO’s recently published guidelines on safe injection best practices provide a solid framework for efforts to reduce health-care-related transmission of HCV and other bloodborne viruses. Prevention messages for people with high-risk drug-using practices should be widely disseminated, especially in the developed world. Risk-modifying educational programmes and harm-reduction efforts that have been successful in reducing HIV incidence in injection drug users should be expanded to meet the needs of HCV prevention, including counselling about the risks of sharing drug preparation equipment.

People with known HCV infection should be counselled regarding ways to reduce the risk of transmitting HCV to others, and means of minimising their risk for HCV-related complications. As part of secondary prevention efforts, HCV-infected people should be referred for medical evaluation and antiviral treatment consideration, and programmes ensuring access to these services should be in place.

Conflicts of interest
We declare that we have no conflicts of interest.

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