Public health issues of hepatitis C virus infection

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Abstract

Hepatitis C virus (HCV) is a leading cause of liver disease worldwide, as 130–170 million individuals are chronically infected and 350,000 patients die every year from HCV infection. The HCV prevalence varies widely among countries being highest in several African and Eastern Mediterranean countries. The incidence of new HCV infections may be declining in developed countries, but there is still a large reservoir of chronic infections. The most important mode of HCV transmission has been injecting drug use in developed countries with low prevalence and unsafe therapeutic injections in developing countries with moderate-high prevalence. Since there are no systematic screening policies, most patients remain undiagnosed. Even among diagnosed patients, a minority receives treatment due to several barriers to therapy. Given the high efficacy of treatment, public health authorities should recognise the importance of HCV and make resources available for the implementation of effective primary prevention, screening and management policies.

Introduction

Hepatitis C virus (HCV) is a leading cause of chronic liver disease worldwide. Acute HCV infection is usually asymptomatic but progresses to chronicity in the majority of cases \[1,2\]. Chronic HCV infection may remain at an inactive carrier state in a small proportion of cases, but usually progresses to chronic hepatitis C which often has a fluctuating course \[1\]. Chronic hepatitis C can be a progressive disease. It is estimated that approximately 20%-30% of patients with chronic hepatitis C develop cirrhosis over
a period of 20 years [1,2]. Patients with established cirrhosis have a poor prognosis, since they are at high risk for decompensation and/or development of hepatocellular carcinoma (HCC) [1,2]. On the other hand, the majority of patients with chronic hepatitis C have a slow progressive liver disease, cirrhosis may never develop and survival is probably not affected [1,2].

Treatment achieves sustained virological response (SVR), which means viral eradication, in 55%–60% of patients with chronic HCV infection [2]. New triple combinations including HCV protease inhibitors have increased the sustained response rates by approximately 30% in difficult to treat, naïve and treatment experienced patients infected with HCV genotype 1 [2,3]. Future treatment options are expected to further improve the sustained virological response rates to over 90% in all HCV patients [3]. It was recently documented that SVR is associated with a 50–60% reduction in risk for mortality among persons who had diagnosed HCV infection [4]. Moreover, a meta-analysis conducted with HCC as outcome revealed that SVR is associated with 69–82% reduction of HCC risk among HCV infected patients [5]. However, only a small proportion of patients receive treatment and therefore the treatment efficacy at the global or community level (effectiveness) remains poor [6]. This review focuses on the public health issues of chronic HCV infection including the prevalence, incidence, modes of transmission, burden of disease, control strategies, screening and barriers to therapy.

Prevalence

Although accurate epidemiological data are missing, it is estimated that around 2.5%–3% of the world’s population or approximately 130–170 million people are chronically infected with HCV [7]. The HCV prevalence varies widely among countries. According to data from WHO, it is highest (>10%) in several African and Eastern Mediterranean countries [7]. In particular, Egypt has an impressively high prevalence of chronic HCV infection (over 14%–20% in adults) and a high morbidity and mortality from chronic liver disease, cirrhosis, and HCC [8]. In USA, the HCV prevalence is estimated to range between 1.3% and 1.9% [9]. In European countries, the HCV prevalence varies from 0.4% in Sweden, Germany and the Netherlands to over 2%–3% in some Mediterranean countries and even over 5% in some communities in Italy [6]. High-risk, vulnerable groups such as intravenous drug users (IDUs), migrants, homeless persons and prisoners tend to be under-represented in general population studies, so that prevalence rates are likely to be considerably underestimated, especially in low-prevalence countries [10].

Incidence

Since only 20%–30% of acute HCV infections are sufficiently symptomatic to gain medical attention [1], the incidence of HCV infection cannot be easily determined. The incidence of HCV infection is affected by age, time and region. In Western developed countries, several data suggest that the incidence of acute HCV infection is declining during the last decades presumably reflecting a decrease in percutaneous exposures [7]. In the USA, the annual incidence of acute HCV infections declined from an average of 7.4 per 100,000 individuals during 1982–1989 to 0.7 per 100,000 during 1994–2006 [11]. In Italy, the HCV incidence has been reported to decrease from 2.02 to 0.55 per 100,000 in all age groups over the period from 1996 to 2006 [12]. Similar trends have been reported in Canada and Western European countries, but contrary trends have been observed in Eastern Europe and Russia [13]. Although the incidence of acute hepatitis C has declined, there is a large reservoir of chronically infected patients who can serve as a source of transmission to others and are at risk of the severe consequences of chronic liver disease. Nevertheless, to reliably track HCV infections, it was recently recommended that chronic HCV infections should be reportable in addition to acute HCV cases [14].

Modes of transmission

HCV is mostly transmitted through large or repeated direct percutaneous exposures to blood (e.g. transfusion or transplantation from infectious donors, injecting drug use) [7]. Blood or blood products transfusion was a common mode of HCV transmission until 1991, when HCV testing was widely implemented, but it has been virtually eliminated since then, at least in countries that implemented routine HCV testing of donors [15]. Injecting drug use has been the predominant mode of HCV
transmission for decades in USA and Australia and now accounts for most newly acquired infections in many other countries, including those in Western, Northern, and Southern Europe [16]. The HCV prevalence among IDUs may vary from country to country starting from around 20% but usually exceeding 50% and reaching to even 90% [17]. Globally, there are 10 millions HCV infected by injecting drug use [17]. These differences show that there are temporal and geographical variations in the extent of contribution of each risk factor among different countries. Thus, while injecting drug use has been the most important mode of HCV transmission in developed countries with low HCV prevalence, unsafe therapeutic injections and generally unsafe medical practices have been responsible for the spread of HCV in the developing countries with moderate or high HCV prevalence [16] (Table 1).

The environment can serve as a reservoir for infectious virus [18] and therefore HCV transmission can occur by inapparent percutaneous exposures from contaminated reused needles and syringes, multiple-use medication vials, infusion bags, tattooing etc [16,19]. As previously reported, unsafe therapeutic injections performed by both professionals and non-professionals have been of greater importance in the spread of HCV worldwide [19]. The use of glass syringes for medical treatment before 1970, or a history of dental therapy, or a history of immunization(s) in the 1950s have been found to represent risk factors of HCV infection in many Western developed countries [13,19]. The prevalence of HCV infection was high in patients undergoing haemodialysis, but the incidence of new HCV infections has been declining in this setting over the last 15 years due to the reinforcement of hygienic precautions and/or isolation strategies, at least in western haemodialysis units [20].

In developing countries, unsafe medical practices still represent a major risk factor for HCV transmission, as approximately 2 million HCV infections may be acquired annually from contaminated health care injections and may account for up to 40% of all HCV infections worldwide [21]. Reuse of glass syringes during the early campaign to treat schistosomiasis in Egypt appeared to be responsible for the HCV epidemic in this country [22]. In addition, lack of appropriate cleaning and disinfection of equipment used in hospital and dental settings can also be a source for HCV transmission [19].

Other modes of transmission may be less relevant from a public health perspective [7]. Although HCV transmission can occur from percutaneous exposures to contaminated material, there is a low (<3%) probability of HCV transmission from single small dose percutaneous exposures such as accidental needlesticks [23]. Similarly, HCV is not transmitted very efficiently from mucosal exposures to blood or serum-derived fluids, such as birth to an infected mother or sexual contact with an infected partner [24,25]. In particular for sexual contacts, the risk of HCV transmission does not seem to increase among heterosexual couples in regular relationships, while it is increased among persons with multiple sexual partners and in patients with human immunodeficiency virus (HIV) or other sexually transmitted infections [25]. A number of recent reports suggest an increased risk of HCV infection in men having sex with men (MSM) with a sole risk factor being the sexual exposure. The risk is four times higher in HIV infected MSM compared with the HIV seronegative MSM [26].

**Burden of disease**

The burden of disease is critical for the decisions on the national health policies and therefore there is a need for accurate estimations globally, regionally and nationally. However, accurate data on the burden of chronic HCV infection are not available globally.

<table>
<thead>
<tr>
<th>Mode of HCV transmission</th>
<th>HCV prevalence</th>
<th>Low (≤2%)</th>
<th>Moderate/high (&gt;2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral drug use</td>
<td>++</td>
<td>++/++</td>
<td>++/++</td>
</tr>
<tr>
<td>Unscreened blood/blood products, transfusions</td>
<td>++</td>
<td>++/+</td>
<td></td>
</tr>
<tr>
<td>Unsafe therapeutic injections/medical practices</td>
<td>+</td>
<td>+/+++</td>
<td></td>
</tr>
<tr>
<td>Needle-stick injuries in health care settings</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Sexual exposure</td>
<td>++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Perinatal exposure</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Shearing personal items contaminated with infectious blood (less common)</td>
<td>+</td>
<td>++/++</td>
<td></td>
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</tbody>
</table>

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**Table 1**

Importance of modes of HCV transmission in relation to HCV prevalence.
Despite the lack of good data, it is currently estimated that approximately 350,000 deaths occur each year as a result of HCV infections [7]. In addition, several clinical cohorts have shown that chronic hepatitis C is a leading cause of cirrhosis and HCC, which ranks as the third cause of cancer deaths worldwide [2]. In Western countries, HCV is the first or a major cause of liver transplantation [27]. Similarly, several current studies show that HCV patients have higher morbidity and mortality rates compared to those of the general population [28–30]. Finally, several models based on the epidemiological data and the evolution of chronic HCV infection in untreated patients or patients treated with pegylated interferon and ribavirin suggest that HCV related cirrhosis and death from HCC are likely to increase dramatically in the next one to two decades reflecting the increased incidence of HCV infection in the 1970s and 1980s [31–36]. Thus, although HCV transmission has been largely reduced and general prevention strategies have been relatively effective [37], the issue of the existing chronic HCV patients needs to be addressed, as they will represent a heavy disease burden in the coming years [30,35,36]. Therefore, the need for additional and more accurate data on the burden of disease must not be an excuse for delaying policy actions and recognising HCV as a major public health problem [6].

**Strategies to control HCV**

Recent progress in understanding the natural history of HCV and substantial progress in the diagnostic and treatment landscape support the notion that HCV can be controlled and even to be eliminated at least in developed countries. This is clearly reflected in the World Health Assembly Resolution WHA 63.18 and in the World Health Organization (WHO) Framework for Global Action to prevent and control viral hepatitis [38]. The vision is ‘a world where viral hepatitis transmission is stopped and all have access to safe and effective care and treatment’. The goals of the WHO viral hepatitis strategy are: a) to reduce transmission of the agents that cause viral hepatitis, b) to reduce morbidity and mortality due to viral hepatitis and improve the care of patients, c) to reduce the socio-economic impact at individual community and population levels. This comprehensive framework proposes 4 axes for regions and countries to develop effective strategies and plans according to their specific hepatitis burden and challenges:

Axis 1. Raising awareness, promoting partnerships and mobilizing resources.  
Axis 2. Evidence-based policy and data for action.  
Axis 3. Prevention of transmission,  

To effectively raise awareness and mobilize resources, a strong surveillance system is necessary. A surveillance system should provide data not only on the incidence and prevalence of acute and chronic infections but should provide sufficient information to estimate the HCV infected, HCV–diagnosed linked to HCV care, retained to HCV care, HCV-infected on treatment and successfully treated (SVR) (Fig. 1). Any screening effort must be coupled with sufficient linkage and retention to care and high treatment coverage of those needed. Modelling studies suggest that the treatment as prevention strategy is feasible and it is anticipated to become a central issue with the upcoming interferon-free regimens [39,40].

Given the magnitude of burden of diseases in many countries, a comprehensive national plan is necessary in order to achieve cost-effective results. Community effectiveness of treatment is not synonymous to treatment efficacy. The current estimate of treatment efficacy for chronic hepatitis B and chronic hepatitis C are 40–90%, while the community effectiveness in the USA is 3.5–5% [41,42]. Raising treatment effectiveness is a major goal of any comprehensive national strategy.

**Screening**

The majority of chronic HCV patients are unaware of their asymptomatic condition and therefore screening will be important in order to identify the infected individuals and offer them appropriate management [6]. For public health, the cost-effectiveness of screening is certainly of paramount importance given the high direct cost of HCV antiviral treatment. However, several analyses have
shown that the cost of HCV screening and treatment for infected individuals compares well with other medical public health interventions [36,43–45], and this should reassure decision makers.

Although HCV screening is now considered to be necessary, targets for screening may vary among countries and from one programme to another [6,7]. In many Western countries with relatively low (<2%) HCV prevalence, HCV screening efforts have been focused on high-risk groups [6]. High-risk groups for HCV infection usually include current or past IDUs, recipients of blood/blood products transfusions before 1992, patients who have ever received long-term haemodialysis, persons who have known parenteral exposures to HCV, all HIV positive patients, patients with elevated aminotransferases, children born to HCV positive mothers, sexual and household contacts of HCV positive patients, subjects with multiple sexual partners, and immigrants from high-prevalence areas [2,6,14,46]. In addition, subjects that may directly expose others to HCV, such as blood, tissue and organ donors as well as pregnant women, should be offered HCV screening [2,14]. An updated summary of the high-risk populations for hepatitis C included in the US Institute of Medicine recommendations is presented in Table 2 [14].

Despite the existing recommendations, there is a striking heterogeneity in screening practices across countries. This heterogeneity is clearly presented in a recent report from the European Centre
for Disease Prevention and Control on the screening practices for viral hepatitis in European
countries [10]. In addition, although high-risk group screening is often recommended by the
scientific associations [46], it may not be effective for two main reasons. First, surveys of primary
care physicians show that they often do not ask their patients about HCV risk factors [47,48]. Second,
even if the physicians ask about HCV risk factors, they can never be sure that the patient will easily
admit that he/she had been transiently exposed to HCV (e.g. by transient injecting drugs) some
decades ago. Based on data showing that the HCV prevalence is substantially higher in US residents
born between 1945 and 1970, two recent analyses suggested that birth-cohort screening targeting
US residents born from 1945–1970 are more cost-effective than risk-based HCV screening
[49,50]. Recently, the HCV screening among persons born during 1945–1965 was officially recom-
mended by CDC [5]. These results may also apply to other Western countries with similar HCV
epidemiology.

Regardless of the screening strategy, many aspects should be considered for the implementation of
a successful screening programme. These should include clear public awareness campaigns targeted at
the general public and at risk groups, a clear clinical strategy to deal with HCV infected patients,
integration of screening into existing public health and care practices whenever possible, education of
providers about the needs for screening and about the management pathways for HCV infected
individuals, appropriate counselling of the individual and his or her family, securing absence of stig-
matisation [6].

Table 2
High-risk populations for hepatitis C. Adapted from the recommendations of the US Institute of Medicine [14] and CDC [5].a

<table>
<thead>
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<tbody>
<tr>
<td>- They should receive one-time testing for HCV without prior ascertainment of HCV risk.</td>
</tr>
<tr>
<td>Person who have ever injected illegal drugs, including those who injected only once or a few times many years ago and do not consider themselves as drug users.</td>
</tr>
<tr>
<td>Recipients of blood transfusions or solid-organ transplants before July 1992.</td>
</tr>
<tr>
<td>Recipients of blood or organs from donors who later tested HCV positive.</td>
</tr>
<tr>
<td>Recipients of clotting factor concentrates made before 1987.</td>
</tr>
<tr>
<td>Patients who have ever received long-term hemodialysis treatment.</td>
</tr>
<tr>
<td>Patients who have signs or symptoms of liver disease (e.g., abnormal liver enzyme tests).</td>
</tr>
<tr>
<td>Persons who have known exposures to HCV, such as health care workers after needlesticks involving HCV-positive blood.</td>
</tr>
<tr>
<td>Children born to HCV-positive mothers (to avoid detecting maternal antibody, these children should not be tested before the age of 18 months).</td>
</tr>
<tr>
<td>All persons who have HIV infection.</td>
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</tbody>
</table>

a All persons identified with HCV infection should receive a brief alcohol screening and intervention as clinically indicated, followed by referral to appropriate care and treatment services.

Barriers to therapy

Despite the increased morbidity and mortality in untreated chronic hepatitis C patients and the high
efficacy of antiviral therapy, only a minority of chronic HCV patients is currently treated [6,14,51] (Fig. 1). In USA, only up to 30% of HCV patients followed in Academic tertiary centers receive antiviral
therapy, while this proportion is lower than 5% for HCV patients followed in primary care settings [51]. Since the larger proportion of HCV patients remains undiagnosed and only a small proportion of diagnosed HCV patients receives treatment, it is clear that the vast majority of chronic HCV patients
remains untreated even in developed countries [6,14,51]. The understanding of the barriers to therapy is critical for the improvement of the proportion of treated cases and eventually for the reduction of the negative outcomes of this disease. Among diagnosed HCV cases, barriers to therapy may include patient factors, physician factors, and government and payer factors.

Since chronic HCV patients may remain completely asymptomatic for decades, they often neglect to seek treatment or to adhere to their evaluation process [51,52]. Additional factors that may prevent HCV diagnosed patients from seeking appropriate treatment include economic issues, such as lack of health insurance and/or fears of missed work obligations, fears for negative treatment effects on their
quality of life, and social pressures including family obligations, language difficulties for immigrants, lack of social support, social rejection and stigmatization [51,52]. IDUs represent a group with very low treatment rates worldwide for several reasons. They do not often adhere to physicians’ recommendations, while physicians may also hesitate to start antiviral therapy in IDUs because of their relatively high prevalence of depression and psychiatric illness and mainly because of concerns regarding poor adherence and increased risk of adverse effects and post-treatment reinfection [53]. On the other hand, the majority of IDUs express a willingness to be treated [53,54] and several studies have shown favourable treatment outcomes in cases receiving methadone maintenance therapy but even in active IDUs [55–57]. Given the lack of good data for anti-HCV therapy in active IDUs, no general recommendation for treatment is provided for such cases [2]. In contrast, antiviral therapy is recommended for IDUs on methadone substitution therapy who should be carefully evaluated at baseline by both hepatologists and addiction specialists and should remain under close monitoring and support for adherence and mental health [2,46]. Psychiatric disorders may represent another barrier to anti-HCV therapy, as clinicians often hesitate to start interferon-alfa based therapy in patients with an underlying psychiatric illness [58]. However, given that the patients will remain under regular psychiatric monitoring, psychiatric disorders are no longer considered as absolute contraindications to interferon-alfa-containing regimens [2,46].

Barriers to anti-HCV therapy may arise from the providers, including both primary care physicians and specialists. Due to limited knowledge and awareness, primary care physicians may not only forget to test individuals from high-risk groups, but may not refer HCV patients and even reassure them for a benign course of the disease too [48,51]. There may also be limited number of hepatologists, while the patients may face difficulties to reach them or to communicate with them due to distance issues, long waiting times, lack of scheduling flexibility and even negative interactions [51,59].

Finally, the national health systems, which vary widely among countries, and eventually governments and payers, are critical for the overall HCV management. The reimbursement policies for HCV drugs and diagnostic tests are very important for the individual patient, while the implementation of screening and surveillance programmes, the dissemination of information and the efforts for increasing public and provider awareness are crucial for the public health. The latter has been shown in some European countries, in which government sponsored screening and surveillance programmes have resulted in greatly increased rates of HCV diagnosis of [6,37]. Thus, governments and payers should recognise HCV infection as an important public health threat and make resources available for the implementation of effective and lasting screening and management policies.

Summary

HCV is a major public health issue worldwide. It is estimated that 130–170 million individuals (2.5%–3% of the globe population) are chronically infected with HCV. The HCV prevalence varies widely among countries being highest in Egypt and several African and Eastern Mediterranean countries, but it is 1%–2% in many developed Western countries. The incidence of new HCV infections may be declining in developed countries, but there is still a large reservoir of chronically infected patients who can serve as a source of transmission to others and are at risk of the severe consequences of chronic liver disease. The most important mode of HCV transmission has been injecting drug use in developed countries with low prevalence and unsafe therapeutic injections in developing countries with moderate–high prevalence. Blood transfusion was a common mode of HCV transmission until the implementation of HCV testing in early nineties. Other modes of transmission, such as needlestick injury, sexual or perinatal transmission, are less relevant from a public health perspective. The burden of disease has not been accurately estimated, but chronic HCV infection is a major cause of cirrhosis, hepatocellular carcinoma and liver transplantation and causes 350,000 deaths annually. There are currently recommendations for high-risk group screening and some recent analyses supporting a superiority of birth-cohort screening, but HCV screening is not widely applied. Thus, most patients remain undiagnosed. Even among diagnosed patients, a minority receives treatment due to several barriers to therapy. Given the high efficacy of treatment, public health authorities should recognise the importance of HCV and implement national strategies for prevention and control of viral hepatitis.
making resources available for the implementation of primary prevention, effective screening and management policies.

**Practice points**

- Globally, 130–170 million individuals (2.5%–3% of the world’s population) are chronically infected with HCV.
- The HCV prevalence varies widely among countries being highest in several African and Eastern Mediterranean countries.
- The incidence of new HCV infections seems to be declining in developed countries.
- The most important mode of HCV transmission has been injecting drug use in developed countries with low HCV prevalence and unsafe therapeutic injections in developing countries with moderate or high HCV prevalence.
- The burden of HCV disease is anticipated to increase in the next one or two decades reflecting the increase transmission in the 1970s and 1980s.
- Control of HCV transmission and progression of chronic infection is feasible with an integrated and widespread prevention care and treatment strategy.
- Even among diagnosed HCV patients, a minority receives antiviral therapy due to several barriers.
- Barriers to HCV therapy may include patient factors, provider factors and government and payer factors.

**Research agenda**

- The prevalence and incidence of HCV infection needs to be better defined.
- The burden of HCV infection needs to be more accurately estimated.
- A national strategy is necessary in order to address effectively the prevention, care and treatment of HCV in each country.
- The optimal and more cost-effective screening strategy should be decided.
- The barriers to therapy should be clarified separately for each country.

**Conflict of interest statement**

George Papatheodoridis: advisor and/or lecturer for Abbott, Boehringer, Bristol-Myers Squibb, Gilead, Janssen, Merck, Novartis and Roche; research support from Bristol-Myers Squibb, Gilead and Roche.

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