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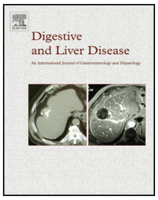

Review article

HCV burden in Europe and the possible impact of current treatment

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ABSTRACT

An important proportion of hepatitis C virus patients in Europe are unaware of their condition with substantial discrepancies between European countries in terms of hepatitis C virus screening. Factors contributing to low screening rates likely include limited physician awareness, reluctance of patients to admit to unsafe past behaviours, and lack of efficient public health policy for HVC screening. It becomes urgent to define innovative public health policy to improve hepatitis C virus screening that is the only choice allowing non-tested hepatitis C virus patients access to therapy as hepatitis C virus patients remain undiagnosed until they develop advanced liver disease. European health authorities should encourage innovative approaches to increase the proportion of hepatitis C virus persons aware of their condition, such as those proposed recently by the Centers for Disease Control and Prevention. Antiviral treatment will impact on hepatitis C virus-related morbidity and mortality with marked differences between European countries. In genotype 1 patients, protease inhibitors-based triple therapy would considerably impact the hepatitis C virus-related incidence of cirrhosis and deaths. There is an urgent need for the reinforcement of hepatitis C virus screening and access to therapy when considering their major impact on hepatitis C virus-related morbidity and mortality. In Europe, although clinicians from different countries are using the same therapies, impact on morbidity and mortality across countries will significantly vary.

1. Background

Hepatitis C virus (HCV) is a leading cause of chronic liver disease and cirrhosis, and the most common indication for liver transplantation in most European countries. A large-scale study of liver disease-related mortality and all cause mortality showed that people diagnosed with community acquired hepatitis B and hepatitis C infection had an overall mortality rate 1.5–5 times greater than the standard population, with the highest rates in those co-infected with hepatitis B and C virus [1]. In hospital based cohorts, liver-related mortality and mortality are substantially increased in HCV hospitalized population [2–4]. As a consequence HCV is considered as a major public health concern throughout Europe. Nevertheless, it has not been made a priority by European governments and it still deserves more effective action to prevent unnecessary deaths from this treatable disease.

Male gender, older age, excessive alcohol consumption, immunosuppressive regimen, and HIV infection are independent risk factors of hospitalization [2,4,5]. It is important to note that alcohol abuse and HCV frequently coexist in the same patient. Several studies have shown increased rate of fibrosis progression and development of cirrhosis in drinking HCV subjects compared with teetotaler HCV subjects [6,7]. The interaction between lifetime daily alcohol intake and HCV is additive for consumption between 50 and 125 g/day and multiplicative for consumption above 125 g/day [2].

An important proportion of HCV patients in Europe are unaware of being HCV infected, with substantial discrepancies between European countries in terms of HCV screening. For example, in 2004, observational studies disclosed HCV screening ranking at 60% in France, 40% in Germany and 30% in United Kingdom. A recent study estimated HCV screening rates in 2011 at 50% in Belgium, 64% in France, 48% in Germany, 46% in Italy, 35% in Spain and 34% in United Kingdom. However, reliable studies to estimate HCV screening are still necessary [8].

Factors contributing to low screening rates likely include limited physician awareness, reluctance of patients to admit to unsafe past behaviours, and lack of efficient public health policy for HVC screening. It is thus urgent to define innovative public health policy to improve HCV screening that is the only possibility for allowing non-tested HCV patients access to therapy as HCV patients remain undiagnosed until they develop advanced liver disease. Conversely, antiviral therapy will reduce the risk of development of liver complications among patients who achieve sustained virological response (SVR) as most sustained virological responders are cured of liver disease.

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Table 1
Distribution of genotypes in 6 European countries.

	Belgium	France	Germany	Italy	Spain	UK
HCV genotype distribution						
G1	60%	56%	60%	62%	65%	44%
G2/3	27%	32%	37%	34%	23%	53%
Other genotypes	13%	12%	3%	4%	12%	3%

Adapted from [8].

The Centers for Disease Control and Prevention (CDC) originally recommended risk-based HCV screening: a strategy consisting of restricting screening only to the at-risk population such as injection drug users, recipients of a blood transfusion or organ transplant before 1992, or clotting factor concentrates produced before 1987, long-term dialysis patients, children born to HCV-positive women, and health care, emergency medical, and public safety workers exposed to HCV. When considering that up to 70% of HCV Americans remain undiagnosed, the CDC has since declared the risk-based screening a useless strategy [9]. The fact that antiviral therapy efficacy continuously progresses over time makes this paradox even more obvious. Taking into account all these data, the CDC has recently modified its previous recommendations for HCV screening. It recommends one-time testing without prior ascertainment of HCV risk for persons born during 1945–1965, a population with a high prevalence of HCV infection [9]. In addition, the CDC clearly states that its former recommendation to screen the population with known risk factors and clinical indications still stands. A recent study based on an economic model showed that the HCV birth-cohort screening recommended by the CDC will reduce the HCV-related morbidity and mortality and is cost-effective at American and European willingness-to-pay thresholds of <$50,000 per QALY gained [9].

Substantial discrepancies can be observed in Europe in terms of HCV burden and access to antiviral therapy. The observed HCV prevalence ranged from 4% in Italy, 1.9% in Spain, 0.87% in Belgium, 0.84% in France, 0.6% in Germany to 0.7% in UK [8]. Distribution of HCV genotypes varies according to geographical localization as some genotypes are associated with specific routes of infection or exposure that differs from one country to another (Table 1). The highest proportion of genotypes 2 and 3 was observed in United Kingdom, where most HCV infections occurred in intravenous drug users (Table 1). In addition to these discrepancies the proportion of HCV patients treated with antiviral therapy varied across European countries because these patients face important inequities in terms of health care, access to therapy, and drug delivery. These discrepancies in health care were estimated in 2005 by the analysis of the market uptake of peginterferon alpha in 21 European countries [10]. The fastest and earliest increase in peginterferon alpha sales rates was observed in the EU founder states, followed by countries that joined after EU foundation and EU non-member states. The number of patients treated ranged from 16% of HCV prevalent cases in France, 12% in Germany, 3% in Italy and the UK to less than 1% of cases in Romania, Poland, Greece and Russia. These differences in Peginterferon market uptake illustrate the unequal access to antiviral therapy across Europe. These wide heterogeneities in access to therapy are related to numerous causes, such as lack of funds and restricted reimbursement, bureaucratic obstacles, exclusion of patients with mild hepatitis from treatment, ineffective therapy policies and screening heterogeneity. In summary, in most European countries there will be an increase in the number of patients receiving treatment; however, these issues will become urgent for those European countries in which HCV-related morbidity and mortality will continue increasing over the next 20 years.

The value of a plan of action for the hepatitis B and C virus needs to be highlighted. The improvement in screening rates and access to therapy in France was mainly a consequence of the two action plans during the periods 1999–2002 (Plan National De Lutte Contre L'hépatite C) and 2002–2005 (Programme national hépatites C et B) [11,12]. A study evaluating the impact of the French HCV action plans observed that the proportion of anti-HCV positive persons aware of their condition increased from 24 to 56% and anti-HCV screening activity increased by 45% from 2000 to 2005 [11]. Taking into account the effectiveness of those 2 former plans, in 2009 the French health authorities launched the third Hepatitis B and C action plan ("Plan National De Lutte Contre L'hépatite C 2009–2012"). Despite the three French HCV action plans, the number of HCV French subjects aware of their condition remains far from the government objective of 75%. This proportion is particularly low among those who either did not report transfusions prior to 1992 or did not acknowledge former/current intravenous drug use, which underscores the difficulty and the need to better identify those chronically infected by HCV. European health authorities should encourage innovative approaches to increase the proportion of HCV persons aware of their condition, such as those proposed recently by the CDC [9].

Among HCV patients, the development of specific health policies is required for the group of active or former injecting drug users because this group is frequently defenceless and marginalized. It is not possible to manage and treat HCV infected injecting drug users without considering their social condition and addiction profile. The lack of networks between primary care, general practitioner, specialists, hospital unit, addiction structure, and prison and social care services results in few HCV patients accessing antiviral therapy. European countries need to share their experience on the effectiveness of the HCV action plans devoted to these difficult-to-treat persons. The Scottish hepatitis action plan is an attractive approach that deserves to be brought to the attention of other European countries [13]. This action plan aims to coordinate all operational structures implicated in prevention, diagnosis, and care of HCV persons in order to provide and improve education in schools about the dangers of injecting drug use; support services to prisoners; annual surveys of HCV prevalence and incidence among injecting drug users; interventions designed to increase uptake and reduce sharing of injection equipment, and reduce hepatitis C transmission; interventions to increase the number of persons undergoing antiviral therapy in Scotland [13].

The challenge for clinicians when deciding whether to treat HCV patients lies in the fact that therapy is intended to prevent risks of morbidity and mortality that may occur several decades later. To evaluate the impact of survival, a randomized study with and without antiviral therapy in HCV patients would have been the most efficient approach. However, randomization is nowadays considered unethical by patients and clinicians who refuse to exclude patients from the established benefit of antiviral therapy in terms of viral eradication. The modelling approach is relevant to determine the impact of antiviral therapy on HCV morbidity and mortality. The relationship between viral eradication and lives saved is a complex and dynamic knowledge of the natural history of HCV infection can help to develop models for predicting the future course of HCV infection. As a consequence, several models have been developed during the last decade to predict the future course of HCV infection [14–17]. A study using a modelling approach showed that pegylated interferon and ribavirin therapy will save 14,400 lives in France compared to absence of therapy [17]. This study observed that the impact of antiviral therapy on HCV mortality needs to take into account the extent of therapeutic accessibility at a population level, which depends at least in part on treatment practice and screening.

Some clinicians are still questioning the benefits of antiviral therapy in HCV patients with slow disease progression, such as those with normal ALT, in light of their slower progression to cirrhosis [18]. Despite a probability of receiving treatment three to