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2014 French guidelines for hepatitis B and C screening.

A combined targeted and mass testing strategy of chronic viruses namely HBV, HCV and HIV

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Abbreviations :

AFEF : Association Française pour l'Étude du Foie
ANRS: Agence Nationale de Recherche contre le SIDA et les Hépatites virales
CDC: Centers for Disease Control and Prevention
HBs Ag: Hepatitis B surface Antigen
HBV: Hepatitis B Virus
HCC: Hepatocellular carcinoma
HCV: Hepatitis C virus
HIV: Human immunodeficiency Virus
GPs: General Practitioners
POC: Point-Of-Care

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KEY POINTS

- Worldwide, a minority of individuals infected with hepatitis B or C is aware of its status. Given the limits of a targeted strategy and given that the majority of unaware individuals in France are men, without any specific age-trend for HCV, France established new recommendations for HBV and HCV testing:
 - HBV, HCV and HIV tests should be quasi-systematically combined
 - Targeted screening should be strengthened using rapid point-of-care tests and large information campaigns
 - A routine testing for these 3 viruses should be offered to all pregnant women and, at least once, to men of 18 to 60.

ABSTRACT (249 words)

Background & Aims

Worldwide and, to a lesser extent, in France, a minority of individuals infected with hepatitis B (HBV) and C (HCV) is aware of its status. Given the current availability of highly effective anti-HBV and anti-HCV agents, the high rate of undiagnosed people, associated with individual and community prejudices (liver disease worsening, persistence of a hidden transmission reservoir, and medico-economic burden of delayed care), is unacceptable.

Methods

On the occasion of the first French general report on viral hepatitis, new recommendations for HBV and HCV testing were issued. We aim to introduce the new French strategy for HBV and HCV screening, and to describe the underlying epidemiological data.

Results

These recommendations comprise various items. First, the screening of chronic viruses namely HBV, HCV and HIV should be quasi-systematically combined. Second, the targeted screening of groups at risk of viral exposure must be strengthened. Third, routine testing for each of these three viruses should be offered at least once to men of 18 to 60 years old who had never been tested. In parallel, in pregnant women, in addition to HIV-HBV screening currently recommended, HCV testing should be routinely performed during the first trimester of pregnancy.

In order to best achieve the target populations, community initiatives that propose testing actions should be encouraged, particularly those including rapid point-of-care tests.

Conclusions

Overall, these recommendations aim to define a comprehensive testing strategy for chronic viral infections, emphasizing both targeted screening and mass screening and considering jointly HBV, HCV and HIV.

KEY WORDS

Hepatitis B; Hepatitis C; Testing; Screening

TEXT

Introduction

In France, as in other developed countries, testing for infection with hepatitis B (HBV) and C virus (HCV) is a major public health issue. With the arrival of direct-acting antivirals that allow a viral cure in 90% of patients [1], HCV infection is currently undergoing a therapeutic revolution which lead to hope, if associated with a significant improvement of HCV-awareness among infected individuals, HCV eradication. For HBV, current treatments allow viral control in the majority of patients, with little resistance and good tolerance. For these two infections, treatments and viral replication termination are associated with a reduced risk of developing cirrhosis and hepatocellular carcinoma (HCC) [2, 3].

In parallel to therapeutic advances, screening tools get diversified with the development of HCV and HBV point-of-care (POC) rapid tests, which enable a broader variety of screening strategies, including testing for people outside the structures care.

In addition to individual benefit, early detection generates a collective benefit associated to the reduction of the infection transmission risk, but also, by limiting progression to cirrhosis or HCC, long-term reduction of the cost of care. For HBV, testing also precise the immune status and thus incite to vaccinate unvaccinated persons at risk of exposure.

Compared to these benefits, the rate of under-detection of viral hepatitis observed in most of the developed countries is no longer acceptable. Therefore, for HCV diagnosis, some countries such as the United States or Canada recommend now population screening for certain age groups, regardless of risk factors, in addition to targeted screening [4, 5].

However, recommendations for HBV testing have not recently been amended. Despite a slightly more favourable position than other European countries or the United States [5-8], France faces also under-detection with about half of the 500,000 people with HBV or HCV who are unaware of their viral status [9].

In this context, and taking the opportunity of the first French report on the care of people infected with HCV or HBV [10], new recommendations for testing were issued. The purpose of this article is first to review past testing strategies for HCV and HBV, to describe what were their results and their impact, and based on this to introduce the new French strategy for hepatitis B and C screening.

Materials and methods

Expert Panel

In spring 2013, as part of the preparation of the report on the management of people infected with HCV or HBV, a group of 19 "Testing experts" was established and validated by the National Research Agency against AIDS and Viral Hepatitis (ANRS) and the French Association for the Study of the Liver (AFEF). This group comprised general practitioners, hepatologists, infectious disease specialists, virologists, epidemiologists and representatives of patient groups. A list of questions was set up to guide the group on the evaluation of the status of the viral hepatitis screening and the development of recommendations (Table 1) [11]. Questions were dealing with the description of previous testing strategies, their impact and in particular data on characteristics of HBV and HCV epidemics, and their limits in terms of organisation namely tools and actors. All the data on these themes were considered, whether or not published. The texts related to each of these themes were written in sub-working groups and submitted for review to all group members. The final document was forwarded to the committee for report validation and summary.

Data sources

Previous screening guidelines

Current recommendations were, for HCV, those issued by the National Agency for Accreditation and Health Evaluation in 2001 [12]. For HBV, testing of HBs antigen (HBsAg) is mandatory in pregnant women in the 6th month of pregnancy, and in the context of blood donations [13]. In addition previous guidelines [14] recommend screening focused on people with at least one risk exposure from those listed in Table 2.

Sociodemographic characteristics of overall infected individuals

Sociodemographic characteristics of HBV or HCV infected individuals and those of them unaware of their status were provided by the 2004 national seroprevalence survey [9] that was updated for HCV in 2014 [15]. Methods used to conduct this survey have been previously described [9, 15]. In summary, the 2004 seroprevalence survey was a cross-sectional survey conducted among a random sample of 18–80 years old residents of mainland France. The survey protocol was approved by a national ethical review board (CCPPRB, October 25, 2002, no. 02-035). Selected individuals received an invitation for a free medical checkup. Overall, 14,416 people were included after written informed consent and received HBV and HCV antibody screening. Data were collected for demographic characteristics, potential exposure to HBV or HCV, prior testing and infection awareness. For HCV, the 2014 estimates were determined using an epidemiologic model taking into account mortality, HCV incidence and diagnosis rates and applied to undiagnosed

chronically-infected HCV cases aged 18 to 80 in 2004. Analyses were performed for each year from 2004 to 2014, for each gender and age-group. Multiple data sources were compiled to feed the model. To take into account uncertainties of the model parameters and estimate plausible interval around the estimated number of undiagnosed HCV persons in 2014, several scenarios were studied.

No updated estimation was determined for HBV epidemiological data.

Characteristics of infected individuals at diagnosis

The Hepatology Reference Centers surveillance network based on university hepatology wards in hospitals throughout France which report, for every HBV or HCV newly referred patients, circumstances of testing, at risk exposures co morbidities and severity of the liver disease [16, 17].

HBV and HCV testing activity

To evaluate HBV and HCV activity The “LaboHep” national survey [18, 19] were carried out in France from a random sample of 1,412 laboratories in 2010 and 1,504 laboratories in 2013, taking into account the sampling design and the laboratories’ activity.

Barriers to HBV and HCV testing

Published and grey data on testing organization and in particular actors and tools was reviewed in order to address current barriers to screening implementation and to refine the HBV and HCV testing strategy. We mostly focused on the French literature.

Results

Characteristics of overall infected individuals

In 2004, the prevalence of chronic infection with HCV (HCV RNA) and HBV (HBsAg) among the general adult population in metropolitan France was estimated at 0.53% (95% CI: 0.40 to 0.70) and 0.65% (95% CI: 0.45 - 0.93), accounting for 232,196 (95% CI: 167,869 – 296,523) and 280,821 people (95% CI: 179,730 – 381,913), respectively [9]. HCV RNA prevalence was slightly different in men (0.45%; 95% CI: 0.28 - 0.71) and in women (0.62%; 95% CI: 0.40 - 0.95) and tended to increase with age (Figure 1). Conversely, HBV prevalence was higher among men (1.1%, CI 0.73 - 1.67) than women (0.21% CI: 0.10 - 0.47) and tended to decrease with age (Figure 1).

Among infected individuals, only 57% (95% CI 41-71) of people with chronic hepatitis C and 45% (95% CI: 23-69) of HBsAg positive persons [9] were, in 2004, aware of their status. Of

note, for HCV the overall proportion of persons aware of their HCV seropositivity may have evolved from 24% in 1994 to 57% in 2004 [20] and to 65% in 2014 [6, 15].

For both viruses, based on 2004 data, the proportion of infected people aware of their status differs across age groups (Figure 2).

For HCV, among the 232,196 people chronically infected in 2004, 100,868 (95% CI 58,534-143,202) were unaware of their status, including 55,385 women (95% CI, 20,162-90,608) (55%) and 45,483 men (95% CI, 17,986-72,980) (45%). Figure 3 illustrates distribution by age and gender of undiagnosed individuals. Apart from the high proportion of undiagnosed patients among women aged over 60 years of age, who are in 2016 more than 70 years of age, there is no age trend in the proportion of undiagnosed hepatitis C patients and especially among men. The update of these estimates for 2014 [15] showed that the rate of men aged 18 to 59 among undiagnosed people for hepatitis C was higher in 2014 (45%) than in 2004 (27%). Conversely, the rate of undiagnosed women aged over 60 years has declined. For hepatitis B, a large majority (81%; 95% CI: 87,988-221,923) of the 154,956 undiagnosed people were, in 2004, men, aged 18 to 59 years for 90% of them. In HBV-undiagnosed women, nearly two-third of the 29,079 [95% CI 775 - 57,384] women was aged 18 to 39 (Figure 3).

Overall, the comparison of distributions by age and sex of HBV-undiagnosed and HCV-undiagnosed people showed that 55% of all of these undiagnosed people in 2004 are men aged 18 to 59 years [15].

The rate of infected people aware of their status also depends on the risk exposure. For HCV, rates have been estimated between 73% and 91% among people who inject drugs at least once in life [21], 51% among those transfused before 1992, and 35% among those who have no history of drug use or transfusion before 1992 [9]. For HBV, it ranges from 57% among those born in low endemic area to 16% for those born in area moderately or highly endemic for HBV [9].

Characteristics of infected individuals at diagnosis

A significant proportion of patients diagnosed for hepatitis C or B at the end of 2000 and followed in liver diseases reference centres were at late stages of disease : 13% of men and 10% of women newly diagnosed for hepatitis C had advanced disease (cirrhosis or hepatocellular carcinoma) [16]. For HBV, it reached 13% of men and 3% of women [17]. Of note among the overall diagnosed patients, less than a quarter were detected thanks to risk factors targeting. For most of them, testing was performed incidentally during an overall health assessment [22].

HBV and HCV testing activity

Testing activity rose steadily since the early 2000s [18, 22] and was estimated at 55 anti-HCV tests per 1000 and 58 HBsAg tests per 1000 inhabitants in 2013 versus 53 anti-HCV tests per 1000 and 53 HBsAg tests per 1000 inhabitants in 2010 [18, 19]. The estimated positivity rates of anti-HCV and HBsAg screening test performed in France in 2013 were 0.9% for anti-HCV and 0.8% for HBsAg [19], i.e., not much better to the estimated positivity test prevalence in the general population (respectively 0.84% and 0.65% for anti-HCV and HBsAg) [9].

Current barriers to screening implementation

Some barriers to screening implementation are related to the widespread lack of knowledge about viral hepatitis and their exposure risk factors among the general population [23, 24] and among those at risk [25]. In turn, some physicians are insufficiently aware of the weight of the various risk factors [26], or are sometimes struggling to explore the potential exposure of their patient. Several studies have shown inadequate testing practices. According to a survey of a random sample of 2,083 general practitioners (GPs) in France, HBV testing is not systematically proposed to people at risk of HBV infection: 38.6% of GPs said they routinely propose screening to people from highly endemic countries, 55.9% to those with sexual risk behaviours and 61.8% to the household of HBsAg-positive patients [27]. Similarly, only 59.5% of surveyed physicians reported routine HCV testing proposal to people having got transfused before 1992. However, the HCV and HBV testing are more frequently proposed to intravenous drug addicts (76.6% and 73.1%, respectively) [27]. Two other surveys showed that only 34 to 40% of at-risk patients had HCV screening test [28, 29]. The main barriers to testing are the physician unawareness of the patient exposure to a risk situation [24], and his/her ignorance of some risk factors as such [26, 28, 29], in a context where people at risk sometimes deny their own risk exposure, which further complicates the targeted testing. Moreover the difficulty of identifying people at risk, the complexity of the prevention exercise for physicians involved in many missions must also be pointed out. Therefore, it rules out a monothematic approach, but enables to take every opportunity to propose a hepatitis screening test, combined with the detection of other sexually transmitted infections where appropriate. In addition, previous experience of low compliance to the routine HIV screening recommendations issued in France in 2008 [30] shows the need for a clearly understandable and pragmatic strategy. Indeed, the recommendation to screen for HIV at least once the general population aged 15 to 70 years regardless of their risk exposure was rarely applied [31]. The low implementation of this testing recommendation is partly due to a lack of

perceptible benefit by the doctor, given the small number of expected positive tests despite an expected impact of this recommendation at the societal level [32].

Testing access/ Point-of-care tests

The development of HBV and HCV POC tests enables community initiatives to propose screening interventions for these infections, along with HIV. As for the POC HIV tests used for many years [30, 33], these tests require minimal equipment and a puncture capillary whole blood from the fingertip or a simple cravicular liquid sampling. Easy to perform, including by non-medical personnel, the result is obtained in less than 30 minutes. Rapid tests performances have been supported by several studies [34-37]. To date, the use of POC tests for HCV has been validated by the CDC in the US [11] and the High Authority of Health in France [38]. However POC tests for HBV screening have not yet been formally validated, and are not used in current practice in Western countries. Although POC tests have a slightly lower sensitivity than classical serological tests and require a specific organization to allow traceability of results, several studies attest to the importance of these practice tests to promote access to screening for target audiences [39-41].

Discussion

Epidemiologic data of HCV and HBV-infected patients presented here illustrate, that under current testing strategies, France faces under-detection of people infected with HCV or HBV. One strategy to increase the rate of diagnosed people is to complement the targeted screening based on risk exposures by a population-based screening, likewise the recent recommendations issued by the United States and Canada (i.e., people born between 1945 and 1965 for the former, and those born between 1945 and 1975 for the latter) [4, 5]. However, in the French epidemiological context showing no specific age trend for overall undiagnosed population but also the limits of target approach and the necessity to promote a pragmatic, easily expandable and pluri-thematic testing strategy, a similar birth-cohort HBV-HCV testing strategy would not be appropriate. In contrast, based on these data, in addition to targeted screening on risk exposures, a strategy targeting men would be more pragmatic (males accounted for 67% of undiagnosed HCV and HBV in 2004 [42]). Moreover, in this population, because of common demographic characteristics, a combined HIV and HBV-HCV population-based testing strategy (chronic viral infections) would be more acceptable to health professionals and probably cost-effective; males accounted for 70% of undiagnosed HIV in 2010 [43].

Screening should be promoted in various medical environments such as during a medical consultation (general practitioner, or specialists), in sexually-transmitted diseases clinics, during inpatients visits, in prisons, but also during interventions organised within communities thanks to new POC tests. Indeed these settings host at-risk populations such as migrants, and people who inject drugs, who do not necessarily attend health care settings and who feel more comfortable to report difficulties or unsafe practices within the associative framework.

During pregnancy, due to the possible need for HBV treatment at the last trimester, combined to the delay in specialized management initiation, it appeared desirable to advance the mandatory HBV testing (previously recommended during the last trimester) just after the initial pregnancy assessment, along with other serological tests. For HCV, given the possible risk of mother-to-child transmission (about 5% [44]), and the recent availability of highly effective antiviral agents with few adverse events (and although their safety during pregnancy need to be demonstrated), the routine testing among pregnant women, previously not recommended, is now considered and could be performed in combination with the HIV and HBV testing during the 1st trimester of pregnancy.

In summary, based on the inventory carried out, the main recommendations issued by the Group and included in the first French report on the care of people infected with HCV or HBV published in May 2014 are the followings [10]:

- 1) Combine the testing for the chronic viruses (namely, HBV, HCV and HIV), given the epidemiological similarities, and in order to simplify screening indications and favour empowerment by all medical and associative. In this perspective, the development of combined HIV-HBV-HCV rapid tests should be encouraged;
- 2) Continue targeted screening strategy for hepatitis B and C, according to the risk exposure, as currently recommended. It should be supported by large-scale information of the general population and information of general practitioners. Importantly, HCV testing should be renewed regularly in some populations at risk (such as injectable drug users).
- 3) Set up a population-based testing for HBV, HCV and HIV, by offering a screening test of the following populations at least once in their life: (1) Men aged 18 to 59 years, mainly following a proposal from their general practitioner, and (2) Pregnant women at the first prenatal visit.
- 4) Encourage the use of rapid POC tests for screening populations who do not attend traditional medical facilities. The training of the non-health professional staff who will offer

these tests is essential for the screening acceptance and the subsequent appropriate treatment;

Of note, in addition to testing recommendations, it is important to promote interventions that allow a better linkage-to care of infected individuals. The importance of linkage to care, in line with screening strategies improvement has been recently illustrated in particular in France [41, 45, 46]. To evaluate the proportion of infected patients aware of their infection, national epidemiological studies should be regularly conducted and should, likewise in HIV, provide data to estimate HCV/ HBV cascade of-care.

Overall, 2014 French HBV-HCV-testing recommendations aimed to clarify the respective indications of testing for hepatitis B and hepatitis C, and, above all, to define a global strategy emphasizing both targeted screening and mass testing, and considering jointly the three chronic viral infections, HBV, HCV and HIV.

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Tables

Table 1 : Questions to guide the implementation of a status report on hepatitis B and C screening and the development of subsequent recommendations [11]

- What are the current screening recommendations?
- What are the epidemiological data enabling to assess the screening effectiveness and guiding the development of new recommendations?
- Who are the screening actors and what are their tools?
- What are the screening barriers and leverages?
- Should screening strategies and players change with the availability of more effective treatments and of new tools?
 - General population-based screening
 - Screening for birth cohorts
 - Targeted repeated screening
 - Community-based screening
- Should screening strategies for HCV, HBV be combined with HIV screening ? If so, how?

Table 2 : French guidelines for HBV and HCV screening, before 2014 [12, 14]

2. a. HBV

- People born or who have lived in countries with an HBV endemic level either high (Sub-Saharan Africa, Asia) or medium (DOM-TOM, Eastern and Southern Europe, North Africa, Middle East, Indian Subcontinent and South America);
- The household and sexual partners of HBV-carrier subject;
- Users of intravenous or intranasal drug;
- Patients who may have received massive or iterative blood transfusions;
- Travelers in a country with high or medium HBV endemicity;
- Adults and children attending psychiatric institutions;
- Persons with tattoos or body piercing;
- Prisoners and previously incarcerated persons;
- People who have sex with different partners;
- People with occupational exposure;
- Persons with a positive serology for HIV or HCV, or having a current or recent sexually transmitted infection.

2.b. HCV [12] :

- Persons who have received blood products or tissue transplant, cells or organs, before 1992;
- Persons who injected drugs at least once in their lives;
- Persons exposed to nosocomial invasive procedures before 1997;
- Patients undergoing hemodialysis;
- Children born to HCV-positive mother;
- Persons with positive serology for HIV;
- Sexual partners and members of the household of subjects infected with HCV;
- Prisoners and previously incarcerated persons;

- People from or who received care in countries with a high HCV endemicity (Southeast Asia, Middle East, Africa, South America);
- Persons who have had tattoos, body piercing, acupuncture or mesotherapy procedures without the use of disposable or personal equipment
- Persons with elevated ALT blood levels of unknown etiology.

Figures :

Figure 1 : Estimated prevalence of HCV RNA and HBs antigen among the general population of metropolitan France in 2004, according to age and gender [9]

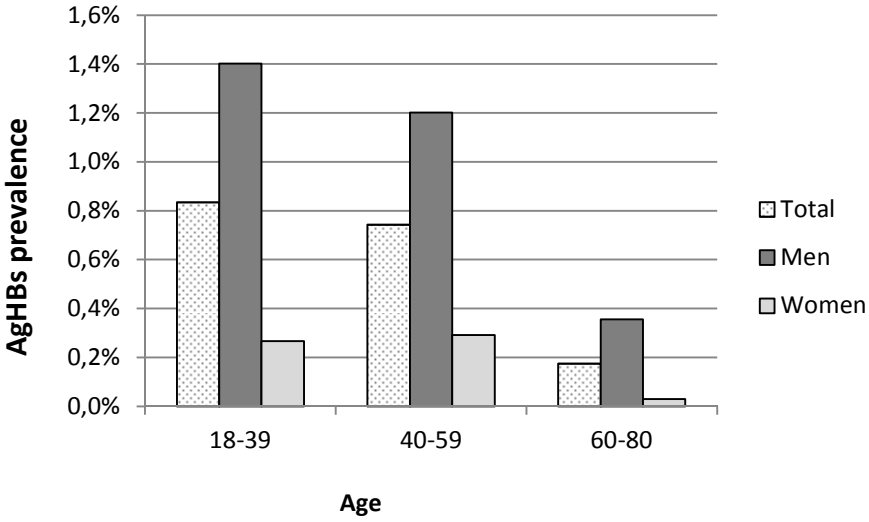
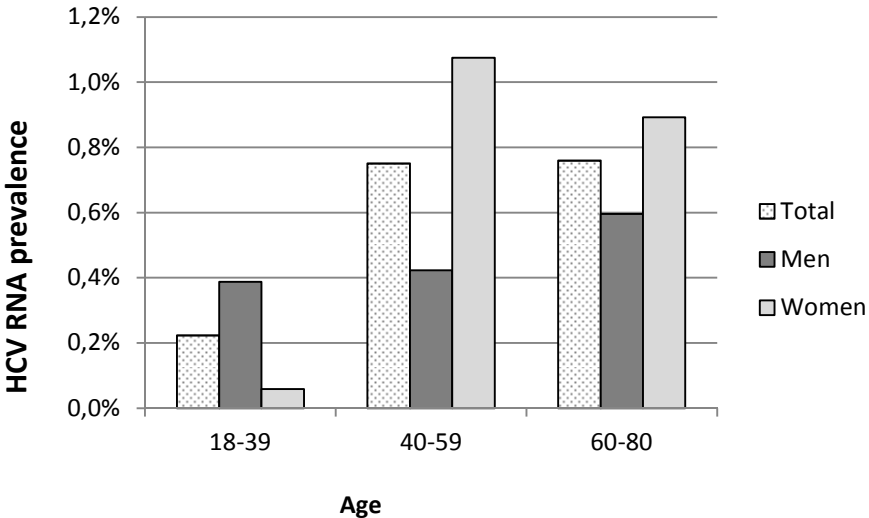


Figure 2: Estimated rate of people with chronic HCV or HBV and aware of their viral status among the French metropolitan general population in 2004, according to age [9]

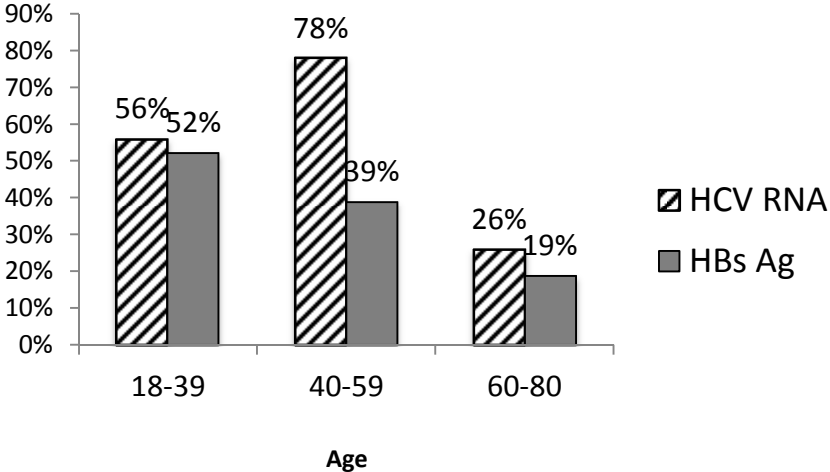


Figure 3: Distribution by age and gender of undiagnosed people for chronic HCV or HBV among the French metropolitan general population in 2004 [42]

