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Research article

Hepatitis C virus seroprevalence and prevalence of chronic infection in the adult population in Ireland: a study of residual sera, April 2014 to February 2016

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Robust data on hepatitis C virus (HCV) population prevalence are essential to inform national HCV services. In 2016, we undertook a survey to estimate HCV prevalence among the adult population in Ireland. We used anonymised residual sera available at the National Virus Reference Laboratory. We selected a random sample comprising persons ≥ 18 years with probability proportional to the general population age-sex distribution. Anti-HCV and HCV Ag were determined using the Architect anti-HCV and HCV Ag assays. Fifty-three of 3,795 specimens were seropositive (age-sex-area weighted seroprevalence 0.98% (95% confidence interval (CI): 0.73–1.3%)). Thirty-three specimens were HCV-antigen and antibody-positive (age-sex-area weighted prevalence of chronic infection 0.57% (95% CI: 0.40–0.81%)). The prevalence of chronic infection was higher in men (0.91%; 95% CI: 0.61–1.4%), in specimens from the east of the country (1.4%; 95%CI: 0.99–2.0%), and among persons aged 30–39 years and 40–49 years (1.1% (95% CI: 0.59–2.0%) and 1.1% (95% CI: 0.64–1.9%) respectively). Ireland ranks at the lower end of the spectrum of prevalence of chronic HCV infection internationally. Men born between 1965 and 1984 from the east of the country have the highest rate of chronic HCV infection.

Background

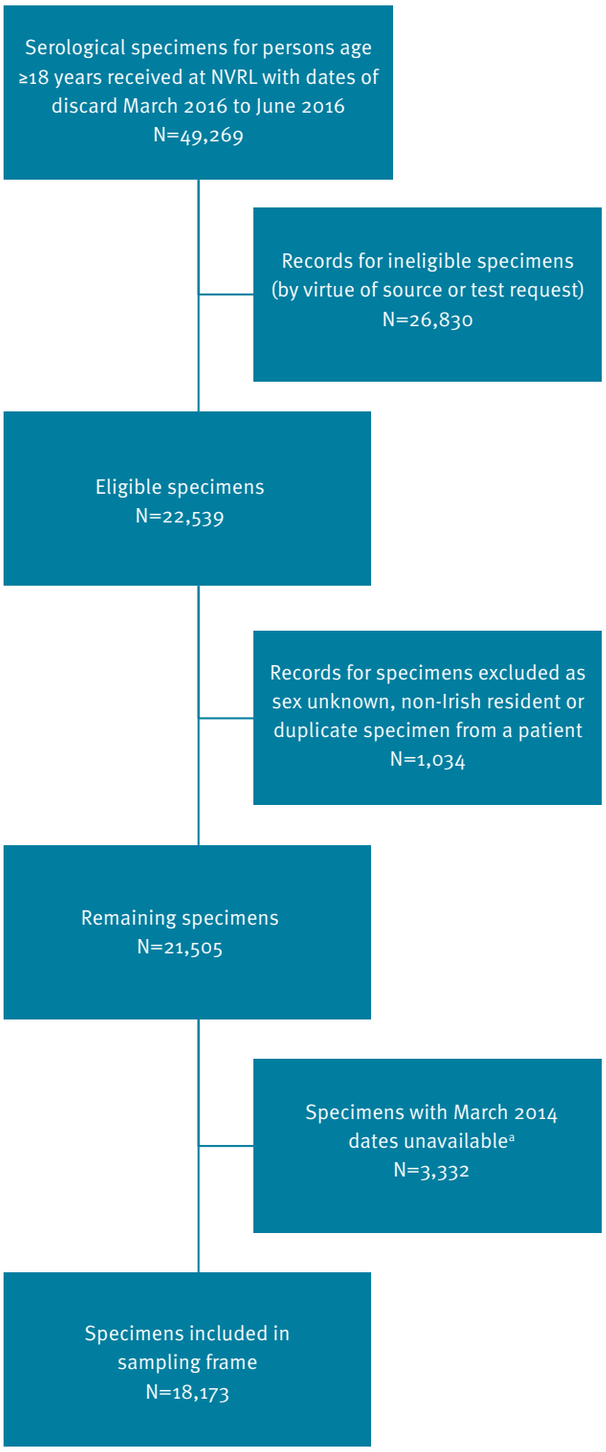
Acute hepatitis C virus (HCV) infection is typically asymptomatic or associated with non-specific symptoms. Studies have indicated, however, that up to 80% of those infected will develop chronic infection, which can lead, over many decades, to cirrhosis, liver cancer and death [1,2]. Because of the asymptomatic nature of HCV infection, individuals can be infected for many years before diagnosis. Globally, the World Health Organization (WHO) has estimated that between 130 and 150 million people are HCV-infected [3,4], with the prevalence of HCV in some countries in central Asia (5.4%), western Africa (5.3%), central Africa (4.2%), eastern Europe (3.3%), and North Africa/Middle East (3.1%) being higher than countries in North America (1.0%) and western Europe (0.9%) [5]. Within Europe, prevalence estimates of 0.4% to 5.2% have been reported, with countries in the north and west of Europe having lower estimates (0.9%) than countries in the east of Europe (3.3%) [5,6].

Historically, there was limited success in treating HCV, but in recent years, treatment with new direct-acting antivirals (DAAs) that possess high efficacy and improved safety profiles, has led many to suggest that the elimination of HCV is now possible [7]. Successful treatment not only benefits the individual by reducing his or her risk of cirrhosis and other liver-related outcomes, but also benefits the general population by reducing rates of onward transmission.

With the advent of highly potent and curative DAAs, many countries are now developing national strategies for population screening for HCV infection, and national HCV treatment programmes. Initiatives in Ireland include the formal establishment in 2015 by the Health Service Executive (HSE) of a National Hepatitis C Treatment Programme for known HCV-infected individuals [8]. Concurrently, a Guideline Development Group was convened by the HSE to develop national HCV screening guidelines to identify HCV-infected individuals who are currently unaware of their HCV status. For these approaches to be successful, the availability of robust data on population HCV seroprevalence is key, a fact recognised both by the Irish National Hepatitis C Strategy 2011–2014 [9], and likewise in December 2015, by the European Centre for Disease Prevention and Control (ECDC) [10].

Figure 1

Construction of hepatitis C virus study sampling frame, Ireland, 2014–2016



NVRL: National Virus Reference Laboratory

[a] Specimens collected in March 2014 and due for discard in March 2016 had been inadvertently discarded.

Ireland is believed to be a low-prevalence country for HCV, and prior studies that measured the HCV seroprevalence in selected high-risk or localised populations, and in antenatal women [11-16], support this view; however, no national HCV prevalence studies in the general population have been conducted and the true burden of infection is unknown. We undertook a national cross-sectional study to estimate HCV seroprevalence and prevalence of HCV chronic infection among the adult population in Ireland.

Methods

Study design and population

The target population for our study was the adult population in Ireland. The sample was based on anonymised residual sera taken from persons aged 18 years or over submitted to the National Virus Reference Laboratory (NVRL). The NVRL provides a diagnostic and reference service for clinicians investigating viral infections throughout Ireland. Typically, around 200,000 blood specimens are received annually, equating to ca 150,000 serum specimens. They include specimens received for diagnostic purposes, antenatal screening, and pre-employment screening.

Laboratory residual sera

Specimens are classified as residual at the point where they are deemed no longer required for the purpose for which they were originally collected. It is NVRL policy to retain diagnostic samples for 4 months, antenatal samples for 24 months, needlestick source samples for 24 months, and occupational health screening specimens as requested. These time periods are intended to facilitate supplementary testing of the original sample should a clinical need arise. After the relevant time period has elapsed however, samples are discarded. For this study, residual specimens were available at the NVRL for a 3-month period for those specimens normally retained for 2 years (specimens collected April to June 2014), and for a 4-month period for those specimens normally retained for a 4-month period (specimens collected November 2015 to February 2016). Laboratory testing for the purposes of this study took place in July and August 2016.

Sample size

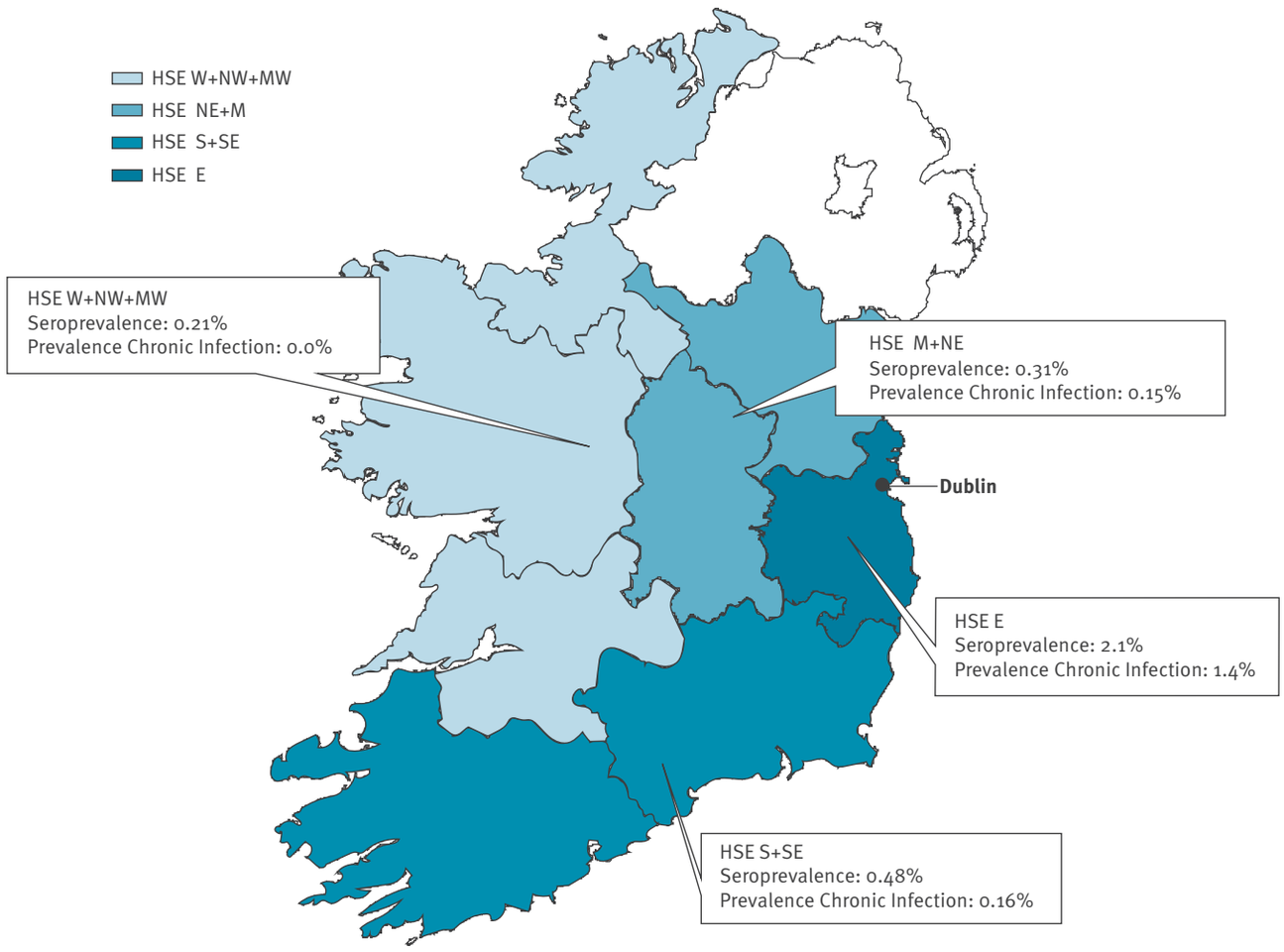
We estimated a sample size of 3,814 corresponding to an expected prevalence of chronic infection of 0.5%, an absolute precision of 0.2%, an alpha error of 0.05, a design effect of 1, and an eligible pool of ca 18,891 specimens.

Sampling procedure

The NVRL laboratory information management system was used to identify eligible specimens. Specimens marked on the system as being specifically retained for other reasons, e.g. sample from organ donors, were excluded. Antenatal specimens (where submitted for general antenatal screen at first 'booking') and pre-employment screening specimens were all included in

Figure 2

Seroprevalence and prevalence of chronic hepatitis C virus infection by region, Ireland, 2014–2016



HSE: Health Service Executive; M: Midlands; MW: Mid West; NE: North East; NW: North West; S: South; SE: South East; W: West.

the sampling frame. To avoid the over-representation of persons who could have a HCV prevalence higher than expected in the general population, specimens collected from certain sources were considered ineligible for the study. These included: specimens sourced from drug treatment clinics or sexually transmitted infection (STI) clinics; specimens from hepatology or infectious disease services; specimens submitted specifically for a hepatitis, or STI screen; or specimens from asylum seekers (who are routinely screened for HCV in Ireland). Where possible, duplicate specimens from the same individual were identified by individually cross-checking the submission details for specimens from patients with the same initials and date of birth, and only one specimen per person was included in the sampling frame. We stratified the eligible specimens in the sampling frame by age group and sex. We selected a sample with probability proportional to the size of the age group and sex strata in the general population (as specimens submitted for diagnostic tests are likely to be biased at least by age). Within age-sex strata, we selected specimens using simple random sampling.

Laboratory specimen analysis

Where a selected specimen was found to have insufficient volume (‹500 µL) for conducting the required laboratory tests, a replacement was selected randomly from the remaining specimens in the sample frame.

HCV antibody status was determined using the HCV Ab Architect Abbott HCV antibody test (Abbott Diagnostics, Wiesbaden, Germany), which detects only anti-HCV IgG, as the first line screen. Specimens exceeding the manufacturer's cut-off of 1.0 were investigated for the presence of HCV antigen using the HCV Ag Architect Abbott HCV antigen test. Samples reactive in the anti-HCV assay but negative for HCV Ag were subsequently tested using the Bio-Rad Monolisa anti-HCV Plus vs 3.0 (Bio-Rad, Marnes-la-Coquette, France) to confirm the presence of anti-HCV. Specimens which generated discordant anti-HCV results were tested

Table 1

Demographic characteristics of the study sample (n=3,795) and the general adult population in Ireland (n=3,439,565), 2014–2016

Characteristic		Study sample		General adult population in Ireland (> = 18 years)[a]	
		n	%	n	%
Sex	Female	1,931	51%	1,754,648	51%
	Male	1,864	49%	1,684,917	49%
Age group	18–29 years	856	23%	772,275	22%
	30–39 years	838	22%	758,206	22%
	40–49 years	705	19%	635,997	18%
	50–59 years	574	15%	518,908	15%
	60–69 years	436	11%	392,424	11%
	70 + years	386	10%	361,755	11%
HSE area	East	2,288	60%	1,236,870	36%
	Midlands and North East	535	14%	522,465	15%
	South and South East	556	15%	869,316	25%
	West, North West and Mid West	416	11%	810,914	24%
Category	Antenatal	646	17%	NA	NA
	Pre-employment	131	3%	NA	NA
	Other (e.g. diagnostic specimens)	3,018	80%	NA	NA
Total		3,795	100%	3,439,565	100%

[a] Census 2011, Central Statistics Office, Ireland

HSE: Health Service Executive; NA: not available.

using the Fujirebio INNO-LIA HCV score line immunoassay (Fujirebio Europe, Gent, Belgium) to determine the anti-HCV status of the sample.

Definitions

Specimens that were both HCV-antigen- and antibody-positive were considered to have been collected from an individual with chronic HCV infection. Specimens that were anti-HCV-positive but HCV-antigen-negative were considered indicative of resolved infection. Specimens that were HCV-antigen-positive but that gave an indeterminate anti-HCV profile were considered as having been obtained from a subject with possible acute HCV infection. Specimens with indeterminate anti-HCV antibody status and that were HCV-antigen-negative were recorded as being of inconclusive HCV status.

Information collected

As the specimens used were derived from residual sera that had been submitted for a wide variety of reasons, the only information common to all specimens comprised basic demographic data such as age, sex, geographic area (Health Service Executive (HSE) areas are the public health administrative units in Ireland) and sample category (pre-employment screening, antenatal or other). These data were linked with the laboratory results in the study database.

Statistical analysis

We calculated the prevalence of HCV antibodies and chronic HCV infection and 95% confidence intervals (overall and by age, sex and area), weighted for undersampling in some age-sex strata and for geographical bias in sample selection. As a comparison group for antenatal studies previously conducted in Ireland, we also calculated the weighted prevalence of HCV antibodies in specimens from women aged 18–49 years.

Extrapolating from the prevalence in the sample, we estimated the number of persons seropositive or chronically HCV infected in the adult population in Ireland. Stata version 14.0 (Stata Corporation, Texas, US) statistical software was used for analyses

Protection of human subjects and confidentiality

The study received ethical approval from the Royal College of Physicians of Ireland (RCPI) Research Ethics Committee. All testing was anonymous and the identities of those whose specimens were tested were unknown to investigators. No contact was made with these individuals and they were unaware that they were included in the study. Before testing, eligible specimens were decanted and irrevocably anonymised using new specimen numbers. Only these new anonymised specimen numbers were recorded in the database.

Results

Construction of the study sampling frame

NVRL database records for serological specimens received during the period of interest (due for discard

Table 2

Estimated hepatitis C virus (HCV) seroprevalence and prevalence of chronic HCV infection, and estimated number HCV seropositive and chronically infected, in the adult population in Ireland, by age and sex and Health Service Executive-area, Ireland, 2014–2016

Group		Seropositive in study sample (chronic and resolved infections)			Seropositive adults in general population		Chronically infected adults in study sample			Chronically infected adults in general population	
		Number	Weighted prevalence (%)	95% CI	Number	95% CI	Number	Weighted prevalence (%)	95% CI	Number	95% CI
Sex	Female	14	0.42	0.25–0.71	7,370	4,387–12,458	8	0.24	0.12–0.49	4211	2,106–8,598
	Male	39	1.57	1.12–2.19	26,453	18,871–36,900	25	0.91	0.61–1.37	15333	10,278–23,083
Age	18–29 years	1	0.07	0.01–0.47	541	77–3,630	0	0	0	0	0
	30–39 years	20	1.94	1.21–3.10	14,709	9,174–23,504	12	1.07	0.59–1.95	8113	4,473–14,785
	40–49 years	18	1.53	0.96–2.43	9,731	6,106–15,455	13	1.11	0.64–1.91	7060	4,070–12,148
	50–59 years	6	0.83	0.33–2.09	4,307	1,712–10,845	3	0.30	0.10–0.94	1557	519–4,878
	60–69 years	5	0.69	0.29–1.66	2,708	1,138–6,514	2	0.27	0.07–1.09	1060	275–4,277
	70+years	3	0.50	0.16–1.57	1,809	579–5,680	3	0.50	0.16–1.57	1809	579–5,680
Area	HSE E	47	2.13	1.60–2.83	26,345	19,790–35,003	31	1.41	0.99–2.01	17440	12,245–24,861
	HSE M+NE	2	0.31	0.08–1.22	1,620	418–6,374	1	0.15	0.02–1.08	784	104–5,643
	HSE S+SE	3	0.48	0.15–1.47	4,173	1,304–12,779	1	0.16	0.02–1.12	1391	174–9,736
	HSE W+NW+MW	1	0.21	0.03–1.45	1,703	243–11,758	0	0	0	0	0
All	**Population 18+years**	**53**	**0.98**	**0.73–1.31**	**33,708**	**25,109–45,058**	**33**	**0.57**	**0.40–0.81**	**19,606**	**13,758–27,860**

CI: confidence interval; E: East; HCV: hepatitis C virus; HSE: Health Service Executive; M: Midlands; MW: Mid West; NE: North East; NW: North West; S: South; SE: South East; W: West.

March to June 2016) were reviewed to see if they met the study inclusion and exclusion criteria. Excluding records for specimens flagged for specific retention for other reasons, and those from persons less than 18 years of age, records were available for 49,269 specimens.

10,382 records were identified for antenatal screening specimens and 615 records for pre-employment screen specimens. After exclusions were applied to the 38,372 records for diagnostic specimens, 11,542 records remained, which, when combined with the antenatal and pre-employment screen records, totalled 22,539 records (Figure 1).

A further 1,034 records were excluded for the following reasons: no sex was recorded, the patient had a non-Irish residential address, or more than one specimen had come from the same individual. At this point, we also became aware that specimens collected in March 2014 and due for discard in March 2016 had already been discarded, leaving 18,173 specimens in the final sampling frame (Figure 1).

Antenatal specimens made up 7,600 (42%), pre-employment screen specimens 499 (3%) and the remaining diagnostic specimens 10,074 (55%) of this sampling frame.

Demographic and specimen characteristics of study sample

From a sampling frame of 18,173 specimens, a study sample of 3,814 specimens was selected. After including replacements for specimens of insufficient volume (where possible), the final sample comprised 3,795 specimens (99.5% of the desired number), with minimal under-sampling in three age-sex strata. Reflecting the referral bias we might expect in a national service based in the east of the country, the study sample contained a higher proportion of specimens from individuals resident in HSE-East (60%), which includes the greater Dublin area, compared with the general adult population in Ireland (36%) (Table 1). This geographical bias was accounted for in the weighted analysis presented below.

Laboratory findings and interpretation

Laboratory findings were consistent with 33 specimens having been collected from patients with chronic HCV infection, 20 from patients with resolved HCV infection, and one from a patient with possible acute infection; 3,737 specimens tested negative for anti-HCV. Four specimens yielded inconclusive anti-HCV results: in the ordinary course of events, the NVRL laboratory testing algorithms would have indicated that further specimens should be requested from these individuals, but this was not possible in this situation. Thus, in this study sample, the HCV chronicity rate was calculated as 62% (33 chronic out of 53 chronic plus resolved infections).

Seroprevalence

Overall, the 53 specimens confirmed as seropositive (Table 2) corresponded to a weighted seroprevalence of 0.98% (95% CI: 0.73–1.3%). Based on these findings, we estimate that 33,708 people in the adult population in Ireland have had previous exposure to HCV.

Seroprevalence was significantly higher in men (1.6%; 95% CI: 1.1–2.2%) than in women (0.42%; 95% CI: 0.25–0.71%), and in specimens from HSE-East (2.1%; 95% CI: 1.6–2.8%) than in specimens from other areas (Table 2 and Figure 2). Although not statistically significant, there was also a higher seroprevalence among specimens from people aged 30–39 years (1.9%; 95% CI: 1.2–3.1%) and 40–49 years (1.5%; 95% CI: 0.96–2.4%) than in other age groups.

We calculated the weighted seroprevalence among women aged between 18 and 49 years old to be 0.40% (95% CI: 0.20–0.76%).

Prevalence of chronic infection

The 33 specimens with serology consistent with chronic HCV infection corresponded to a weighted prevalence of chronic infection of 0.57% (95% CI: 0.40–0.81%). Based on this, we estimate that 19,606 persons in the adult population in Ireland have chronic HCV infection (Table 2).

The prevalence of chronic HCV infection was again significantly higher in men (0.91%; 95% CI: 0.61–1.4%) than in women (0.24%; 95% CI: 0.12–0.49%), and higher but not significantly so in specimens from HSE-East (1.4%; 95% CI: 0.99–2.0%) compared with specimens from other areas (Table 2 and Figure 2). There was also a higher prevalence of chronic infection among persons aged 30–39 years and 40–49 years (Table 2), although again, this was not statistically significant. No chronic infections were noted in the 18–29 years age group for either sex, and overall, the highest prevalence of chronic infection was in men aged 40–49 years in HSE-East (5.2%; 95% CI: 2.8–9.3%) and in men aged 30–39 years in HSE-East (3.5%; 95% CI: 1.8–6.9%).

Discussion

This is the first HCV population prevalence study to have been undertaken in Ireland. Compared with published studies, the estimated prevalence of 0.57% for chronic HCV infection suggests that Ireland ranks at the lower end of the spectrum in terms of HCV prevalence internationally [5,6]. Our findings furthermore suggest that based on age, sex, and geographical area, men born between 1965 and 1984 from the east of the country have the highest rate of chronic HCV infection in Ireland.

Our findings are broadly in line with those of a previous study that calculated a chronic HCV infection rate based on the number of new HCV laboratory diagnoses between 1989 and 2004, combined with Irish HCV notification data for 2004–2009 [17]. After applying a number of assumptions in relation to reporting bias, under-diagnoses, establishment of chronic infection, and case fatality, the authors estimated a population prevalence of chronic HCV infection of between 0.5 and 1.2% in 2011.

Our findings for women aged 18–49 years are also in line with estimates from HCV antibody prevalence studies conducted in two Dublin hospitals on antenatal women in 2007 [16] and 2007–2008 [15], which estimated seroprevalences of 0.7% with 57% HCV RNA positive [16], and 0.9% with HCV RNA positivity of 64% [15], respectively. The slightly lower weighted seroprevalence among women aged between 18 and 49 years in our study is perhaps not surprising given that it represents a wider geographical area, with the earlier published studies having been performed in settings largely serving women from the greater Dublin area.

HCV is a notifiable disease in Ireland both by clinicians and laboratories. Our findings are also consistent with recent Irish HCV notification data in terms of age, sex and geographical area; 69% of Irish HCV notifications in 2014 were reported from HSE-East, with injecting drug use reported as the most common risk factor at 80% [18]. It seems plausible given the age-sex-geographical distribution of our data, that our findings could also be substantially influenced by the occurrence of HCV infection in people who currently inject drugs, or have done so in the past.

Since the introduction of screening of donated blood for HCV in the early 1990s, HCV transmission through blood and blood products is rare. Prior to that, however, around 1,700 cases of HCV infection were acquired through blood and blood products in Ireland; their disease history is being documented in the National Hepatitis C Database [19,20]. Some of these have been successfully treated with antiviral therapy; however, the group remains an important sub-group of the seropositive population in Ireland, and may explain some of the seropositive specimens we identified in older adults.

In a review of the natural history of HCV infection, Seeff and colleagues described chronic infection rates of up to 80% in studies of HCV-infected adults, with lower rates of ca 50% in infected children or young women [1]. Our overall estimated chronicity rate of 62% is at the lower end of this range, but the study was not designed to reflect the natural history of HCV infection in Ireland or to take into account factors such as antiviral treatment.

Compared with previous studies in Ireland, based on high-risk, localised or antenatal populations [11-16], this study has the advantage of being a national survey representative of the general adult population. Large in size, it provides good precision in our overall estimate and in selected subgroups. As it used specimens already collected for other diagnostic and screening investigations, it was relatively inexpensive to perform, and provided a population estimate in a short time frame.

The main limitation of our study is potential bias because individuals whose specimens are submitted to NVRL for testing are not likely to be completely representative of the general adult population. To minimise bias by age group and sex, we stratified the sampling frame before sampling, and sampled with probability proportional to the size of the strata in the general population. In addition, to adjust for geographical bias in sample selection and for under-sampling in three age-sex strata, we weighted for HSE area, age group and sex in the analysis.

Attempts were made to minimise potential bias by excluding certain categories of residual specimens from persons who would be expected to have a higher risk of being HCV-seropositive (e.g. specimens from STI clinics, drug treatment services, or those that were submitted specifically for HCV testing). The intent was to avoid the over-representation of persons in risk groups that might arise from inclusion of specimens from these sources. Due to the large number of specimens excluded on such grounds however, it could be argued that we have selected a sample biased towards low-risk specimens, and therefore the estimate obtained should be considered the minimum.

Compared with other study designs [15,21,22], we had limited opportunity to look at risk factors other than age, sex and geographical area, as the sample was drawn from residual sera. The anonymous nature of the survey also precludes us from knowing what proportion of these individuals are already aware of their HCV status, what proportion of resolved infections were consequent to antiviral treatment, and also prevents referral of patients with positive specimens to care pathways.

Notwithstanding these limitations, these data are the best estimates to date in Ireland of HCV seroprevalence in the general population and we believe they will serve to: (i) provide more accurate information for the public on their likely risk of infection; (ii) inform health service planning regarding future screening programmes, future burden of HCV-associated disease and demand for antiviral treatment in Ireland; and (iii) provide a benchmark for evaluating the effectiveness of primary and secondary HCV prevention programmes. Owing to its simplicity, low cost, and rapidity, we would also recommend this study design as a model for sero-epidemiological studies for other diseases in Ireland, or for HCV sero-epidemiological studies elsewhere in Europe.

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Conflict of interest

None declared.

Authors' contributions

Patricia Garvey: Contributed to study concept and design, developed the research protocol, contributed to laboratory protocol and laboratory specimen selection, performed the statistical analysis and interpretation of statistical findings, and drafted the manuscript.

Brian O'Grady: Contributed to laboratory protocol and laboratory specimen selection, managed laboratory data and read and approved the manuscript for submission.

Geraldine Franzoni, Maeve Bolger and Katie Irwin Crosby: Conducted laboratory testing and read and approved the manuscript for submission.

Deirdre Burke: Contributed to laboratory protocol, supervised laboratory testing and read and approved the manuscript for submission.

Jeff Connell and Cillian De Gascun: Contributed to study concept and design, research protocol and laboratory protocol. Had overall responsibility for laboratory aspects of the study, including interpretation of laboratory findings, and read and approved the manuscript for submission.

Lelia Thornton: Contributed to study concept and design, research protocol and interpretation of statistical findings. Responsible for overall study supervision and read and approved the manuscript for submission.

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Research article

Severe liver disease related to chronic hepatitis C virus infection in treatment-naive patients: epidemiological characteristics and associated factors at first expert centre visit, France, 2000 to 2007 and 2010 to 2014

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Given recent profound improvements in the effectiveness of antiviral treatment for chronic Hepatitis C virus (HCV) infection, we aimed to describe the characteristics of patients referred to hepatology expert centres in France from 2000 to 2007 and from 2010 to 2014, and to identify factors associated with severe liver disease at their first visit for evaluation. We analysed data from two sources covering all of France: the former hepatitis C surveillance network, which included patients between 2000 and 2007, and the ANRS CO22 HEPATHER multi-centre cohort, which included patients between 2012 and 2014. Severe liver disease (SLD) was defined as the presence of either cirrhosis (histological, biochemical or clinical) or hepatocellular carcinoma. Multivariable Poisson regression models were used to identify the factors associated with SLD in complete-case analysis and after multiple imputation. Overall, 16,851 patients were included in the analysis and SLD was diagnosed in 11.6%. SLD at first visit was significantly associated with known risk factors (male sex, history of excessive alcohol intake, HCV genotype 3), late referral to hepatologists after diagnosis and HCV diagnosis at an older age. Providing earlier specialised care and treatment may be an important target for public health action.

Introduction

French public health policies have targeted hepatitis C virus (HCV) infection since the mid-1990s. Health authorities have promoted HCV-screening among individuals at risk of infection, and have enhanced and improved access to specialised care and antiviral treatment. They have also effectively reduced HCV transmission in the following contexts: blood transfusion [1], healthcare and PWID (people who inject drugs) [2].

France is a low endemic country for HCV infection. In 2004, the prevalence of chronic HCV infection in the general population was estimated at 0.53% (95% confidence interval (CI): 0.40–0.70), corresponding to 232,196 adults (95% CI: 167,869–296,523) 18–80 years of age, nearly 43% of whom were unaware of their infection [3]. Among the infected PWID population, 91% were aware of their infection, but among the blood transfusion recipients, only 50.7% were [3]. Prevalence has tended to decrease since then, with prevalence in 2011 being 0.42% (192,700 adults) [4]. In addition, the estimated number of undiagnosed chronically HCV-infected individuals has also decreased (72,102 adults in 2014) [5].

Chronic HCV infection can evolve into cirrhosis in 10–20% of cases over a period of 20 to 30 years. Cirrhosis is its main complication, along with hepatocellular carcinoma (HCC) [6]. Alcohol abuse, hepatitis B virus (HBV) and human immunodeficiency virus (HIV) co-infections, as well as metabolic disorders have all been shown to be major determinants of liver disease progression to cirrhosis, but individual-specific variations exist because of virus-host interactions. Cirrhosis

Table 1

Study criteria for presence of cirrhosis, France, 2000–2007 and 2010–2014

Liver fibrosis assessment	Criteria for cirrhosis
Yes	**Liver biopsy:** METAVIR score F4
	Serum biomarker (in absence of liver biopsy): FibroTest ≥ 0.75 [34]
	Transient elastography (in absence of liver biopsy and serum biomarkers): FibroScan liver stiffness ≥ 12.5 kPa (cut-off correlated with METAVIR score F4) [35]
No	**Clinical evidence of cirrhosis:** association of clinical signs, laboratory findings and imaging [36].

and HCC have a significant impact on morbidity and mortality related to chronic HCV infection [6]. However, successful treatment of the viral infection can stop evolution to severe liver disease (SLD), can limit the risk of cirrhosis decompensation and its associated liver-related mortality [7] and can even lead to fibrosis regression [8].

Results from treatment with new direct-acting antivirals (DAAs) show very high success rates (sustained virologic response (SVR) rates can reach up to 95–99% with slight variations according to the viral genotype), good tolerance and short therapeutic course [9].

In most European countries, access to these drugs is limited because of their high cost. Priority is given to patients with significant liver fibrosis or cirrhosis (METAVIR score F2-F4), extra-hepatic complications, or HBV or HIV co-infection [10]. However, to increase treatment effectiveness, treatment before the occurrence of cirrhosis (i.e. before METAVIR score F4) is preferable. In fact, SLD is an important negative predictor of SVR in DAAs-based therapy. Moreover, SVR in patients with a METAVIR score of F4 do not necessarily protect from further hepatic complications (e.g. decompensated cirrhosis, HCC) [9].

In France, hepatology expert centres have a pivotal role in chronic HCV infection evaluation and treatment. Until June 2016, their approval was necessary for any HCV antiviral drugs prescription [11].

Given these points, a better understanding of factors associated with late-stage liver disease in patients seeking care at an expert centre for the first time would help inform public health policymaking. It would indeed allow patients identified as at risk of developing hepatic complications to benefit from closer follow-up, and earlier referral and treatment access. Concrete interventions could include increasing HCV screening coverage, comorbidity prevention, and training of physicians involved in the follow-up of such patients.

The main objective of our study is to describe the chronic HCV-infected population seeking care at the hepatology expert centres in France from 2000 to 2007 and from 2010 to 2014, and to identify the factors associated with having HCV infection-related SLD at the time of their first evaluation there.

Methods

Study population

For the present analysis, we included data from patients who sought care for chronic HCV infection at hepatology expert centres across France from two periods: 2000 to 2007 and 2010 to 2014.

Patients with first visit to an expert centre in 2000–2007

For the period 2000 to 2007, patients were recruited by the hepatitis C hospital service-based surveillance network coordinated by Santé publique France (the French National Public Health Agency) [11]. A total of 26 of the 30 hepatology expert centres located in university hospitals throughout France participated in the network. Every newly-referred adult (≥ 18 years of age) patient with anti-HCV antibodies visiting any of these 26 centres (as an outpatient or inpatient) for the first time was included after consent and without further inclusion criteria.

Patients with first visit to an expert centre in 2010–2014

For the period 2010 to 2014, patients who agreed to participate in the nationwide multi-centre cohort study ANRS (France Recherche Nord & Sud Sida-HIV Hépatites) CO22 HEPATHER (ClinicalTrials.gov, number: NCT01953458) [12] that actively recruited individuals infected with HBV or HCV in 2012–2014, were also included. A total of 32 expert centres were involved in cohort recruitment, 26 of which had participated in the former hepatitis C surveillance network. Every adult (≥ 18 years of age) attending centres for HCV or HBV infection follow-up in 2012–2014 was eligible for inclusion in the cohort, regardless of infection duration and duration of the follow-up at the expert centre, with the exception of HIV co-infected patients, pregnant women and adults who could not independently provide consent to participate.

For our analyses, data for patients from these two populations that met the following criteria were included: we selected individuals (i) seeking care for chronic hepatitis C as defined in the following section, (ii) with no history of liver biopsy at the time of first expert centre visit, (iii) who were antiviral treatment naive, and (iv) whose first expert centre visit occurred in the 24 months preceding inclusion in the ANRS CO22 HEPATHER cohort study so as to avoid overlap between the two study periods. Analyses were also restricted to patients who (v) were HIV-negative and (vi) 18 years of age or older.

Table 2a

Characteristics of patients with chronic hepatitis C at time of their first visit to a hepatology expert centre, France, 2000–2007 and 2010–2014 (n = 16,851).

Patient characteristics		Overall		Period of first visit at expert centre following referral					
				2000–2003[a]		2004–2007[a]		2010–2014[a]	
		n or (median)	% or (IQR)	n or (median)	% or (IQR)	n or (median)	% or (IQR)	n or (median)	% or (IQR)
Total number of patients		16,851	NA	8,648	NA	6,881	NA	1,322	NA
Sex	**Female**	7,374	43.8	3,848	44.5%	3,011	43.8	515	39
	Male	9,386	55.7	4,709	54.5	3,870	56.2	807	61
	Missing	91	0.5	91	1.1	0	0	0	0
Country of birth	**France**	10,615	63	5,762	66.6	3,988	58	865	65.4
	Europe (outside France)	818	4.9	336	3.9	380	5.5	102	7.7
	North Africa and Middle East	973	5.8	430	5	426	6.2	117	8.9
	Sub-Saharan Africa	802	4.8	327	3.8	330	4.8	145	11
	Asia, Pacific, Americas	622	3.7	229	2.6	304	4.4	89	6.7
	Missing	3,021	17.9	1,564	18.1	1,453	21.1	4	0.3
HCV endemicity in country of birth [b]	**≤0.85%**	10,722	63.6	5,812	67.2	4,029	58.6	881	66.6
	0.86–1.4%	738	4.4	318	3.7	295	4.3	125	9.5
	1.5–2%	751	4.5	364	4.2	299	4.3	88	6.7
	2.1–3.2%	219	1.3	64	0.7	129	1.9	26	2
	›3.2%	1,363	8.1	526	6.1	639	9.3	198	15
	Missing	3,058	18.1	1,564	18.1	1,490	21.7	4	0.3
Age at HCV infection diagnosis	**Years**	(44)	(35–56)	(43)	(34–56)	(44)	(35–55)	(49)	(40–57)
Circumstances of HCV infection diagnosis	**Systematic screening**	8,344	49.5	3,911	45.2	3,466	50.4	967	73.1
	Exposure to a HCV infection risk	3,145	18.7	1,871	21.6	1,182	17.2	92	7
	Symptoms or laboratory findings	3,551	21.1	2,037	23.6	1,292	18.8	222	16.8
	Unknown	1,811	10.7	829	9.6	941	13.7	41	3.1
Time between HCV diagnosis and first expert centre visit	**Months**	(4)	(2–32)	(4)	(1–27)	(5)	(2–39)	(5)	(2–38)
French area/region of first visit	**Paris area**	3,481	20.7	1,775	20.5	1,259	18.3	447	33.8
	North-West	3,825	22.7	2,200	25.4	1,504	21.9	121	9.2
	North-East	2,978	17.7	1,545	17.9	1,184	17.2	249	18.8
	South-West	2,586	15.3	1,370	15.8	1,039	15.1	177	13.4
	South-East	3,746	22.2	1,644	19	1,788	26	314	23.8
	French Caribbean islands	235	1.4	114	1.3	107	1.6	14	1.1
HCV infection risk factor	**Intravenous drug use**	5,234	31.1	2,756	31.9	2,105	30.6	373	28.2
	Nasal drug use	347	2.1	151	1.7	139	2	57	4.3
	Blood-derived product transfusion before 1991	4,402	26.1	2,427	28.1	1,679	24.4	296	22.4
	Other risk factors	4,029	23.9	1,863	21.5	1,574	22.9	592	44.8
	No risk factor found	2,839	16.8	1,451	16.8	1,384	20.1	4	0.3

ALT: alanine aminotransferase; HCV: hepatitis C virus; IQR: interquartile range; NA: not applicable.

[a] Data for the time periods 2000–2003 and 2004–2007 came from France's hepatitis C surveillance network while that for the time period 2010–2014 came from the nationwide multi-centre cohort study ANRS CO22 HEPATHER.

[b] Endemicity of HCV in countries of birth was defined according to anti-HCV prevalence estimated by Gower et al. [14] and Lavanchy et al. [15]. Global HCV prevalence data were then categorised into 5 quintiles: ≤0.85%, 0.86–1.4% and 1.5–2% (low HCV prevalence), 2.1–3.2% (intermediate HCV prevalence) and ›3.2% (high HCV prevalence).

[c] Excessive alcohol intake was defined as consumption of more than 140 g of pure ethanol per week for women and 210 g of pure ethanol per week for men, corresponding to 14 and 21 glasses of wine, respectively. Present and past consumption were recorded at the moment of the interview.

[d] The ALT ratio was calculated as function of the upper limit of normal; during the first two periods, this data was already reported as a ratio and during the last period, it was calculated using an upper limit of normal compatible with that used by clinicians during the first period (35 IU/L).

[e] Severe liver disease (SLD) was defined by the diagnosis of either cirrhosis or hepatocellular carcinoma.

Table 2b

Characteristics of patients with chronic hepatitis C at time of their first visit to a hepatology expert centre, France, 2000–2007 and 2010–2014 (n = 16,851).

Patient characteristics		Overall		Period of first visit at expert centre following referral					
				2000–2003[a]		2004–2007[a]		2010–2014[a]	
		n or (median)	% or (IQR)	n or (median)	% or (IQR)	n or (median)	% or (IQR)	n or (median)	% or (IQR)
HBV co-infection at first visit	**No**	12,283	72.9	5,764	66.7	5,523	80.3	996	75.3
	Yes	315	1.9	149	1.7	141	2	25	1.9
	Missing	4,253	25.2	2,735	31.6	1,217	17.7	301	22.8
Excessive alcohol intake [c]	**None**	10,946	65	5,459	63.1	4,742	68.9	745	56.4
	Current	466	2.8	288	3.3	178	2.6	0	0
	Current and past	1,293	7.7	815	9.4	426	6.2	52	3.9
	Past	2,303	13.7	1,049	12.1	910	13.2	344	26
	Missing	1,843	10.9	1,037	12	625	9.1	181	13.7
HCV genotype	**1**	7,023	41.7	3,198	37	3,142	45.7	683	51.7
	2	1,391	8.3	683	7.9	601	8.7	107	8.1
	3	2,402	14.3	1,125	13	1,065	15.5	212	16
	4	1,146	6.8	471	5.4	511	7.4	164	12.4
	5, 6 or 7	281	1.7	132	1.5	118	1.7	31	2.3
	Missing	4,608	27.3	3,039	35.1	1,444	21	125	9.5
ALT ratio [d]	**Times the upper limit of normal**	(1.5)	(1–2.5)	(1.5)	(1–2.5)	(1.5)	(1–2.3)	(1.71)	(1.03–2.91)
Severe liver disease[e]	**None**	13,566	80.5	7,053	81.6	5,622	81.7	891	67.4
	Cirrhosis	1,798	10.7	710	8.2	748	10.9	340	25.7
	Hepatocellular carcinoma	151	0.9	57	0.7	66	1	28	2.1
	Missing	1,336	7.9	828	9.6	445	6.5	63	4.8
Severe liver disease diagnostic tool	**No severe liver disease**	13,566	80.5	7,053	81.6	5,622	81.7	891	67.4
	Liver biopsy	834	4.9	485	5.6	283	4.1	66	5.0
	FibroTest	391	2.3	0	NA	301	4.4	90	6.8
	FibroScan	107	0.6	0	NA	0	NA	107	8.1
	Clinical evaluation	617	3.7	282	3.3	230	3.3	105	7.9
	Missing	1,336	7.9	828	9.6	445	6.5	63	4.8

ALT: alanine aminotransferase; HCV: hepatitis C virus; IQR: interquartile range; NA: not applicable.

[a] Data for the time periods 2000–2003 and 2004–2007 came from France's hepatitis C surveillance network while that for the time period 2010–2014 came from the nationwide multi-centre cohort study ANRS CO22 HEPATHER.

[b] Endemicity of HCV in countries of birth was defined according to anti-HCV prevalence estimated by Gower et al. [14] and Lavanchy et al. [15]. Global HCV prevalence data were then categorised into 5 quintiles: ≤ 0.85%, 0.86–1.4% and 1.5–2% (low HCV prevalence), 2.1–3.2% (intermediate HCV prevalence) and > 3.2% (high HCV prevalence).

[c] Excessive alcohol intake was defined as consumption of more than 140 g of pure ethanol per week for women and 210 g of pure ethanol per week for men, corresponding to 14 and 21 glasses of wine, respectively. Present and past consumption were recorded at the moment of the interview.

[d] The ALT ratio was calculated as function of the upper limit of normal; during the first two periods, this data was already reported as a ratio and during the last period, it was calculated using an upper limit of normal compatible with that used by clinicians during the first period (35 IU/L).

[e] Severe liver disease (SLD) was defined by the diagnosis of either cirrhosis or hepatocellular carcinoma.

Data collection

For all patients in the study, standardised forms were used to collect data from the visit (interview and patient assessment) on the following: sociodemographic characteristics; history of HCV infection; HCV infection risk factors; stage of liver disease when first examined at expert centre (liver fibrosis was evaluated by METAVIR score, clinical signs and liver biochemical markers such as alanine aminotransferase (ALT)); comorbidities such as alcohol consumption and HBV–co-infection; HCV-RNA viral load; and HCV genotype. We analysed data collected at the time of patients' first visit to the centres or, when this was not possible, the earliest available data from a consultation after the first visit.

Definitions

Chronic hepatitis C was defined as testing positive for anti-HCV antibodies with persistent detection of HCV-RNA for at least six months after diagnosis.

Table 3a

Estimation of adjusted prevalence ratios of severe liver disease in patients with chronic hepatitis C at first visit in hepatology expert centres in France using multivariate models in a complete cases analysis and after multiple imputation, France, 2000–2007 and 2010–2014

Patient characteristics		Complete cases multivariate analysis (n = 8,171)					Multiple imputation multivariate analysis (n = 16,851)		
		Number of patients with SLD/total number patients per strata	% SLD[a] per strata	aPR	95% CI	p value	aPR	95% CI	p value
Sex	**Female**	341/3,472	9.8	1	Ref	<0.001	1	Ref	<0.001
	Male	744/4,699	15.8	1.58	1.40–1.75		1.53	1.40–1.67	
Country of birth	**France**	NA	NA	NA	NA	NA	1	Ref	0.002
	Europe (outside France)	NA	NA	NA	NA	NA	1.06	0.89–1.26	0.504
	North Africa and Middle East	NA	NA	NA	NA	NA	1.34	1.16–1.56	<0.001
	Sub-Saharan Africa	NA	NA	NA	NA	NA	1.00	0.80–1.26	0.975
	Asia, Pacific, Americas	NA	NA	NA	NA	NA	0.98	0.78–1.22	0.827
Age at HCV infection diagnosis	**18 years**	0/35	0.0	1	Ref	<0.001	1	Ref	<0.001
	19–30 years (25)[b]	37/1,118	3.3	2.36	2.17–2.57		2.23	2.10–2.38	
	31–40 years (35)[b]	124/2,002	6.2	5.69	4.80–6.75		5.09	4.47–5.79	
	41–50 years (45)[b]	309/2,175	14.2	10.98	8.68–13.89		9.40	7.87–11.24	
	51–60 years (55)[b]	285/1,416	20.1	18.56	13.93–24.72		15.36	12.36–19.09	
	61–70 years (65)[b]	196/899	21.8	28.73	20.66–39.94		23.11	18.01–29.67	
	71–90 years (80)[b]	133/482	27.6	49.44	33.72–72.50		38.41	28.74–51.33	
Circumstances of HCV infection diagnosis	**Systematic screening**	555/4,585	12.1	1	Ref	<0.001	1	Ref	<0.001
	Exposure to a HCV infection risk	119/1,629	7.3	0.90	0.74–1.08	0.254	0.90	0.78–1.05	0.176
	Symptoms or laboratory findings	411/1,957	21.0	1.41	1.26–1.58	<0.001	1.47	1.34–1.61	<0.001
Time between HCV diagnosis and first expert centre visit	**0 months**	124/672	18.5	1	Ref	<0.001	1	Ref	<0.001
	1–6 months (3)[b]	496/4,098	12.1	1.02	1.01–1.02		1.01	1.01–1.02	
	7–12 months (9)[b]	105/754	13.9	1.05	1.04–1.06		1.04	1.04–1.05	
	13–24 months (18)[b]	64/504	12.7	1.11	1.09–1.13		1.09	1.07–1.11	
	25–48 months (36)[b]	72/527	13.7	1.22	1.18–1.27		1.19	1.15–1.23	
	48–96 months (72)[b]	94/770	12.2	1.50	1.39–1.61		1.42	1.33–1.50	
	97–192 months (144)[b]	104/770	13.5	2.24	1.94–2.58		2.01	1.78–2.26	
	193–288 months (240)[b]	26/76	34.2	3.83	3.02–4.86		3.19	2.61–3.90	

ALT: alanine aminotransferase; aPR: adjusted prevalence ratio; CI: confidence interval; HCV: hepatitis C virus; NA: not available, not applicable or not known; Ref: reference group for comparison; SLD: severe liver disease.

[a] Severe liver disease (SLD) was defined by the diagnosis of either cirrhosis or hepatocellular carcinoma.

[b] Numbers in brackets are the middle value of the category, used to estimate the aPR.

[c] Data for the time periods 2000–2003 and 2004–2007 came from France's hepatitis C surveillance network while that for the time period 2010–2014 came from the nationwide multi-centre cohort study ANRS CO22 HEPATHER.

[d] Excessive alcohol intake was defined as consumption of more than 140 g of pure ethanol per week for women and 210 g of pure ethanol per week for men, corresponding to 14 and 21 glasses of wine, respectively. Present and past consumption were recorded at the moment of the interview.

[e] The ALT ratio was calculated as function of the upper limit of normal; during the first two periods, this data was already reported as a ratio and during the last period, it was calculated using an upper limit of normal compatible with that used by clinicians during the first period (35 IU/L).

Table 3b

Estimation of adjusted prevalence ratios of severe liver disease in patients with chronic hepatitis C at first visit in hepatology expert centres in France using multivariate models in a complete cases analysis and after multiple imputation, France, 2000–2007 and 2010–2014

Patient characteristics		Complete cases multivariate analysis (n = 8,171)					Multiple imputation multivariate analysis (n = 16,851)		
		Number of patients with SLD/total number patients per strata	% SLD[a] per strata	aPR	95% CI	p value	aPR	95% CI	p value
French area/region of first visit	Paris area	229/1,466	15.6	1	Ref	0.047	1	Ref	<0.001
	North-West	214/1,833	11.7	0.96	0.81–1.13	0.600	1.25	1.10–1.42	0.001
	North-East	190/1,417	13.4	1.00	0.84–1.17	0.955	1.21	1.06–1.39	0.004
	South-West	156/1,510	10.3	0.82	0.68–0.98	0.026	1.14	0.99–1.31	0.071
	South-East	271/1,777	15.3	1.08	0.93–1.25	0.316	1.38	1.23–1.55	<0.001
	French Caribbean islands	25/168	14.9	1.19	0.83–1.69	0.343	1.53	1.13–2.09	0.007
Study period at first visit	2000–2003[c]	358/3,602	9.9	1	Ref	<0.001	1	Ref	<0.001
	2004–2007[c]	451/3,697	12.2	1.23	1.08–1.39	0.001	1.31	1.20–1.43	<0.001
	2010–2014[c]	276/872	31.7	2.14	1.84–2.49	<0.001	2.39	2.13–2.69	<0.001
HCV infection risk factor	Intravenous drug use	282/2,631	10.7	1	Ref	0.038	1	Ref	0.004
	Nasal drug use	31/200	15.5	1.21	0.91–1.61	0.196	1.14	0.88–1.48	0.325
	Blood product transfusion before 1991	327/2,152	15.2	1.18	0.99–1.40	0.058	1.19	1.04–1.37	0.011
	Other risk factors	284/2,104	13.5	1.01	0.86–1.19	0.889	1.00	0.87–1.15	0.967
	No risk factor found	161/1,084	14.9	1.25	1.03–1.51	0.026	1.27	1.09–1.47	0.002
Excessive alcohol intake[d]	None	624/5,926	10.5	1	Ref	<0.001	1	Ref	<0.001
	Current	35/257	13.6	1.48	1.08–2.03	0.015	1.39	1.09–1.78	0.009
	Current and past	129/637	20.3	2.15	1.81–2.56	<0.001	2.18	1.90–2.49	<0.001
	Past	297/1,351	22.0	1.90	1.67–2.17	<0.001	2.08	1.87–2.31	<0.001
HCV genotype	1	643/4,701	13.7	1	Ref	<0.001	1	Ref	<0.001
	2	103/919	11.2	0.81	0.67–0.98	0.027	0.84	0.72–0.98	0.031
	3	229/1,602	14.3	1.36	1.19–1.57	<0.001	1.29	1.15–1.45	<0.001
	4	84/765	11.0	1.07	0.88–1.31	0.487	0.99	0.82–1.19	0.887
	5, 6 or 7	26/184	14.1	0.77	0.55–1.08	0.127	0.76	0.57–1.00	0.054
ALT ratio[e]	1	51/1,133	4.5	1	Ref	<0.001	1	Ref	<0.001
	1–2.5 (2)[b]	463/3,684	12.6	1.68	1.52–1.86		1.61	1.50–1.72	
	2.5–10 (6.5)[b]	476/1,936	24.6	2.96	2.54–3.45		2.87	2.55–3.22	
	>10 (20)[b]	11/60	18.3	1.40	0.66–2.97		1.80	1.06–3.04	

ALT: alanine aminotransferase; aPR: adjusted prevalence ratio; CI: confidence interval; HCV: hepatitis C virus; NA: not available, not applicable or not known; Ref: reference group for comparison; SLD: severe liver disease.

[a] Severe liver disease (SLD) was defined by the diagnosis of either cirrhosis or hepatocellular carcinoma.

[b] Numbers in brackets are the middle value of the category, used to estimate the aPR.

[c] Data for the time periods 2000–2003 and 2004–2007 came from France's hepatitis C surveillance network while that for the time period 2010–2014 came from the nationwide multi-centre cohort study ANRS CO22 HEPATHER.

[d] Excessive alcohol intake was defined as consumption of more than 140 g of pure ethanol per week for women and 210 g of pure ethanol per week for men, corresponding to 14 and 21 glasses of wine, respectively. Present and past consumption were recorded at the moment of the interview.

[e] The ALT ratio was calculated as function of the upper limit of normal; during the first two periods, this data was already reported as a ratio and during the last period, it was calculated using an upper limit of normal compatible with that used by clinicians during the first period (35 IU/L).

Liver fibrosis was assessed either by invasive (liver biopsy) or validated non-invasive methods based on serum biomarkers (FibroTest) or based on liver stiffness measurement by transient elastography (FibroScan) [13]. Liver fibrosis assessments were considered for the present analysis if they were performed not more than 12 months before or after the first visit to an expert centre.

In the absence of liver fibrosis assessment, cirrhosis was assessed by a clinical evaluation, which included a physical examination, biochemical tests and imaging, mainly abdominal ultrasound (Table 1). Clinical evaluation was taken into account if performed at the time of first expert centre visit or in the 24 months before inclusion in the ANRS CO22 HEPATHER cohort.

SLD was defined by the diagnosis of either cirrhosis or HCC.

Excessive alcohol intake was defined as more than 140 g of pure ethanol per week for women and more than 210 g per week for men, corresponding to 14 and 21 glasses of wine, respectively. Both present and past consumption were recorded at the time of the interview. Endemicity of HCV infection in countries of birth was defined according to anti-HCV prevalence estimated by Gower et al. [14] and Lavanchy et al. [15]. Global HCV prevalence data were then categorised in five quintiles: ≤ 0.85%, 0.86–1.4% and 1.5–2% (low HCV prevalence), 2.1–3.2% (intermediate HCV prevalence), and > 3.2% (high HCV prevalence).

Patients' referral years were categorised into three periods: 2000 to 2003, 2004 to 2007 and 2010 to 2014.

The ALT ratio was calculated as function of the upper limit of normal; during the first two periods, this data was already reported as a ratio and during the last period, it was calculated using an upper limit of normal compatible with that used by clinicians during the first period (35 IU/L).

Statistical methods

Patient characteristics were presented as numbers and proportions for each category of qualitative data, and as medians and interquartile ranges (IQR) for quantitative data. For each variable, the number and proportion of missing data were also reported.

Bivariate analyses according to the stage of the liver disease (SLD or not) were performed using Poisson regression models. Bivariate modelling of explanatory variables was performed by introducing fractional polynomials to find the best relationship between risk of SLD and the independent variable [16].

Missing data were considered as resulting from a missing at random (MAR) mechanism. A multiple imputation was performed using chained equation [17]. We included all the variables from the multivariate model in the imputation model to ensure that both models (for imputation and analyses) were congenial [17]. For each non-Gaussian continuous variable, we applied the transformation proposed by Nevalainen et al. [18]. We generated 100 imputed datasets. The distributions before and after imputation were compared for every selected variable and were found to be similar.

Factors associated with SLD were identified using multivariate Poisson regression [19] with robust variance and fractional polynomials for continuous explanatory variables [16,20]. The following co-variables were identified a priori and were included in the multivariable model if they had a p value < 0.20 in the bivariate analyses: sex, country of birth, age at HCV diagnosis, circumstances of HCV diagnosis, time between HCV diagnosis and first expert centre visit, French area/region of first expert centre visit, study period at time of first expert centre visit, HCV infection risk factor, excessive alcohol intake, HCV genotype, HBV co-infection and ALT ratio. They were selected using a manual stepwise backward approach. The area/region of referral was forced into the model as an adjustment variable, in order to partially take into account a potential centre effect. We tested interactions between sex and risk factors, sex and excessive alcohol intake, and risk factors and excessive alcohol intake. We also tested interactions between the study period and, respectively, excessive alcohol consumption, HCV infection risk factors, circumstances of diagnosis and HCV genotype. These analyses were performed on both complete cases and after imputation to estimate adjusted prevalence ratios (aPR), their 95% confidence intervals (95% CI) and p values.

All the analyses were performed with STATA 12 (StataCorp, College Station, Texas, United States) and R (version 3.2.3) statistical software. All tests were considered significant with a two-tailed p value ≤ 0.05. The Stata user-written programme ICE was used to perform the imputation process.

Ethical statements

Protocols for the two studies were approved by the French data protection authority (CNIL) and explained to all patients meeting the case definition, and who provided written consent when enrolled.

Results

A total of 16,851 patients matched our inclusion criteria: 15,529 from the hepatitis C surveillance network and 1,322 from the ANRS CO22 HEPATHER study (**Table 2**). Of these patients, 55.7% were men, 72.5% were born in low-endemic areas for HCV infection (HCV infection prevalence ≤ 2%), mostly France and other European countries, and 8.1% were born in areas with high HCV prevalence. The proportion of patients born in areas with high HCV prevalence varied from 6.1% in 2000–2003 to 15% in 2010–2014. The median age at diagnosis was 44 years (IQR: 35-56), corresponding to

a median age of 43, 44 and 49 years in the three study periods, respectively.

Overall, a history of intravenous drug use and blood transfusion before 1991 were found in 31.1% and 26.1% of patients respectively.

In 18.7% of all patients, known exposure to a HCV risk factor was what led to HCV infection diagnosis (ranging from 21.6% in 2000–2003 to 7% in 2010–2014) and in 49.5% of cases, it came through systematic screening such as blood donor screening, pre-surgery and pre-transfusion screening, prenatal testing, screening for insurance contract (ranging from 45.2% in 2000–2003 to 73.1% in 2010–2014).

The median time between diagnosis and referral to the expert centre was 4 months (IQR: 2-32) and seemed homogeneous across the three periods, as did the ALT ratio at referral (1.5 times higher than the upper limit of normal) and the proportion of patients with a HBV-co-infection (1.9%). Patients were mainly infected by HCV genotype 1 and 3, with this being in 57.3% and 19.6% of patients with a known genotype, respectively. Of note, the proportion of patients infected with an unknown genotype varied from 35.1% in the first study period to 9.5% in the third.

Of all patients, 10.5% were found to declare a current excessive consumption of alcohol at the time of the interview.

Overall, cirrhosis diagnosis was present at first visit in 10.7% of the patients and HCC was present in 0.9%. Among patients recruited during the third study period, cirrhosis and HCC were present in 25.7% and 2.1% of patients, respectively.

Factors associated with severe liver disease (SLD)

All selected variables, except for HBV co-infection, were significantly associated with the risk of SLD at patients' first visit based on the bivariate analysis, and were introduced in the initial regression models. These statistically significant associations were confirmed by the multivariable analysis of imputed data. (Table 3)

The following factors were associated with an increased risk of SLD at the time of first visit: male sex (aPR = 1.53; 95% CI: 1.40–1.67); being born in North Africa or the Middle East (aPR = 1.34; 95% CI: 1.16–1.56) compared with being born in France; blood product transfusion before 1991 (aPR = 1.19; 95% CI 1.04–1.37) and no other known HCV risk factor (aPR = 1.27; 95% CI: 1.09–1.47) compared with intravenous drug use; current and/or past excessive alcohol intake ($p<0.001$); and symptom-based HCV diagnosis compared with diagnosis from systematic screening (aPR = 1.47; 95% CI: 1.34–1.61).

Compared with genotype 1, genotype 2 was found to be negatively associated with SLD while genotype 3 was found to be associated with an increased risk of SLD in both complete case and multiple imputed data analyses.

Age at diagnosis and time between diagnosis and first expert centre visit were linked by a positive nonlinear relationship with the risk of SLD (Table 3). The ALT ratio (cf.d with the upper limit of normal) was linked by a nonlinear non-monotonic relation with the risk of SLD (Table 3).

The prevalence of SLD significantly changed across the three study periods ($p<0.001$ in both analyses) and doubled between the first period (2000–2003) and the last (2010–2014).

Apart from the country of birth, which was not significantly associated with the risk of SLD in the complete cases analysis, results from the complete cases multivariate analysis (n = 8,171) and multiple imputation multivariate analysis (n = 16, 851) were similar.

We found no statistically significant interaction.

Discussion

Our observational multi-centre study allows us to describe factors associated with SLD in patients with chronic hepatitis C at the time of their first visit to a hepatology expert centre in France from 2000 to 2007 and 2010 to 2014. It confirms the influence of several known risk factors for SLD in chronic hepatitis C, including male sex, a history of excessive alcohol intake, age at diagnosis and HCV genotype 3 [6,11,21].

During the overall study period we observed a general increase in the percentage of SLD at first visits. This trend is consistent with those observed via the French Hospital Discharge Data System (PMSI) from 2004 to 2011, where both diagnosis of cirrhosis and of HCC among the HCV-infected hospitalised population increased from 17.8% to 33.7% and from 4.0% to 7.3%, respectively [22]. During the same period, the prevalence of chronic hepatitis C tended to decrease in the hospitalised population (from 0.45% to 0.33%) and general population (from 0.53% to 0.42%) in France [22]. These opposing trends could reflect an ageing of patients infected with HCV in recent decades and fewer new HCV infections in France. Patients' evaluation at an expert centre was a key moment before specific treatment, and in general, patients with SLD may have been referred for follow-up and treatment more frequently than non-severe patients. During the 2012–2014 period, which corresponds with the start of HCV treatment with DAAs, patients with severe liver fibrosis or SLD had priority access to these innovative treatments. In this context, patients with SLD were probably referred to expert centres for treatment by their general practitioner more frequently than in the past. It may therefore be the case that the evolution observed in our data reflects increased attractiveness of specialised care services during the last period. In addition, it is possible that patients with SLD were more likely to

have been included in the ANRS CO22 HEPATHER cohort by the expert centres themselves as one of the cohort's objectives is to evaluate and measure the impact of new drug associations on the course of chronic hepatitis C. Consequently, it is possible that the burden of SLD we observed in our study is overestimated, especially for the third period of study, although the change in SLD prevalence might be consistent with an existing trend in French chronic hepatitis C epidemiology.

We found that the longer the time between HCV infection diagnosis and first hepatology expert centre visit, the higher the probability was of having SLD. This highlights the urgent need to raise the awareness among patients and general practitioners about the need for both close monitoring of chronic HCV infection after diagnosis and earlier referral for treatment.

Interestingly, our results suggest a protective effect of genotype 2 on the risk of SLD at a patient's first expert centre visit. Indeed, there is already some evidence linking genotype 2 to a lower prevalence of liver fibrosis [23] and to slower progression to cirrhosis [24,25] compared with other genotypes. We also confirmed the relationship between genotype 3 and liver cirrhosis shown by others [21,25].

Place of birth appears to be linked to the risk of SLD at first hepatology expert centre visit, especially for patients born in North Africa or the Middle East. Although an association between migration and poorer prognosis in hepatitis C has already been described [26,27], it is not well understood and needs further investigation. One possible reason for this observed association is the lack of information concerning comorbidities such as type 2 diabetes and metabolic syndrome, which are potentially not homogeneously prevalent among different ethnic groups. In addition, the evolution of chronic hepatitis C in this sub-group of patients could be different. Age at infection, mode of contamination, lifestyle, access to HCV screening and care may all influence the course of disease progression [28,29]. Another possible reason for the association between place of birth (as a proxy for patients' country) and the risk of SLD at first hepatology expert centre visit could be that people from France might be referred to an expert centre even when not severely ill, while patients from foreign countries (especially those that are mainly francophone) might more frequently seek treatment at an expert centre in France only when they become severely ill.

Age at diagnosis had a positive relationship with the risk of SLD in our study. This variable takes the age of the patient, a known risk factor for the evolution to cirrhosis [30], into account. Age at diagnosis may also reflect the duration of infection: the older the patient at diagnosis, the more likely he or she has been infected longer. The importance of early diagnosis is indicated by the increased risk of SLD at the time of first expert centre visit for patients whose diagnosis is based on hepatic or digestive symptoms (clinical or biochemical).

In addition, our study showed that patients with no identified HCV infection risk factor tended to have a greater probability of SLD at their first visit than well-identified at-risk groups, such as drug users and blood transfusion recipients before 1991. This finding suggests that when both patients and practitioners are unaware of the risk of viral hepatitis, the former tend to be referred when they already have late stage disease and a poorer prognosis.

The limitations of our study include: (i) its cross-sectional design, with retrospective and self-reported assessment of several exposures, including alcohol consumption and risk behaviours, (ii) the inclusion of one group of patients via systematic surveillance and the other via a cohort study, with different recruitment and with slight differences in the forms' wording and structure, that has probably lead to a difference in the quality of data and in missing data proportions, and (iii) other factors known to be associated with fibrosis (e.g. obesity, metabolic syndrome, type 2 diabetes, duration of infection) were not collected for all the periods, with these factors therefore not included in our analysis. Furthermore, our data could only provide estimations on a select population (chronic hepatitis C patients referred to a hepatology expert centre), not necessarily reflecting the characteristics of the overall population of patients with chronic hepatitis C.

Despite these study limitations, our work provides interesting insights in the context of chronic hepatitis C patient care evolution.

First, it underlines the importance of early diagnosis and providing the general population with better information about HCV infection risk factors. In fact, severe disease was more frequently diagnosed when symptoms or biochemical liver abnormalities triggered testing. To increase people's awareness about their HCV infection status, screening recommendations and guidelines were revised [31,32] to emphasise both targeted and mass screening. Accordingly, the utilisation of HCV rapid tests has been authorised in the context of healthcare facilities and approved charities.

Second, our results highlight that a long delay between diagnosis and first visit to a hepatology expert centre increases the risk of having late stage disease when starting specialised care and antiviral treatment. This in turn is associated with a lower probability of treatment success and the continued risk of further complications even after successful treatment. In this light, the French National Authority for Health (HAS) issued new recommendations for treatment in June and December 2016, broadening the eligibility parameters for DAAs treatment to include patients with a METAVIR score of F0-F1, incorporating both individual and collective objectives for HCV infection eradication

[32,33], and allowing the prescription of DAAs outside the expert centres. Health authorities should also urge general practitioners to refer patients with HCV infections to a hepatology specialist or unit as early as possible in order to ensure their steady treatment. As now recommended in France, all adults diagnosed with hepatitis C should be immediately referred for evaluation and HCV treatment.

Finally, particular attention should be paid to migrant patient as they could be at greater risk of already having late stage disease when referred to specialised care. Early referral is even more important for patients with supplementary risk factors such as a history of alcohol excessive consumption, HCV infection diagnosis at an older age, male sex and HCV genotype 3.

These findings originating from French epidemiological data may be important for other European countries dealing with similar challenges in HCV infection care. Indeed, effective tertiary prevention of HCV complications, which have been made possible thanks to the extension of DAAs treatment to new populations, is an ethical obligation of our modern healthcare systems. In this light, effective large-scale screening and earlier referral of HCV-infected patients are two very important public health tools.

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Conflict of interest

None declared.

Authors' contributions

AS, CL and EDA conceived and designed the study. CL, EDA, YLS and PC supervised the study. FRT, SDB, PC, EDA and CL participated in the design of at least one of the two studies (the hepatitis C surveillance network and/or the ANRS CO22 HEPATHER cohort). AS and YLS performed the statistical

analysis. AS drafted the manuscript. All the authors interpreted the data, critically revised the manuscript and gave their final approval of the version to be published.

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Research article

Development and validation of the HCV-MOSAIC risk score to assist testing for acute hepatitis C virus (HCV) infection in HIV-infected men who have sex with men (MSM)

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Current guidelines recommend hepatitis C virus (HCV) testing for HIV-infected men who have sex with men (MSM) with ongoing risk behaviour, without specifying the type of risk behaviour. We developed and validated the HCV-MOSAIC risk score to assist HCV testing in HIV-infected MSM. The risk score consisted of six self-reported risk factors identified using multivariable logistic regression using data from the Dutch MOSAIC study (n = 213, 2009–2013). Area under the ROC curve (AUC), sensitivity, specificity, post-test-probability-of-disease and diagnostic gain were calculated. The risk score was validated in case–control studies from Belgium (n = 142, 2010–2013) and the United Kingdom (n = 190, 2003–2005) and in cross-sectional surveys at a Dutch sexually transmitted infections clinic (n = 284, 2007–2009). The AUC was 0.82; sensitivity 78.0% and specificity 78.6%. In the validation studies sensitivity ranged from 73.1% to 100% and specificity from 56.2% to 65.6%. The post-test-probability-of-disease ranged from 5.9% to 20.0% given acute HCV prevalence of 1.7% to 6.4%, yielding a diagnostic gain of 4.2% to 13.6%. The HCV-MOSAIC risk score can successfully identify HIV-infected MSM at risk for acute HCV infection. It could be a promising tool to improve HCV testing strategies in various settings.

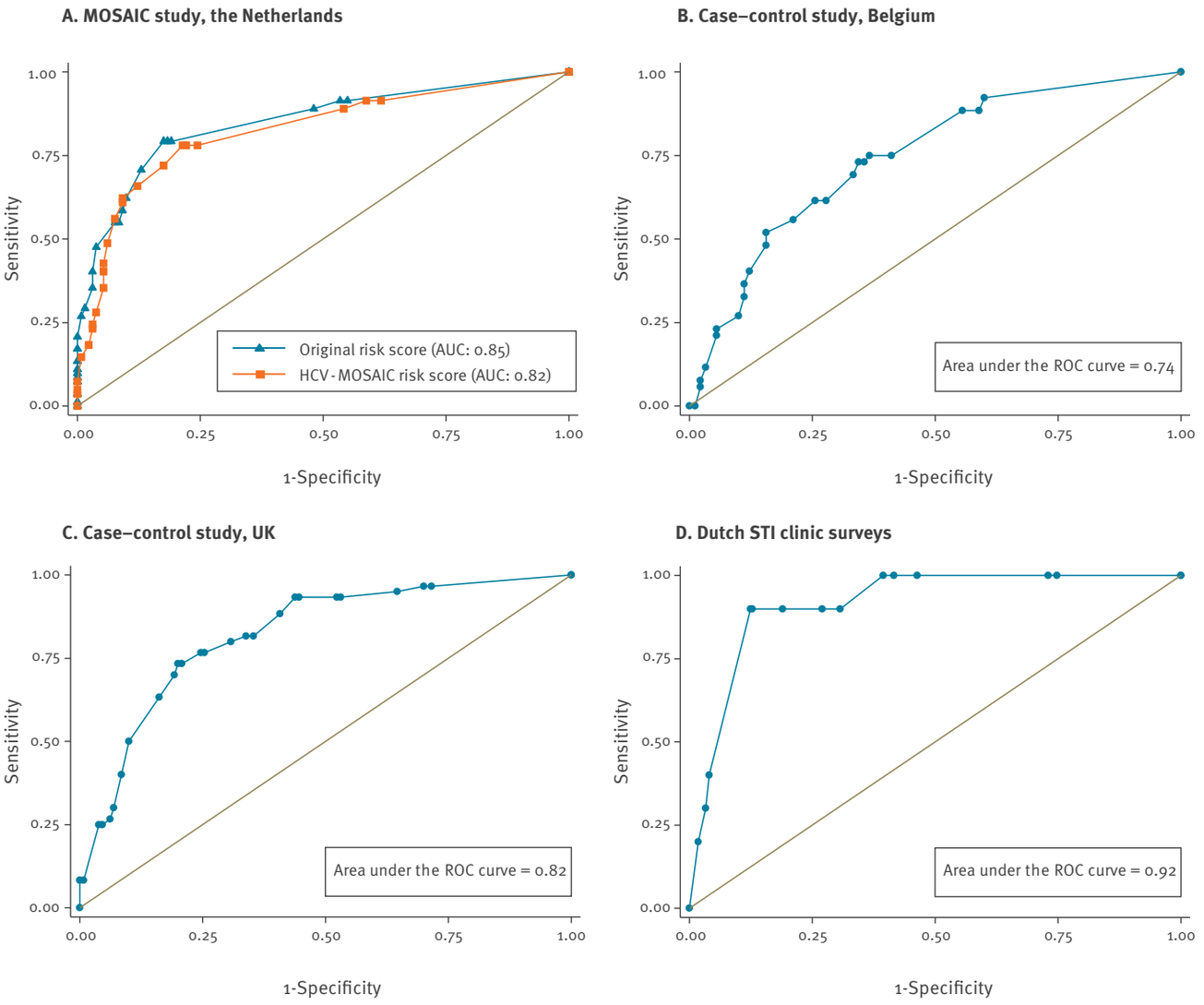
Introduction

Studies on hepatitis C virus (HCV) infections among HIV-infected men who have sex with men (MSM) have provided insights into the epidemiology and risk factors for sexually transmitted HCV acquisition [1,2]. As HCV transmission among MSM is ongoing in high-income countries worldwide [3,4], targeted testing is needed. Current national and international clinical guidelines recommend at least annual HCV antibodies (anti-HCV) testing for HIV-infected MSM who have unprotected (condomless) sex or who have been exposed to other, unspecified risk factors [5-7]. Furthermore, bi-annual alanine aminotransferase (ALT) testing is recommended for all HIV-infected patients [6,7]. In case of unexplained elevated ALT levels, subsequent HCV-RNA testing can be performed at the discretion of the physician. However, ALT is often not routinely measured in sexually transmitted infection (STI) clinics or other places outside of HIV care. Also, anti-HCV testing might not be sufficient in cases of an acute HCV infection as it takes several weeks or even months before anti-HCV can be detected in the presence of HIV [8,9]. Moreover, these guidelines include the presence of risk behaviour without specifying type and frequency.

Since early HCV detection and treatment may prevent onward transmission [10], more specific recommendations are required to identify who should be tested for acute HCV. A risk questionnaire could reduce the number of HCV tests performed in HIV-infected MSM, lowering costs and enhancing implementation of acute HCV testing in, for example, STI clinics. For chronic HCV infections, several risk scores or screening strategies to target those at highest risk for HCV were developed

Figure 1

Receiver operating characteristic curves for the original and HCV-MOSAIC risk score in the development study (A) and for the HCV-MOSAIC risk score in the three validation studies (B–D)



AUC: area under the ROC curve; HCV: hepatitis C virus; MOSAIC: MSM (men who have sex with men) Observational Study of Acute Infection with hepatitis C; ROC: receiver operating characteristic; STI: sexually transmitted infection; UK: United Kingdom.

[11-16]. However, to the best of our knowledge, risk scores identifying MSM at increased risk for acute HCV infection do not exist.

Recently, we examined risk factors for acute HCV infection in the MOSAIC study (MSM Observational Study of Acute Infection with hepatitis C). The MOSAIC study is an ongoing, prospective, observational cohort, enrolling HIV-infected MSM with acute HCV infection (cases) and one or two controls without a history of HCV for each case [17]. In this study we found that a high number (four or more) of risky sex acts was strongly associated with HCV acquisition [18]. Therefore, in the present study, we developed a risk score identifying at-risk MSM using data from this MOSAIC study and evaluated its sensitivity and specificity. In addition, we evaluated the performance of this risk score in three different populations of HIV-infected MSM, to assess whether this tool could be used to assist testing for acute HCV infection in HIV-infected MSM.

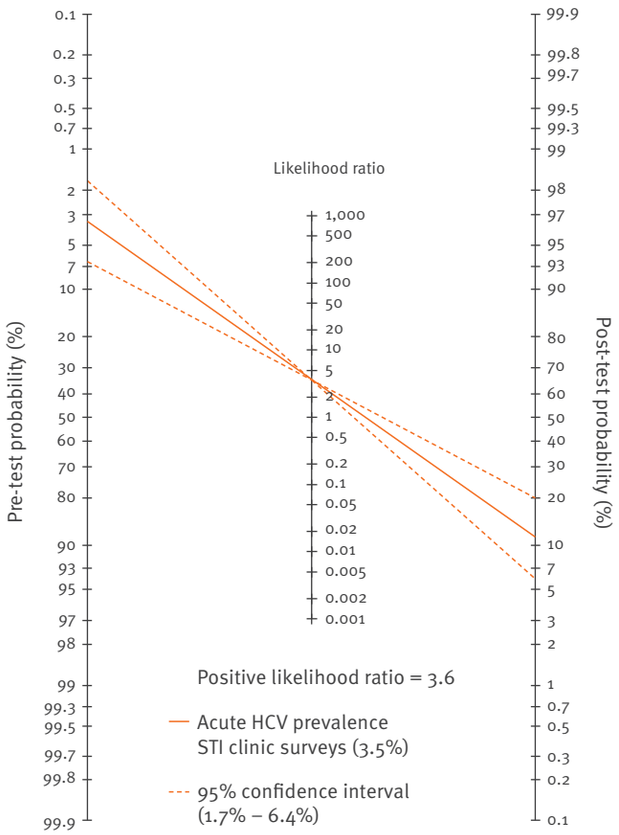
Methods

Development of the risk score

For the development of the risk score, all cases and controls enrolled in the MOSAIC study before February 2014 were selected. Acute HCV infection was defined as an interval ≤ 6 months between the first positive HCV-RNA test and the preceding negative HCV-RNA or anti-HCV test. Information on risk factors for HCV was

Figure 2

Fagan's nomogram for a risk score of ≥ 2.0



HCV: hepatitis C virus; MOSAIC: MSM (Men who have sex with men) Observational Study of Acute Infection with hepatitis C; STI: sexually transmitted infection.

The Fagan's nomogram combines a range of pre-test probabilities of acute hepatitis C virus (HCV) infection (i.e. the prevalence range) with the likelihood ratio (LR) of the risk score, resulting in a range of post-test probabilities of acute HCV infection. It visualises diagnostic gain of the risk score (i.e. post-test probability minus pre-test probability).

obtained using a detailed self-administered questionnaire. Questions about risk behaviour refer to the 6 months preceding the moment of diagnosis with acute HCV for cases, and the 6 months preceding study entry for controls, except for questions about drug use and STIs, which refer to the past 12 months. The MOSAIC study was approved by the Institutional Review Board of the Academic Medical Center at the University of Amsterdam and ethical committees/board of directors of each institute recruiting participants; the assigned study numbers are NL26485.018.09 and NL48572.018.14.

For the development of the original risk score, we selected all risk factors that were statistically significantly associated with acute HCV in the multivariable logistic regression model including variables that potentially have direct effects on acquisition and variables that potentially facilitate transmission of acute HCV, as described elsewhere [18]. Subsequently, an individual risk score for each patient was calculated by summing the logistic regression beta-coefficients of all significant (p value‹0.05) risk factors reported.

Since the questions in the MOSAIC questionnaire are very detailed, we adjusted the original risk score to a revised risk score, which we will refer to as the HCV-MOSAIC risk score. For the HCV-MOSAIC risk score we used simplified definitions of the risk factors identified for the original risk score, making it suitable for validation and implementation. The HCV-MOSAIC risk score was constructed using the different beta coefficients derived from multivariable logistic regression analysis entering these simplified variables.

Validation of the risk score

We validated the HCV-MOSAIC risk score using three different study populations, for which we obtained the primary datasets. The first was a case–control study among HIV-infected MSM in care in three AIDS Reference Centers in Belgium from 2010 until 2013 [19]. Screening for anti-HCV was performed, followed by confirmation of positive samples by detection of HCV-RNA. All included participants had a negative anti-HCV test during the 12 months before their positive HCV test. For each case, the first two HIV-infected anti-HCV-negative MSM who visited the clinic after the case was included were selected as controls. The second was a case–control study in HIV clinics in the United Kingdom (UK) from 2003 until 2005 [20]. Cases were HIV-infected MSM with acute HCV infection, defined as a documented seroconversion to anti-HCV, accompanied by a positive HCV-RNA and/or clinical and biochemical criteria. The aim was to match two MSM controls without HCV for age, length of HIV infection, ethnicity and combination antiretroviral therapy (cART) exposure status. The third cohort was based on anonymous bi-annual cross-sectional surveys conducted at the STI clinic of the Public Health Service of Amsterdam in the Netherlands [21]. We used data collected between 2007 and 2009. Anti-HCV and HCV-RNA testing were performed in all HIV-infected MSM. Acute/recent HCV infection was defined as (i) HCV-RNA-positive and anti-HCV-negative or (ii) HCV-RNA-positive and anti-HCV-positive without a self-reported history of a previous positive HCV test. All other MSM with both a positive HCV-RNA and anti-HCV were excluded from the STI clinic dataset. The MSM who did not fulfil the criteria for acute/recent HCV infection were included in the analysis as HCV-negative.

Risk factors for HCV were collected at interview using a standardised questionnaire [19,21] or by a self-administered questionnaire [20]. Questions about risk behaviour referred to the 12 months before HCV diagnosis or study entry in the two case–control studies, and to the previous 12 months in the cross-sectional surveys.

Table 1

Characteristics of the development and three validation studies and their study populations and the variables of the HCV-MOSAIC risk score

Characteristics	Development study		Validation studies		
	MOSAIC study, the Netherlands (n = 213)		**Case–control study, Belgium (n = 142)**	**Case–control study, UK (n = 190)**	**Dutch STI clinic surveys (n = 284)**
Study design	Case–control		Case–control	Case–control	Cross-sectional
HCV status **- HCV-positive (n)** **- HCV-negative (n)**	82[a] 131		52 90	60 130	10 274
Study period	2009–2013		2010–2013	2003–2005	2007–2009
Median age in years (IQR)	45.7 (41.0–52.2)		45.0 (37.0–51.0)[b]	38.0 (33.5–41.9)[c]	42.0 (35.0–47.0)
Self-reported variables in the risk score	**HCV-MOSAIC risk score**	**beta**	**Deviations from the HCV-MOSAIC risk score**		
Condomless RAI 6M	Yes / no	1.1	RAI and condomless AI asked separately	ND	ND
Sharing of sex toys 6M	Yes / no	1.2	With casual sex partner(s)	ND	ND
Unprotected fisting 6M	Yes / no	0.9	ND	ND	ND
Injecting drug use 12M	Yes / no	1.4	During sex	ND	ND
Sharing of straws when NAD used 12M	Yes / no	1.0	ND	ND	Not asked
Ulcerative STI 12M	Yes / no	1.4	ND	Ever had syphilis or herpes	Not selfreported but tested

AI: anal intercourse; HCV: hepatitis C virus; IQR: interquartile range; MOSAIC: MSM (men who have sex with men) Observational Study of Acute Infection with hepatitis C; NAD: nasally administered drug; ND: no deviation; RAI: receptive anal intercourse; STI: sexually transmitted infection; ulcerative STI: syphilis, genital herpes or lymphogranuloma venereum infection; UK: United Kingdom; 6M: during the past 6 months; 12M: during the past 12 months.

[a] Nine reinfections.

[b] One missing value.

[c] Twenty seven missing values.

Statistical analysis

Using the MOSAIC data, the optimal cut-off point of the risk score to predict HCV positivity, defined as the highest sensitivity in combination with the highest specificity, was determined using Receiver Operating Characteristic (ROC) curves. The area under the curve (AUC) was calculated to assess accuracy of the risk score. Sensitivity and specificity with Wilson Score 95% confidence intervals (CI) were calculated for the optimal cut-off point. Differences between sensitivity and specificity from the development study and validation studies were evaluated using Newcombe's method 10 for independent proportions [22]. If the answer to a risk factor question was missing for a patient, we assumed that this risk factor was not present.

We could not reliably determine the positive and negative predictive value of the risk score, as these measures are dependent on the infection prevalence in the study group, and the case–control distribution in the development and validation studies, except for the Dutch STI clinic surveys, does not reflect the actual prevalence of acute HCV. To assess the clinical relevance, we calculated the post-test probability of HCV infection (i.e. the likelihood of being HCV-positive when given a positive HCV testing advice based on the risk score) using the formula [23]:

Formula 1

$$\frac{(\text{sensitivity} \times \text{prevalence})}{\text{sensitivity} \times \text{prevalence} + (1 - \text{specificity}) \times (1 - \text{prevalence})}$$

As the post-test probability of infection depends largely on the pre-test probability of infection (i.e. the prevalence of acute HCV infection in HIV-infected MSM, which we calculated using the data from the Dutch STI clinic surveys with its 95% CI as range), Fagan's

Table 2

Performance of the HCV-MOSAIC risk score among HIV-infected men who have sex with men in the development and three validation studies

	Development study	Validation studies		
	MOSAIC study, the Netherlands	Case–control study, Belgium	Case–control study, UK	Dutch STI clinic surveys
Sensitivity (95% CI)	78.0% (67.9–85.6)	73.1% (59.7–83.2)	93.3% (84.1–97.4)	100% (72.2–100)
Specificity (95% CI)	78.6% (70.8–84.8)	65.6% (55.3–74.6)	56.2% (47.6–64.4)	60.6% (54.7–66.2)
Proportion to be tested[a]	43%	49%	59%	42%
Area under the ROC curve (95% CI)	0.82 (0.76–0.88)	0.74 (0.66–0.83)	0.82 (0.76–0.88)	0.92 (0.85–0.98)

CI: confidence intervals; HCV: hepatitis C virus; MOSAIC: MSM (men who have sex with men) Observational Study of Acute Infection with hepatitis C; ROC: receiver operating characteristic; STI: sexually transmitted infection; UK: United Kingdom.

[a] Proportion of all cases and controls with a risk score of ≥ 2.0.

Table 3

Performance of the HCV-MOSAIC risk score for a range of different cut-offs among HIV-infected men who have sex with men in the development and three validation studies

	Development study		Validation studies					
	MOSAIC study, the Netherlands		Case–control study, Belgium		Case–control study, UK		Dutch STI clinic surveys	
Cutoff[a]	**Sensitivity (%)**	**Specificity (%)**	**Sensitivity (%)**	**Specificity (%)**	**Sensitivity (%)**	**Specificity (%)**	**Sensitivity (%)**	**Specificity (%)**
≥ 0.9	91.5	38.2	92.3	40.0	96.7	28.5	100.0	25.2
≥ 1.1	89.0	45.8	88.5	44.4	95.0	35.4	100.0	27.0
≥ 1.4	78.1	75.6	75.0	63.3	93.3	47.7	100.0	58.4
≥ 2.0	78.1	78.6	73.1	65.6	93.3	56.2	100.0	60.6
≥ 2.1	72.0	82.4	69.2	66.7	88.3	59.2	90.0	69.3
≥ 2.3	65.9	87.8	61.5	74.4	81.7	64.6	90.0	73.0
≥ 2.5	61.0	90.8	55.8	78.9	80.0	69.2	90.0	81.0
≥ 3.2	48.8	93.9	48.1	84.4	73.3	79.2	90.0	87.6
≥ 3.4	40.2	94.7	36.5	88.9	70.0	80.8	40.0	96.0
≥ 4.6	14.6	99.2	21.2	94.4	30.0	93.1	20.0	98.2

HCV: hepatitis C virus; MOSAIC: MSM (men who have sex with men) Observational Study of Acute Infection with hepatitis C; STI: sexually transmitted infection; UK: United Kingdom.

[a] Results are shown only for the cut-offs that were available in all four studies.

nomogram [24] was used to visualise the diagnostic gain (post-test probability minus pre-test probability of infection) after a positive testing advice. This graphical calculation of Bayes' theorem describes how positive testing advice changes the infection probability by combining the pre-test probability of acute HCV infection with the likelihood ratio (LR) of the risk score (which is calculated from sensitivity and specificity [23]), resulting in the post-test probability of acute HCV infection. All analyses were performed using Stata version 13.1 (Stata Statistical Software: Release 13; StataCorp LP, College Station, Texas, US).

Results

The MOSAIC development study enrolled 82 HIV-infected MSM with acute HCV and 131 HIV-infected MSM without a history of HCV as controls. The first validation study from Belgium included 52 cases and 90 controls and the second from the UK, 60 cases and 130 controls. Third, we included 10 HIV-infected MSM with acute HCV and 274 without HCV from the Dutch STI clinic surveys. Characteristics of the development and validation studies and their study populations are shown in Table 1; the median age of participants in all validation studies was significantly lower than the

median age in the development study (p value < 0.05 for all studies, Mann–Whitney U-test).

Development of the risk score

The previously described logistic regression model [18] identified the following six dichotomous risk factors for the original risk score: (i) condomless receptive anal intercourse (RAI) (beta 1.6); (ii) sharing of sex toys (beta 1.3) (both (i) and (ii) with HCV-positive or HCV-unknown sex partners); (iii) unprotected fisting (fisting without gloves, or with gloves but also group sex reported, beta 0.9); (iv) injecting drug use (IDU) during sex (beta 2.7); (v) sharing of straws when nasally administered drugs (NAD) used (beta 1.2); and (vi) self-reported ulcerative STI (syphilis, genital herpes or lymphogranuloma venereum infection, beta 1.6). Although statistically significant in the model, we excluded CD4 cell count, since its inclusion would make the risk score unusable in a setting where CD4 cell counts are not routinely measured (e.g. STI clinic). The best cut-off point for the original risk score, as determined using the ROC-curve (Figure 1A, AUC 0.85, 95% CI: 0.79–0.90) was ≥ 2.5. Sensitivity and specificity of the risk score using this cut-off point were 79.3% (95% CI: 69.3–86.6) and 82.4% (95% CI: 75.0–88.0) respectively.

For development of the HCV-MOSAIC risk score, as described in the methods we simplified the first four of the six risk factors, resulting in the following risk factors: (i) condomless RAI (with any partner, beta 1.1); (ii) sharing of sex toys (with any partner, beta 1.2); (iii) unprotected fisting (fisting without gloves, beta 0.9); (iv) IDU in the past 12 months (beta 1.4); (v) sharing of straws when NAD used (beta 1.0); and (vi) ulcerative STI (beta 1.4) (Table 1). The optimal cut-off point for the HCV-MOSAIC risk score became ≥ 2.0 and the ROC-curve had an AUC of 0.82 (95% CI: 0.76–0.88) (Figure 1A). When compared with the original risk score, the sensitivity of the HCV-MOSAIC risk score slightly dropped from 79.3% to 78.0% (95% CI: 67.9–85.6) and the specificity from 82.4% to 78.6% (95% CI: 70.8–84.8). The proportion of all participants with a risk score of ≥ 2.0 was 43% (92/213).

Validation of the risk score

The sensitivity and specificity of the HCV-MOSAIC risk score in the Belgian case–control study were 73.1% (95% CI: 59.7–83.2) and 65.6% (95% CI: 55.3–74.6), respectively. In the case–control study from the UK, sensitivity and specificity were 93.3% (95% CI: 84.1–97.4) and 56.2% (95% CI: 47.6–64.4), respectively. In the Dutch STI clinic surveys, sensitivity and specificity were 100% (95% CI: 72.2–100) and 60.6% (95% CI: 54.7–66.2), respectively (Table 2).

In the Belgian case–control study and the Dutch STI clinic surveys the sensitivity was lower and higher respectively than in the development study, but these differences were not statistically significant. In the study from the UK the sensitivity was significantly higher than in the development study (difference 15.3%, 95% CI: 3.3–26.2). Specificity was significantly lower in all validation studies compared with the development study (difference for the Belgian study 13.0%, 95% CI: 1.2–25.0, the UK study 22.4%, 95% CI: 11.1–33.0, and the Dutch study 18.0%, 95% CI: 8.5–26.6). The AUC in the validation studies ranged from 0.74 to 0.92 (Figure 1B–D). The proportion of participants (both cases and controls) with a risk score of ≥ 2.0 (i.e. the proportion of the population to be tested) in the validation studies ranged from 42% to 59% (Table 2). Table 3 shows the performance of the HCV-MOSAIC risk score for a variety of cut-offs in both the development and validation studies.

In the Dutch STI clinic surveys, data on one of the variables in the risk score (sharing of straws when NAD used) were not collected and therefore not scored. In a sensitivity analysis, we restricted the HCV-MOSAIC risk score in the development study to the same risk factors measured in the STI clinic (i.e. excluding sharing of straws): sensitivity decreased from 78.0% to 70.7% (95% CI: 60.1–79.5) and specificity increased from 78.6% to 83.2% (95% CI: 75.9–88.6).

Post-test probability

The post-test probability of acute HCV infection was calculated using the sensitivity and specificity of the HCV-MOSAIC risk score in the development study and using the prevalence of acute HCV in HIV-infected MSM in the Dutch STI clinic surveys, which was 3.5% (10/284 MSM, 95% CI: 1.7–6.4). The Fagan's nomogram (Figure 2) shows the post-test probability for a risk score of ≥ 2.0 and gives a precise overview of diagnostic gain.

The lines that start at the left y-axis show the HCV pre-test probability (i.e. 3.5%, range 1.7–6.4), cross the LR for a risk score of ≥ 2.0 (positive LR, i.e. sensitivity/(1–specificity)), then point to the HCV post-test probability at the right y-axis, which is 11.7% (range 5.9–20.0). The diagnostic gain of the risk score equals the difference between the infection probability for an individual before filling out the risk score (i.e. the prevalence) and the infection probability for an individual after being assigned to undergo HCV testing according to the risk score (i.e. HCV post-test probability). The diagnostic gain was 8.2% (11.7% minus 3.5%) and varied from 4.2% (5.9% minus 1.7%) to 13.6% (20.0% minus 6.4%).

Discussion

We developed and validated the first risk score for acute HCV infection in HIV-infected MSM. Using this risk score, 42–59% of HIV-infected MSM would be advised to undergo HCV testing, correctly identifying 73–100% of HIV-infected MSM with acute HCV infection, potentially making it a useful tool to assist testing for acute HCV infection. Our risk score could be implemented in settings where HIV-infected MSM are being tested for STIs, e.g. STI clinics. Currently, HCV testing is not routinely offered to MSM attending STI clinics in the Netherlands [25]. Moreover, the risk score could be

an addition to the current guidelines for HCV testing where risk behaviour as test criterion is not specified. Since all questions are self-reported, the development of a mobile-compatible website or application containing the risk score could be practical, ensuring confidentiality.

Although we consistently found›70% sensitivity, we need to emphasise that there is a proportion of HIV-infected MSM with acute HCV infection that will be missed when using the risk score. As described above this risk score should therefore be used as an additional tool rather than a replacement of testing practices in HIV clinics. Also, since the specificity was around 60% in the validation studies, a substantial proportion of HCV-negative MSM will be falsely identified as possible HCV-positive. However, since these MSM have a high score, our risk score could also be used to identify those who would benefit from interventions to reduce risk behaviour to prevent HCV infection.

Sensitivity and specificity of our risk score are within the higher range of those reported for existing risk scores to detect chronic HCV infection [11-16] and are also favourably comparable to existing risk scores to predict early HIV infection [26-28]. The diagnostic gain of the risk score ranged from 4.2% to 13.6%, which is slightly higher compared with the diagnostic gain of a risk assessment questionnaire for chronic HCV infection in the general population [14]. However, the diagnostic gain is dependent on the acute HCV prevalence in the population in which the risk score will be used and increases when prevalence is higher. A recent systematic review estimated a prevalence range of active HCV infection in HIV-infected MSM of 5.3–7.3% [29]. This range includes the upper limit of the prevalence we used (i.e. 6.4%). Use of our risk score will result in 42–59% of a population to be tested for HCV instead of everyone, which could potentially reduce test costs. However, cost-effectiveness studies are needed to compare different HCV testing strategies.

Our study has several limitations. First, there is heterogeneity between the development and validation studies. The performance of the risk score may have been influenced by differences in the definition of acute HCV between studies. We found 100% sensitivity in the Dutch STI clinic surveys, where it is likely that none of the acute HCV cases were missed because all men were simultaneously tested for HCV-RNA and anti-HCV. In addition, the questionnaires in the validation studies referred to risk behaviour in the last 12 months, whereas 3 of the 6 risk factors in our risk score refer to the last 6 months. The longer time period could have led to more risk behaviour acts reported, leading to a higher proportion with a risk score of≥2.0. Also, study periods, countries and mode of questionnaire (at interview or self-administered) differed, and changes in risk behaviour over time or the social acceptability of some of the answers could have affected the performance of the risk score. Differences in HCV prevalence over time and between regions may have resulted in differences in the chance for an individual of being exposed to HCV, regardless of the level of risk behaviour. Second, we were unable to take into account the predictive value of an elevated ALT, since for the majority of the MOSAIC cases, HCV testing and diagnosis were based on an elevated ALT level. As current HCV testing practices in HIV treatment centres largely rely on the presence of an elevated ALT, the additional value of our risk score in combination with an elevated ALT can only be measured using a prospective validation study, as this would require testing for acute HCV in all patients with and without elevated ALT. We believe our risk score can be of added value, as ALT levels may remain within normal limits or rapidly normalise after acute HCV infection [30,31] and the sensitivity of an elevated ALT is reported to be as low as 20% for a recent HCV infection [31]. Third, our risk score was developed using data from a case–control study, while preferably a risk score should be developed using a prospective cohort study of HIV-infected MSM who are being regularly tested for acute HCV infection. A fourth limitation is that the sample sizes of the development and validation studies were relatively small.

Our risk score has not been validated among HIV-negative MSM, as their HCV prevalence is relatively low [21,32]. However, HCV infections have been reported in HIV-negative MSM using HIV pre-exposure prophylaxis [33-35]. For those people, it would be worth evaluating whether the risk score could assist HCV testing. Furthermore, our risk score was neither primarily developed nor validated for HCV reinfections. As reinfections are reported to be common in MSM [30,36,37], it could also be useful to validate the HCV-MOSAIC risk score in this group.

In conclusion, the HCV-MOSAIC risk score identifies HIV-infected MSM at risk for acute HCV infection. We encourage the use of this risk score, especially at testing locations where MSM are not regularly tested for HCV or where ALT is not routinely measured. It could be a valuable addition to the current guidelines for HCV testing and potentially reduce the amount of tests performed in MSM at low risk for acute HCV infection. In addition, it could be used as a tool to identify those who would benefit from interventions to reduce risk behaviour to prevent acute HCV infection.

MOSAIC collaborators

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Conflict of interest

MV served on a scientific advisory board for AbbVie, Bristol-Myers Squibb, Gilead Sciences, Johnson and Johnson, MSD and a data safety monitoring board for ViiV healthcare. Through his institution he received non-financial support by MSD. The remaining authors (AN, IS, JM, JS, JV, AB, MD, AH, MP) declared no conflict of interest.

Authors' contributions

All authors contributed significantly to the intellectual content of the manuscript. AN performed data analysis, and drafted the manuscript. IS and JV contributed to data management and analysis. JM and MV are physicians treating HIV-infected MSM, and together with JS, they also contributed to the intellectual content of the manuscript. AB and MP contributed to study concept and design. AB, MD and AH provided the data from the validation cohorts. MP is the principal investigator of the MOSAIC study.

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Research article

Anti-hepatitis C virus seroprevalence in the working age population in Poland, 2004 to 2014

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Hepatitis C virus (HCV) infection is considered by the World Health Organization (WHO) to be a serious public health concern and one of the major public health priorities. In 2005, it was estimated that there are 185 million anti-HCV positive people in the world, which constitutes 2.8% of the global population. Our study estimates the anti-HCV seroprevalence in the working age population (15–64 years-old), mostly urban and suburban residents, in Poland from 2004 to 2014. The studied group consisted of 61,805 working-age population representatives whose data were obtained from electronic medical records of an outpatient clinic network operating on a countrywide level. Positive anti-HCV test results were obtained in 957 patients, representing 1.5% of the whole population studied throughout the analysed period. The average age of all anti-HCV positive patients was 36.8 years. Analysis of the data suggests that the proportion of anti-HCV positive patients decreased over the study period (mean positive anti-HCV = -0.0017 × year+3.3715; R^2=0.7558). In 2004, positive results were noted among 3.2% of patients undergoing HCV antibody tests, but in 2014, the percentage of patients with a positive result stood at 1.1%. The apparent decrease affected men and women similarly. Our study also provides evidence that screening people born before 1965 could be beneficial.

Introduction

Liver cirrhosis, liver failure and hepatocellular carcinoma are possible long-term consequences of untreated hepatitis C virus (HCV) infection [1-5], which the World Health Organization (WHO) considers as a serious public health concern and one of the major public health priorities [6]. HCV is transmitted mostly by percutaneous exposure to blood [7,8], including intravenous drug injection, which is becoming an important route, especially in developed countries [9,10]. Mother-to-child transmission occurs as well; however, it is relatively uncommon, affecting an estimated 4% of children of HCV-infected mothers [11,12].

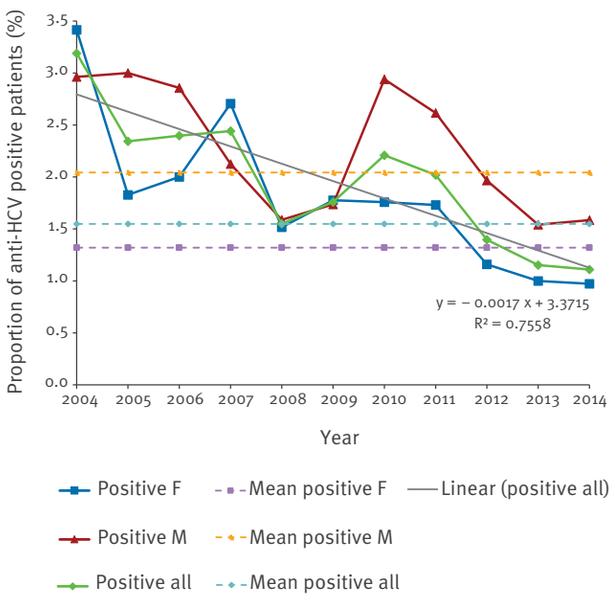
In 2005, ca 185 million people in the world, corresponding to approximately 2.8% of the global population, were estimated to be anti-HCV positive [13]. The prevalence of HCV infection ranges from 1.2% to 3.8% in different parts of the world and is highest in central Asia (3.8%), east Asia (3.7%) and North Africa/Middle East (3.6%) [14,15]. In the United States (US), HCV infection prevalence is at 1.6% (2.1% in men and 1.2 % in women) and higher (75% of all cases) in people born between 1945 and 1965 [16]. For this reason, both the Centers for Disease Control and Prevention (CDC) as well as the American Gastroenterology Association (AGA) recommend screening for all individuals born in this period [17,18].

A study from 2014, based on comprehensive literature search anti-HCV prevalence, found the prevalence in Europe to vary from 0.9% in western Europe, through 1.3% in central Europe to 3.3% in eastern Europe [19]. A report from the European Centre for Disease Control and Prevention estimates that in European Union (EU)/ European Free Trade Association (EFTA) countries over half of persons with HCV infection in 2006 are in the 25–44 year age group and overall men (64.4%) are more affected than women (35.6%) [20]. From the 1990s up to 2007, new infections appeared to decline in western Europe, while they increased in eastern Europe, possibly due to rising numbers of people who inject drugs (PWIDs) in the east and effective needle sharing programmes in the west [15,21,22].

In Poland, newly diagnosed HCV infections are registered and monitored by the National Institute of Public Health since 1997 [23,24]. The data are based on formal notifications from local Sanitary Inspectorates of newly diagnosed HCV infections according to the national case definition [25]. A regulation of the

Figure 1

Proportions of hepatitis C virus antibody positive tests among the study population, stratified by year and sex, Poland, 2004–2014 (n = 61,805 patients)



F: female; M: male; HCV: hepatitis C virus.

Minister of Health of 20 September 2012 made anti-HCV tests mandatory in all pregnant women from that year onwards [26].

The latest estimates for HCV infection incidence in the country are 7.99 newly diagnosed cases per 100,000 inhabitants in 2014 [27] and, preliminarily, 11.14 newly diagnosed cases per 100,000 inhabitants in 2015 [24]. HCV infection incidence is much higher in the cities (10.7/100,000 inhabitants) than in rural areas (4.82/100,000 inhabitants) and in men (8.58/100,000) than in women (7.44/100,000) [27]. As acute HCV infection is usually asymptomatic, 86% of infected people in Poland are estimated to be unaware of their infection [14,28]. Therefore increasing the diagnosis rate of infected persons is important [2], not only to more timely treat hepatitis C, but also to stop further spread of HCV.

Research on HCV prevalence in Poland has so far mainly focused on specific groups (healthcare workers, patients, volunteers, students, blood donors, pregnant women) or on selected areas of Poland [28-36]. There are no epidemiological data for the prevalence of HCV in the general working age population over the whole country, especially based on a large population sample. The purpose of this study is therefore to estimate the anti-HCV seroprevalence in the working age population of Poland, using real-life data obtained from medical records of countrywide outpatient clinics, and accordingly formulate recommendations on age-related HCV infection screening.

Methods

Data source

Data were obtained in February 2015 from electronic medical records of a large countrywide outpatient clinic network operating mainly in big cities (with more than 300,000 inhabitants) representing the capitals of 11 of the 16 regions in Poland (Bialystok, Bydgoszcz, Gdańsk, Katowice, Krakow, Lublin, Łódź, Poznań, Szczecin, Warszawa, Wrocław). The clinics provide medical services predominantly to urban and suburban inhabitants with a negligible share of patients from rural areas. It is estimated that study clinics are accessible to a total of 6 million city dwellers (15% of the Polish population).

Testing for hepatitis C virus antibodies

In order to estimate the seroprevalence in the study population, only the results of anti-HCV were analysed. Anti-HCV in serum was detected by electrochemiluminescence (Roche, ECLIA) and the detection method did not change throughout the study period. All patients with positive results had been referred to special infectious disease clinical departments in order to undergo confirmatory HCV RNA tests if necessary; therefore, those results were not available in the anonymous dataset. Anti-HCV true positive results were not confirmed by immunoblotting. Such a limited approach without final confirmation of anti-HCV positivity was applied on the basis of the European Association for the Study of the Liver (EASL) recommendations, stating that immunoblotting is not recommended to distinguish false positive and true positive anti-HCV result. In order to confirm current viraemia, an HCV RNA test ought to be performed, however this was not the aim of this study [37].

The clinical sensitivity of the test used to detect anti-HCV is estimated at 100% (95% confidence interval (CI): 99.61–100%), the specificity at 99.62% (95%CI: 99.71%–99.92%) [38].

Study population

The total population aimed to be investigated in the study consisted of patients who had been tested for anti-HCV at least once in the period from 2004 to 2014. The study group was extracted from the pool of all medical records of 1.5 million individuals who had been consulted by any doctor in this period. Available records included information on: unique patient number, sex, date of test, age at the date of testing, diagnosis related to the test referral and test result. Only the latest result of testing was included into the study pool, which finally comprised 61,805 single test results of unique patients. The study group was limited to working age population representatives, aged 15–64 years. The working age population was defined according to the definition of the Organisation for Economic

Table 1

Aggregated ICD-10 diagnoses accompanying referrals for testing hepatitis C virus antibodies, Poland, 2004–2014 (n = 36,356 patients)

Diagnosis	ICD-10- codes	Group
Pregnancy and pregnancy-related conditions	O20, O24, O26, Z32, Z34, Z35	1
Preventive consultations of generally healthy persons	Z00, Z01, Z02, Z10, Z24, Z29, Z31, Z71, Z76	2
Various symptoms and signs	R10, R53, R68, R69, R72, R79, Z03, Z04	3
Fatty liver disease	K76, E78	4
Hypertransaminasaemia	R74	5
Others	Other than the above	6

Co-operation and Development (OECD) [39]. In Poland, the working age population consists of 25 million people including 11.768 million women and 12.971 million men.

Data analysis

Analysis of the population tested for hepatitis C virus antibodies

The total population tested for anti-HCV was divided into 10-year age groups stratified by sex and the year of testing for time analysis. In each subgroup, the total number of patients tested was used as a denominator.
Analysis of the population testing positive for hepatitis C virus antibodies

The number of persons with a positive result for HCV antibody were available each year along with demographical data (sex and age). The rate of total positive tests was calculated and stratified by sex and age. The analyses by age group were conducted by comparing the number of patients, the number of tests and the number of positive/negative results for HCV antibody. Two classifications according to age were used. In the first classification the study population age range was split into 10 year-age groups. In the second classification, since the US data indicated a higher prevalence of HCV in people now aged 50 to 70 years [16], the percentage of positive anti-HCV test results was accordingly analysed in age groups 15 to 49 years and over 50 years.

The mean rates of positive patients were analysed over time by regression analysis and stratified by sex.

Analysis of testing and positive tests by referral group

A number of referrals for anti-HCV test (n = 36,356) had preliminary diagnosis information (according to ICD-10 coding) [40]. We compiled those diagnoses into specific groups for further analyses (Table 1). Both 3-digital and 5-digital ICD-10 codes were aggregated.

Statistical methods

Data were analysed using STATISTICA (data analysis software system), version 12, (www.statsoft.com) StatSoft, Inc. (2014) US, to calculate the incidence of newly diagnosed cases per year, and the prevalence in the entire examined population. The independent-sample t-test was used for normally distributed variables, and the nonparametric Mann–Whitney U test was used for not normally distributed parameters. Significance was set at $p < 0.05$. Using linear regression analysis, the trend of the number of the incidence as a function of time (years) was calculated and the R-square value evaluated the goodness of fit of the regression.

Results

Characteristics of the study population

Overall characteristics

A total of 61,805 single patient records were considered in the study, spanning the period from 2004 to 2014 (Table 2). Men (n = 19,531) accounted for 31.6% of the total study group. The overall average age of patients was 34.4 years (standard deviation (SD): 8.6). The average age of men was 36.5 years (SD: 9.6). The average age of women was 33.4 years (SD: 7.9) (Table 3).

Analysis by age group

The most represented age group in terms of number of individuals was the one comprising 25 to 34 year-olds (n = 35,047 patients; 56.7%) and the least numerous group comprised persons over 55 years (n = 2,626 patients; 4.2%) (Table 4).

Time analysis of testing practices

The number of patients examined for anti-HCV increased steadily with time, from 815 patients in 2004, to 14,963 in 2014 (Table 2).

The percentage of all medical-facility-patients tested yearly increased from 0.9% (815/88,177) in 2004 to 4.0% (14,963/376,637) in 2014. Data showed a growing proportion of women being examined. In 2004, a similar number of men and women underwent anti-HCV tests (50.3% (410/815) of women and 49.7% (405/815) of men), whereas in 2014, women accounted for 79.1% (11,620/14,693). This increase may reflect

Table 2

Annual numbers of patients tested for hepatitis C virus (HCV) antibodies and proportions testing positive, stratified by sex, Poland, 2004–2014 (n = 61,805 patients)

Year	All patients			Women			Men			P value
	Number of anti-HCV tests	Number of positive results	Percentage of positive results	Number of anti-HCV tests	Number of positive results	Percentage of positive results	Number of anti-HCV tests	Number of positive results	Percentage of positive results	
2004	815	26	3.2%	410	14	3.4%	405	12	3.0%	0.7143
2005	1,366	32	2.3%	766	14	1.8%	600	18	3.0%	0.1553
2006	1,210	29	2.4%	650	13	2.0%	560	16	2.9%	0.3314
2007	1,761	43	2.4%	961	26	2.7%	800	17	2.1%	0.4322
2008	3,033	47	1.6%	1,648	25	1.5%	1,385	22	1.6%	0.8740
2009	4,263	75	1.8%	2,477	44	1.8%	1,786	31	1.7%	0.9208
2010	5,250	116	2.2%	3,243	57	1.8%	2,007	59	2.9%	0.0075
2011	7,378	149	2.0%	4,970	86	1.7%	2,408	63	2.6%	0.0180
2012	9,527	133	1.4%	6,730	78	1.2%	2,797	55	2.0%	0.0059
2013	12,239	141	1.2%	8,799	88	1.0%	3,440	53	1.5%	0.0216
2014	14,963	166	1.1%	11,620	113	1.0%	3,343	53	1.6%	0.0090
Total	61,805	957	1.5%	42,274	558	1.3%	19,531	399	2.0%	0.0001

Table 3

Characteristics of the study population and that testing positive for hepatitis C virus antibodies, Poland, 2004–2014 (n = 61,805 patients)

Participants	Sex	Mean age	Standard deviation	Number of persons	Column percentage
Study participants	F	33.4	7.9	42,274	68.4%
	M	36.5	9.6	19,531	31.6%
	Total	34.4	8.6	61,805	100.0%
Study participants testing positive	F	36.0	9.8	558	58.3%
	M	37.8	9.7	399	41.7%
	Total	36.8	9.8	957	100.0%

F: female; M: male.

legal requirements for prenatal care during pregnancy in Poland, with HCV testing becoming compulsory for pregnant women from 2012 onwards (Table 5) [26].

Characteristics of the population testing positive for hepatitis C virus antibodies

Overall characteristics

Throughout the analysed period, 1.5% patients (957/61,805) undergoing anti-HCV examination tested positive. Averaged positive results for women and men were 1.3% (558/42,274) and 2.0% (399/19,531) respectively (p = 0.0001). The average age of all anti-HCV positive patients was 36.8 years (SD: 9.8). The average age of anti-HCV positive women was 36.0 years (SD: 9.8), and the average age of men with positive test results was 37.8 years (SD: 9.7).

Analysis by age group

Most anti-HCV positive cases occurred in patients aged 45–54 years (2.9% of tested patients 147/5,107) and in patients older than 55 years (2.6% of tested patients 68/2,626). The lowest proportions of positive test results were noted in the youngest patients: 1.2% (436/35,047) among patients aged 25 to 34 years and 1.5% (52/3,411) among patients aged 15 to 24 years.

In the group of tested women, among those older than 25 years, the percentage of positive anti-HCV test results increased with age, being lowest among women aged 25–34 years (1.1%; 285/26,632) and 35–44 years (1.4%; 132/9,444), and highest for women aged over 55 years (3.2%; 43/1,394). For the youngest group comprising 15 to 24 year-olds, the value 1.5% (33/2,234) was similar to that of the group of 35 to 44 year-olds (1.4%; 132/9,444). In the group of tested men, the smallest proportion of infections was found in the 15 to 24 years age group (1.6%; 19/1,177) and increased

Table 4

Results of anti-hepatitis C virus tests stratified by patient age groups and sex in a study estimating hepatitis C seroprevalence, Poland, 2004–2014 (n = 61,805 patients)

Age group (years)	All patients			Women			Men			P value
	Number	Number testing positive for HCV antibodies	Percentage testing positive for HCV antibodies	Number	Number testing positive for HCV antibodies	Percentage testing positive for HCV antibodies	Number	Number testing positive for HCV antibodies	Percentage testing positive for HCV antibodies	
15–24	3,411	52	1.5%	2,234	33	1.5%	1,177	19	1.6%	0.7561
25–34	35,047	436	1.2%	26,632	285	1.1%	8,416	151	1.8%	0.0001
35–44	15,614	254	1.6%	9,444	132	1.4%	6,170	122	2.0%	0.0051
45–54	5,107	147	2.9%	2,591	65	2.6%	2,536	82	3.2%	0.1318
55–64	2,626	68	2.6%	1,394	43	3.2%	1,232	25	2.0%	0.0893
15–49	56,921	825	1.4%	39,676	480	1.2%	17,245	345	2.0%	0.0001
50–64	4,884	132	2.7%	2,598	78	3.0%	2,286	54	2.4%	0.1687
Total	**61,805**	**957**	**1.5%**	**42,274**	**558**	**1.3%**	**19,531**	**399**	**2.0%**	**0.0001**
Mean age in years (SD)	34.4 (8.6)	36.8 (9.8)	100.0%	33.4 (7.9)	36.0 (9.8)	58.3%	36.5 (9.6)	37.8 (9.7)	41.7%	0.0001

HCV: hepatitis C virus; SD: standard deviation.

Table 5

Proportions of patients undergoing anti-hepatitis C virus tests, Poland, 2004–2014 (n = 61,805 patients)

Year	All patients			Women			Men		
	Number	Number tested	Percentage tested	Number	Number tested	Percentage tested	Number	Number tested	Percentage tested
2004	88,177	815	0.9%	45,417	410	0.9%	42,760	405	0.9%
2005	106,464	1,366	1.3%	54,484	766	1.4%	51,980	600	1.2%
2006	127,195	1,210	1.0%	64,518	650	1.0%	62,677	560	0.9%
2007	157,238	1,761	1.1%	80,478	961	1.2%	76,760	800	1.0%
2008	200,031	3,033	1.5%	103,257	1,648	1.6%	96,774	1,385	1.4%
2009	219,905	4,263	1.9%	114,630	2,477	2.2%	105,275	1,786	1.7%
2010	240,307	5,250	2.2%	125,217	3,243	2.6%	115,090	2,007	1.7%
2011	269,140	7,378	2.7%	139,882	4,970	3.6%	129,258	2,408	1.9%
2012	303,813	9,527	3.1%	157,812	6,730	4.3%	146,001	2,797	1.9%
2013	335,526	12,239	3.6%	173,902	8,799	5.1%	161,624	3,440	2.1%
2014	376,637	14,963	4.0%	195,787	11,620	5.9%	180,850	3,343	1.8%
Total	2,424,433	61,805	2.5%	1,255,384	42,274	3.4%	1,169,049	19,531	1.7%

with age up to 3.2% (82/2,536) in the age group including 45 to 54 year-olds. For individuals over 55 years the value was similar (2.0%; 25/1,232) to that of the age group with 35 to 44 year-olds (2.0%; 122/6,170) (Table 3).

Because a higher prevalence of HCV was reported in 50 to 70 year-olds in the US [16], the percentage of positive anti-HCV test results was also analysed in age groups 15 to 49 years (representing 92.1% of those tested 56,921/61,805) and over 50 years (7.9%; 4,884/61,805). A higher percentage of anti-HCV positive patients was found in those aged over 50 years (2.7%; 132/4,884) compared with younger participants (1.4%; 825/56,921) ($p < 0.0001$). This percentage was higher for both women and men aged over 50 years, with, in women 3.0% (78/2,598) vs 1.2% (480/39,676) in those aged under 50 years ($p = 0.0001$) and, in men, 2.4% (54/2,286) vs 2.0% (345/17,245) in those less than 50 years-old ($p = 0.2507$).

Time analysis of patients testing positive for hepatitis C virus antibodies

An analysis of the data in the years 2004 to 2014 suggests a downward trend for the proportion of positive anti-HCV results (mean positive

Table 6

Primary diagnoses resulting in the referral for anti-hepatitis C virus tests, Poland, 2004–2014 (n = 36,356 patients)

LBIDo12_Diagnosis	Number of patients tested	Number of patients with positive results	Proportion of positive patients	Proportion of positive women	Proportion of positive men	Proportion positive in column	Proportion of diagnosed patients
Pregnancy and pregnancy related conditions	16,130	122	0.8%	0.8%	NA	25.4%	44.4%
Preventive consultations of generally healthy persons[a]	6,456	75	1.2%	0.7%	1.0%	15.6%	17.8%
Various symptoms and signs	5,151	108	2.1%	1.0%	2.1%	22.5%	14.2%
Hypertransaminasaemia[b]	1,093	25	3.7%	1.1%	1.7%	5.2%	3.0%
Fatty liver disease	1,115	23	3.4%	0.8%	1.7%	4.8%	3.1%
Others[c]	6,411	127	1.5%	0.9%	2.6%	26.5%	17.6%
Total	36,356	480	1.1%	0.8%	1.9%	100.00%	100.0%

NA: not applicable.

[a] Spontaneous or obligatory health check-ups.

[b] Excluding people with elevated transaminase level as a reason of additional anti-HCV test.

[c] Most often before surgical procedures.

anti-HCV = -0.0017 × year + 3.3715; R2 = 0.7558) (Figure).

In 2004, positive results were noted in 3.2% (26/815) of patients examined for anti-HCV, but in 2014 the percentage of patients with a positive result stood at 1.1% (166/14,693). Similar tendencies were observed in both women and men. In 2004, the percentage of anti-HCV positive results in women was 3.4% (14/410), and in men 3.0% (12/405) ($p > 0.05$), whereas in 2014, anti-HCV positive results were noted among 1.0% (113/11,620) of women and 1.6% (53/3,343) of men ($p = 0.0090$).

Referral group testing and test results

We analysed the diagnoses ascribed to each anti-HCV test referral. The predominant reason for anti-HCV testing was pregnancy and pregnancy-related conditions – 44.4% (16,130/36,356) –, followed by preventive testing of otherwise healthy people (occupational health or preventive screening) with 17.8% (6,456/36,356). Various symptoms and signs were the reason for testing in 14.2% of patients (5,151/36,356), fatty liver disease in 3.1% (1,115/36,356) and elevated alanine transaminase levels (ALT) as single diagnosis in 3.0% (1,093/36,356) (Table 6). Only 0.8% (122/16,130) of patients with a diagnosis of pregnancy and pregnancy-related conditions were anti-HCV positive. Preventive action and anti-HCV testing revealed positive results in 1.2% (75/6,456), of patients, while 2.1% (108/5,151) of patients with various symptoms and signs were anti-HCV positive, as well as 3.4% (23/1,115) of patients with a diagnosis of fatty liver disease and 3.7% (25/1,093) of people with elevated ALT (Table 6).

Discussion

Our study presents an evaluation of anti-HCV prevalence in a large country-wide sample of (sub)urban working-age Polish people between 2004 and 2014. Data from electronic medical records of ambulatory patients visiting doctors due to different conditions, including prophylactic and screening reasons, were analysed. The overall anti-HCV prevalence in our study was 1.5%. Similar to previous studies [29,30] and studies from other countries [41-43], anti-HCV positivity was significantly more frequent in men than women (2.0% vs 1.3% respectively; $p = 0.0001$).

We also found that in contrast to younger age groups (15 to 49 years), anti-HCV prevalence in people aged between 50 and 64 years was higher (2.7% vs 1.4%; $p < 0.0001$), and surprisingly more frequent in women (3.0%) than men (2.4%) although, this difference was not statistically significant. Higher HCV infection prevalence in people born before 1965 has also been observed in the US [16], therefore, the recommendation of CDC and AGA to screen people born before 1965 [17,18] might also be justified in Poland and could be implemented as part of primary healthcare. According to the authors' own research on 16,130 pregnant women, the prevalence of HCV in this group was only 0.8% which is close to the European average (1%) [44]. Low anti-HCV prevalence in pregnant women and high prevalence in people of post-reproductive age might be a subject of debate in terms of allocating effective financial resources for HCV screening in these two groups.

To our knowledge, our study constitutes one of the currently largest performed in the Polish population of working age. Indeed, although previous studies in the country have attempted to assess HCV prevalence, these have either been conducted either some time ago, or have been mainly based on small samples and/or on selected population groups – pregnant women, students, blood donors or deceased organ donors

– with, in some cases, only a single district or town in the country considered [28,29,31-35,45]. For example, the study by Bielawski et al. in 1999, which is still the point of reference for many epidemiological studies on HCV infection in Poland, was conducted on a group of 2,561 volunteers enrolled by a laboratory in Gdansk in response to press advertisements. It estimated the overall HCV infection prevalence at 1.9% [29], with 2.3% of men versus 1.7% of women seropositive for hepatitis C virus antibodies. Limitations of this study were however the restricted geographical area and the group chosen to be tested (volunteer bias) [29]. Since then, larger studies have been performed, an important one being that of Seyfried et al., where 4,233,119 blood donors were screened between 1994 and 2003. Anti-HCV prevalence in this group was found to be on average 0.5% [36]. The most recent study by Flisiak et al. in 2011, which was performed from 2009 to 2010 in 26,057 Polish adults (healthcare workers and hospital patients), presented anti-HCV prevalence in healthcare workers at 1.4%, whereas in ambulatory patients of different general practice and specialist outpatient clinics it was 1.9% [30]. Here we investigate 61,805 people of working-age over the whole country between 2004 and 2014 and find a prevalence of 1.5%, similar to what is currently estimated for central Europe (1.3%) [19].

Hepatitis C infection has been registered as a distinct disease entity in Poland since 1997. Until 2004, the annual number of newly diagnosed cases of HCV infection, logged by the National Institute of Hygiene, did not exceed 2,000. In the years 2005 and 2006 the number increased to 3,000 (2,997 and 2,949 in each year respectively), but this increase was most likely caused by the modification of disease reporting methods. In the following years, the number of newly diagnosed cases decreased steadily (2,753 in 2007, 2,353 in 2008). Since 2009 however, another upward trend can be observed. The number of reported cases of new HCV infections in Poland accumulated to 1,891 in 2009, 2,178 in 2010, 2,189 in 2011, 2,265 in 2012 and increased to 2,600 cases in 2013 [46].

Our analysis on the proportions of persons with HCV antibodies in working age people from 2004 to 2014 does not find such an increasing trend in the latest years of the study. Instead we find a higher proportion of patients with HCV antibodies in the first year of the study compared to the end of the analysed period (3.2% in 2004 vs 1.1% in 2014). This could be due to a general drop in HCV infections in working age people, but also to a change of indication for testing. Indeed, the most common indication for evaluating HCV serological status in the early years of the study was elevated serum ALT, which per se is regarded as a laboratory manifestation of liver injury. With the introduction of obligatory anti-HCV testing in all pregnant women from 2012 onwards, the proportion of anti-HCV positive persons dropped significantly, possibly coming closer to the actual prevalence of HCV infection in this relatively young and overall healthy group.

This study presents however a number of limitations. First, the prevalence of HCV infection is known to vary according to risk groups. The study by Flisiak et al. on 17,930 persons found that significant factors of HCV infection in Poland are more than three hospitalisations during a life time (odds ratio (OR) = 1.8), blood transfusion before 1992 (OR = 2.9) and intravenous drug use (OR = 6.2) [30]. Transmission of HCV via intravenous drug use has been increasingly observed and in 2007, 10 of 16 million of PWID worldwide were estimated to be HCV positive. The number of active PWIDs in the EU is estimated at ca 1 million [10]. In Poland, 70% of PWIDs are infected with HCV, predominantly men under 45 years of age [47]. In our study, we had no access to individual medical records; therefore, intravenous drug use could not be accounted for. Moreover, we did not have information on patients' profession either, so we could not evaluate any possible occupational risk.

Second, our study only analysed HCV antibody prevalence, and western blot tests were not performed. Thus results do not distinguish between current infections and probable infections in the past (resolved infection). A final diagnosis of current HCV infection requires the finding of HCV RNA in serum samples by RT-PCR. We had no access to HCV RNA results that were stored in the form of scans and required patients' consent for access. The results of this study can therefore not be compared with any studies using the EU HCV case definition [48]. A Polish study in 2011 showed that only 31% of those with HCV antibodies were also positive for HCV RNA by RT-PCR [30]. Moreover the sensitivity of the electrochemiluminescence (Roche, ECLIA) assay used in this study is very high, so specificity will be lower, which may result in false positive results. Taking these points into consideration, the prevalence of current HCV infection in the Polish urban working population is likely to be lower than 1.5%. Further studies on positive anti-HCV test results and HCV RNA detection may reveal if HCV infection is resolved more frequently than has been presumed up to now (ca 30% of cases being resolved [49]).

Finally, although our study was conducted on a large number of patients, another important limitation was the inclusion of only people living in big cities and their suburbs. One risk factor for HCV infection is the use of medical care, which is less frequent in inhabitants of rural areas. Accordingly, anti-HCV prevalence in rural areas has been shown to be lower than in urban areas [27,50]. Therefore our results cannot be extrapolated to the whole population and it can be assumed that the prevalence of HCV infection among people of working age in the country may be lower than 1.5%.

Conclusions

There is evidence that an improvement of diagnostics and treatment effectiveness may significantly reduce the burden of HCV infections in Poland [5,51]. A study using a modelling approach estimated that, until 2030, the HCV prevalence is projected to decrease by 5%. In

contrast, an increase in the number of treated patients to 15,000 yearly would reduce the number of total infections by 90% until 2030, which would also contribute to a decrease of HCV-mortality by 80% [49]. The results obtained in this study suggest that the proportion of people infected with HCV in Poland in the working population is decreasing, which may be a consequence of increasing social awareness, including preventative activities after or before exposure to blood-borne infections. Moreover, a higher prevalence of anti-HCV was found in the population of post-reproductive age. We therefore recommend screening HCV tests mainly in individuals over 45 years-old. Examining healthy and young people should not be carried out as part of screening, however testing may be recommended to individuals who are subjected to risk factors. The continuous monitoring of HCV prevalence and incidence in Poland is important to estimate the resources needed for screening and treatment as well as their costs. Knowing the age groups at higher risk for infection will help to establish recommendations for more effective detection of cases of HCV infection, which in turn is also crucial to reduce further transmission.

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Conflict of interest

Bożena Walewska-Zielecka and Piotr Soszyński are current employees of Medicover Sp. z o.o.

Authors' contributions

Conception or design of the work: BWZ, GJ; data acquisition: BWZ; data analysis: ZW, BWZ, GJ, UR, PS; interpretation of the data for the work: BWZ, UR, GJ, ZW, AC, PS, AF; drafting the work or revising it critically for important intellectual content: All; approval of manuscript submission: All.

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Towards elimination of hepatitis B and C in European Union and European Economic Area countries: monitoring the World Health Organization's global health sector strategy core indicators and scaling up key interventions

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The World Health Organization 'Global Health Sector Strategy on Viral Hepatitis 2016–2021' aimed at the elimination of viral hepatitis as a public health threat provides a significant opportunity to increase efforts for tackling the epidemics of hepatitis B and hepatitis C virus infections across Europe. To support the implementation and monitoring of this strategy, core epidemiological and programmatic indicators have been proposed necessitating specific surveys, the systematic collection of programmatic data and the establishment of monitoring across the care pathway. European Union and European Economic Area countries already made progress in recent years implementing primary and secondary prevention measures. Indeed, harm reduction measures among people who inject drugs reach many of those who need them and most countries have a universal hepatitis B vaccination programme with high coverage above 95%. However, while a further scaling up of prevention interventions will impact on incidence of new infections, treating those already infected is necessary to achieve reductions in mortality. The epidemiological, demographic and socio-political situation in Europe is complex, and considerable diversity in the programmatic responses to the hepatitis epidemic exists. Comprehension of such issues alongside collaboration between key organisations and countries will underpin any chance of successfully eliminating hepatitis.

Background

It is estimated that ca 4.7 million people living in European Union (EU) and European Economic Area (EEA) countries are chronically infected with the hepatitis B virus (HBV) and 5.6 million have been infected with the hepatitis C virus (HCV). Both are major causes of chronic liver disease, liver cirrhosis and hepatocellular carcinoma [1]. The resulting burden of disease presents a public health challenge for national health systems. While the incidence of new infections has declined in many European countries due to implementation of effective vaccination programmes (against hepatitis B) and prevention strategies targeting transmission through injecting drug use and healthcare, modelling suggests that morbidity and mortality will continue to increase [2,3]. Indeed, deaths from hepatitis now exceed those from HIV and tuberculosis combined and latest published estimates show that 96,000 people die each year in EU/EEA countries from HBV and HCV-related liver disease [4].

In May 2016, the World Health Assembly adopted the first 'Global Health Sector Strategy (GHSS) on Viral Hepatitis' aimed at eliminating viral hepatitis as public health threat [5]. The concept of elimination for these infections is based on reducing the incidence of chronic infections and the associated mortality, with the World Health Organization (WHO) setting global targets for reducing the incidence of chronic infections by 90% and mortality by 65% by 2030. Achieving these targets will require significant scaling-up of key interventions, including hepatitis B childhood vaccination, birth-dose vaccination or other means to prevent mother-to-child transmission, improved systems to assure safe blood transfusions/blood products, injection safety, interventions aimed at preventing transmission among people who inject drugs, and increased testing with linkage to care and treatment.

Table

Core indicators for the World Health Organization's monitoring and evaluation framework for hepatitis B and hepatitis C virus elimination 2016–2021

Indicator number	Indicator name
C1	Prevalence of chronic HBV and HCV infection
C2	Infrastructure for HBV and HCV testing
C3	a. Coverage of timely hepatitis B vaccine birth dose (within 24 hours) and other interventions to prevent mother-to-child transmission of HBV b. Coverage of third-dose hepatitis B vaccine among infants
C4	Needle–syringe distribution
C5	Facility level injection safety
C6	People living with HCV and/or HBV diagnosed
C7	a. Treatment coverage for hepatitis B patients b. Treatment initiation for hepatitis C patients
C8	a. Viral suppression for chronic hepatitis B patients treated b. Cure for chronic hepatitis C patients treated
C9	a. Cumulated incidence of HBV infection in children 5 years of age b. Incidence of HCV infection
C10	Deaths from hepatocellular carcinoma, cirrhosis and liver diseases attributable to HBV and HCV infection

HBV: hepatitis B virus; HCV: hepatitis C virus.
Source: [6].

To support the implementation and monitoring of this strategy, a framework with 10 core indicators has been proposed by WHO, which include a mix of epidemiological and programmatic indicators (Table) [6].

The process and criteria for selecting the indicators are described in detail in the WHO technical report [6]. In this paper we provide an overview of the current situation across EU/EEA countries in the context of the global WHO indicators to highlight gaps in programmatic responses and challenges in achieving elimination in Europe.

The European situation

The WHO Regional Office for Europe (WHO/Europe), in consultation with the Member States and partner organisations, has developed an action plan to guide the implementation of the GHSS in the European Region [7]. This regional plan was launched following endorsement by the Regional Committee in September 2016 and provides the structural framework for countries to use when organising their responses. It includes regional targets, some of which are more ambitious than the global targets in recognition of already existing prevention and control efforts in the Region and the capacity of existing systems to further impact on the epidemics. The plan refers to the WHO monitoring and evaluation framework with 10 core indicators as a tool intended to facilitate the generation, collection and analysis of standardised data for the monitoring of the response on the national and Regional level (Table).

The European Centre for Disease Prevention and Control (ECDC) and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), both EU agencies, are well placed to provide technical support to assist EU/EEA countries develop tailored national plans for achieving the WHO targets. In 2016, the two agencies, in collaboration with WHO/Europe, assessed the availability of data for each of the core indicators and concluded that current data sources in most EU/EEA countries are insufficient, particularly for assessing the epidemiological burden and for monitoring the different steps along the cascade of care [8]. Further collaboration with the countries and clinical associations will be required to improve data sources. Regular seroprevalence surveys and sentinel-site surveys will be required to determine (i) estimates of prevalence and incidence, (ii) the attributable fraction of liver cirrhosis and hepatocellular carcinoma cases related to HBV and HCV infections and (iii) the size of the undiagnosed population [6]. The systematic collection of programmatic data related to testing and to prevention and treatment coverage will also need to be conducted.

While some EU/EEA countries have well-developed data systems providing comprehensive epidemiological information on hepatitis B and C to support local policy initiatives, there is variation between countries [9]. In an attempt to address such differences and standardise notification data, ECDC implemented in 2011 an enhanced surveillance system to facilitate the collection of data on newly diagnosed cases. Recognising the limitations of routine notification data to provide a clear epidemiological overview of the numbers and groups affected by infection, EMCDDA and ECDC have started work to collect and collate seroprevalence data from key risk groups and the general population using standardised methodologies and will publish this information when available.

From an epidemiological perspective, the prevalence of HBV and HCV is low-to-intermediate in most EU/EEA countries, but the situation is diverse and dynamic. National estimates of seroprevalence in the general population vary from 0.1% to 4.4% for HBV and from 0.1% to 5.9% for HCV [1]. Among key risk groups, prevalence estimates show similar variation. For the population of people who inject drugs (PWIDs) and former PWIDs in Europe, the prevalence of HCV is high, with 11 of the 16 countries with recent data reporting national estimates of over 40% [1]. Harm reduction programmes, especially those combining needle and syringe programmes (NSP) and opioid substitution treatment of people who inject opioids, as well as more recently, treatment with the new direct-acting antiviral drugs, may have the potential to contribute considerably to reducing transmission in many countries. In spite of this, prevalence rates found in national and subnational seroprevalence studies among PWID in most EU/EEA countries are high (›50%) [10], including among young and new injectors [11]. Reports suggest that only a small proportion of those infected with HBV or HCV are aware of their infection [2,12]. Among PWIDs, the proportion of those undiagnosed for HCV is likely to be very high, with estimates ranging from 24% to 76% [13]. This highlights a clear need to extend existing testing programmes.

Migrants, defined as individuals born outside their country of residence, contribute to the HBV and HCV prevalence pool. A recent analysis estimated that 1 to 2 million chronically HBV-infected migrants from endemic countries with a prevalence of over 2%, reside in the EU/EEA and account for 25% of all chronic HBV cases [14]. For HCV, estimates indicate that chronic infections among migrants account for 14% of all chronic infections [14].

Men who have sex with men (MSM) are a key risk group for current HBV and HCV transmission in most European countries. Vaccination has reduced HBV transmission, however, there have been increasing reports from European countries of acute HCV infections among HIV-infected MSM [15]. Reports of HCV infections among HIV-negative MSM have raised concern that HCV is an expanding epidemic among MSM [1].

Despite the emerging trends described above and high levels of infection among key risk groups, the incidence of HBV and HCV has declined slightly across Europe in recent years [2,12]. For HBV, this is demonstrated by the surveillance data reported to ECDC which have shown a steady decline in the rates of acute infections across EU/EEA countries, with rates in most countries now less than 1 case per 100,000 [16]. However, there remains considerable diversity between countries with notification rates for acute HBV cases in 2014 ranging from 0 cases in Malta to 3.2 per 100,000 in Bulgaria. While chronic viral hepatitis is known to be one of the leading causes of end-stage liver disease, estimation of the proportion of deaths from liver cirrhosis and hepatocellular carcinoma attributable to HBV and HCV infection is difficult due to scarcity of data [17].

Data on hepatitis B vaccination coverage are routinely collected by WHO and the United Nations Children's Fund (UNICEF) through Joint Reporting Form on Immunization [18]. Twenty-three of the 31 EU/EEA countries reported data on coverage with three doses of HBV vaccine among 1-year-olds in 2014. Of these 23 countries, 11 reported coverage of 95% or over [18]. EU/EEA countries offer the first dose at birth either as a general recommendation to all newborns (7/31) or targeted to newborns from mothers from groups at risk or mothers with HBV infection (24/31) [19].

In relation to the indicator on injection safety, there is no systematic data collection of facility level injection safety in EU/EEA countries, but evidence from the notification data submitted to ECDC indicates that nosocomial transmission remains an ongoing transmission route for both infections in some countries [16,20].

Data on the levels of testing and treatment in EU/EEA countries are currently not systematically collected at the EU/EEA level or even nationally in most countries, but the available published evidence of ad hoc reviews suggests that provision is suboptimal in many countries, with high numbers of infections undiagnosed and only a small proportion of those who have been diagnosed effectively treated [13,21].

Programmatic data relating to prevention programmes for HBV and HCV across EU/EEA countries, although incomplete, show similar levels of diversity. The data collected by EMCDDA on harm reduction measures targeting injecting drug users show considerable variation across the region with suboptimal levels in many countries. Indeed, while the data indicate that one in two problem opioid users in Europe receive opioid substitution treatment (OST), in some countries the fraction of high-risk opioid users receiving OST is less than 20% [10]. In 14 countries providing recent estimates of the size of the PWID population, the number of syringes distributed per year from specialised NSPs remains below 50 syringes per injector in three countries and only four countries were able to document coverage above the recommended threshold of 200 syringes/PWID/year [10].

In addition to current gaps in prevention programmes and the available data required to monitor the implementation of these programmes, EU/EEA countries face other challenges to the successful elimination of hepatitis B and C. While recent data indicate that injecting drug use is stable or declining in Europe, the prevalence of injecting drug use ranges between 1 and 9 cases per 1,000 population aged 15-64 years and is high (› 4 /1,000) in five countries [22]. Furthermore, a potentially large population of HCV infected ex-injectors might need to be included in future healthcare estimates [11].

The population of migrants coming from countries with high endemicity for HBV and HCV is dynamic and recent studies indicate that estimates of prevalence from the country of origin may not be a good proxy for prevalence in all migrant groups. The prevalence in migrant populations has been found to be lower, especially for hepatitis B, so the true extent of the burden among different migrant groups is unclear [14].

Interventions are further hampered as stigma and discrimination surround hepatitis B and C, migrants, MSM and injecting drug use. In some parts of eastern Europe, repression is the prevailing response to drug use, while across most of the EU, a balanced approach with public health and criminal justice elements is now common [23-25]. Indeed, stigma and discrimination are barriers to testing and treatment access among PWID. Stigma around hepatitis B infection has been shown to impact negatively on testing behaviour of some migrant groups [26].

The EU/EEA is mostly comprised of high income countries. However, resources dedicated to the prevention and control of hepatitis have been described as suboptimal [21] and in striving towards elimination and the necessary scaling up of services, this will need to be addressed. The current cost of antiviral drugs for curing hepatitis C remains high and this could undermine national efforts in impacting upon the growing disease burden. Indeed, while prevention measures are able to impact on the incidence of new infections [13,16], it is only through identifying and treating those already infected that a reduction in mortality will be possible. EU mechanisms such as the joint procurement of medical countermeasures [27] could be one option for countries to consider, to help reduce the costs of antiviral treatment, while continued advocacy by non-governmental organisations remains important. WHO has developed several tools to assist countries in their prevention and control efforts including global testing and treatment guidance and national planning toolkits [28-30]. ECDC and EMCDDA provide complementary tools, such as specific evidence-based recommendations for action, tailored to the EU context, and both agencies will continue to work in close collaboration with WHO to support countries in their efforts to scale up activities.

Further development of existing monitoring platforms and working to minimise the reporting burden for countries is important and prevention and control efforts for hepatitis could benefit from understanding some of the lessons learnt in relation to HIV in this area. Indeed, developing a standardised monitoring approach for interventions including diagnosis and treatment along the continuum of care, which is already established for HIV, could now be considered for hepatitis B and C. A recent review of operational interventions along the chronic viral hepatitis care continuum for people with diagnosed or undiagnosed chronic viral hepatitis demonstrated that a range of relatively simple, inexpensive operational interventions can substantially improve engagement and retention along the cascade of care, thereby optimising the implementation of screening, care, and treatment programmes [31].

Conclusions

The launch of a global strategy aimed at the elimination of viral hepatitis provides an opportunity to increase efforts aimed at tackling the HBV and HCV epidemics. European countries have already made progress in recent years implementing primary and secondary prevention measures. Indeed, measures aimed at reducing health-related harm among PWIDs, such as OST and NSP, now reach many of those who need them and most countries have in place a hepatitis B vaccination programme with high levels of coverage. These measures have had an impact on the epidemiology of HBV and HCV. However, the epidemiological, demographic and socio-political situation is complex in Europe and diversity and inequities in the programmatic responses to the epidemics exist. Stigma and discrimination are both important in Europe in relation to hepatitis B and C and efforts to reducing or eliminating stigma are essential if disease elimination is to be achieved. Comprehension of such issues alongside collaboration between key organisations and countries will underpin any chance of successfully eliminating hepatitis.

Conflict of interest

None declared.

Authors' contributions

All authors contributed to the paper. EFD conceived the idea for the paper, led its coordination and prepared the first draft of the article. DH, OM and AM reviewed and revised the draft. All authors read and approved the final manuscript.

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Quarterly, print and online. In Dutch, summaries in English.
http://www.infectieziektebulletin.be

Bulletin d'information de la section d'Epidémiologie
Institut Scientifique de la Santé Publique, Brussels
Monthly, online. In French.
http://www.iph.fgov.be/epidemio/epifr/episcoop/episcoop.htm

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Print version. In Bulgarian.
http://www.ncipd.org/

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Newsletter of the Network for Surveillance and Control of Communicable Diseases in Cyprus
Medical and Public Health Services, Ministry of Health, Nicosia
Biannual, print and online. In Greek.
http://www.moh.gov.cy

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Zdravotního Ústavu, Prague
Monthly, print and online. In Czech, titles in English.
http://www.szu.cz/cema/adefaultt.htm

EPIDAT (Notifications of infectious diseases in the Czech Republic)
http://www.szu.cz/cema/epidat/epidat.htm

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Department of Infectious Disease Epidemiology, National Public Health Institute, Helsinki
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http://www.oek.hu/oek.web?to=839&nid=41&pid=7&lang=hun

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Notiziario dell'Istituto Superiore di Sanità
Istituto Superiore di Sanità, Reparto di Malattie Infettive, Rome
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http://www.iss.it/publ/noti/index.php?lang=1&tipo=4

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Istituto Superiore di Sanità, Reparto di Malattie Infettive, Rome
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http://www.epicentro.iss.it/ben

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Epidemiologijas Bileteni
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http://www.sva.lv/epidemiologija/bileteni

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http://www.insp.gov.ro/cnscbt/index.php?option=com_docman&Itemid=12

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http://www.ivz.si

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The website of European Commission Directorate General for Health and Consumer Protection (DG SANCO).
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