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DOI: 10.17235/reed.2019.6768/2019
Link: PubMed (Epub ahead of print)

Please cite this article as:

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Principles for implementing a population screening strategy for hepatitis C in Spain

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Received: 29/11/2019
Accepted: 06/12/2019

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Conflicts of interest: Joaquín Cabezas has no conflicts of interest. Federico García has received personal fees from Abbvie, MSD, Gilead, Qiagen and Roche. José Luis Calleja Panero is consultant and speaker for Abbvie, Gilead and MSD. María Buti has received grants and personal fees from Gilead and Abbvie. José María Molero García has received honoraria as speaker and lecturer for Gilead Sciences. Antonio Javier Blasco and Pablo...
Lázaro have received funding from the Fundación Española del Aparato Digestivo for the methodological development and writing of the manuscript. Javier Crespo is consultant and speaker for Abbvie, Gilead, MSD, Cellgene and Novartis, and has received grants from Gilead, Abbvie and MSD.

ABSTRACT

Background: hepatitis C, besides health impairment, results in significant loss of productivity and diminished quality of life, and noticeably contributes to health expenditure increases. Because of all this, the Spanish Ministry of Health (Ministerio de Sanidad, Consumo y Bienestar Social – MSCBS) implemented in 2015 a strategic plan for managing hepatitis C (Plan Estratégico para el Abordaje de la Hepatitis C – PEAHC) within the National Health System. However, the PEAHC includes no screening plan. The MSCBS developed a framework document on population screening (Documento Marco sobre Cribado Poblacional) that defines the criteria a disease must meet in order to consider implementing a screening program. Specifically, it defines 4 criteria related to the health issue, 4 related to the screening test, and 3 criteria dealing with diagnosis confirmation and treatment.

Objective: to identify whether there is scientific evidence to support hepatitis C meeting the criteria to be considered a disease qualifying for a population screening strategy in Spain.

Methods: a literature search for scientific evidence concerning each required criterion for implementing a population screening plan for hepatitis C in Spain.

Results: sufficient scientific evidence was found to support hepatitis C meeting the criteria required by the MSCBS for the implementation of a population screening program.

Conclusions: according to the available scientific evidence, hepatitis C in Spain meets the required criteria to qualify for consideration of population screening plan.

Keywords: Hepatitis C. Screening. Diagnosis.
INTRODUCTION
Hepatitis C is the primary cause of liver cirrhosis and hepatocellular carcinoma (HCC), and represents the most common indication for liver transplant in Europe. Besides burden of disease, hepatitis C results in considerable economic overload with loss of productivity, activity impairment and reduced quality of life, and noticeably contributes to health expenditure increases (1,2).

According to the most recently published study in Spain, whose field work was carried out in the primary care (PC) setting between May 2017 and May 2018, the prevalence of anti-HCV antibodies among the general population aged 20 to 80 years was 0.85%, and the prevalence of viremia was 0.22% (3). This means that, in the Spanish population aged 20 to 80 years, there were 337,107 anti-HCV-positive individuals, with 76,839 viremic patients, in the PC setting; of these 29.4% were unaware of their infection. These estimates do not include the population secluded in prisons, and underrepresent subgroups at risk for HCV infection such as injection drug users (IDUs) and men who have sex with men (MSM) (3). Prior studies (4-7) revealed similar seroprevalence values with a higher prevalence of viremic patients. This discrepancy may be accounted for by the large number of patients treated in Spain since the implementation of the Plan Estratégico para el Abordaje de la Hepatitis C (PEAHC) within the national health system (NHS) (8).

Starting in 2015, with the availability of orally administered direct-acting antivirals (DAAs), HCV can be eliminated in over 95% of patients. However, in 2015, in Europe, only 34% of infected individuals had been diagnosed, and fewer than 5% of all HCV cases had received treatment (9). Identifying and treating people with hepatitis C, particularly in at-risk groups, is key to minimize the burden of disease and healthcare expenditure associated with this infection, and to achieve the elimination goals put forth by the World Health Organization (WHO) for 2030 (10,11). Screening programs are among the best strategies available to identify undiagnosed cases.
The UK National Screening Committee defines screening as “the process of identifying healthy people who may have an increased chance of a disease or condition. The screening provider then offers information, further tests and treatment. This is to reduce associated problems or complications” (12). The Spanish Health Ministry (Ministerio de Sanidad y Política Social) issued a document titled “Framework document on population screening” (13). The document was developed by the Screening Task Force, Public Health Commission, and was based on prior scientific papers by, among other institutions, the WHO (14). This document includes “Criteria for strategic decision-making regarding population screening programs”. These are 18 criteria concerning the health condition (4 criteria), screening program (4 criteria), confirmation diagnosis and treatment (3 criteria), and the program itself (7 criteria) (13).

In Spain there is no univocal screening strategy for hepatitis C, but some Autonomous Communities have developed initiatives including early detection of hepatitis C (15-17). Recently, the Asociación Española para el Estudio del Hígado (AEEH) has published guidelines for the elimination of hepatitis C, which include age as risk factor for HCV infection, hence considering age-related screening (18).

The goal of this work was to identify scientific evidence to support hepatitis C meeting the criteria to be considered a disease qualifying for a population screening strategy in Spain. To that end the present document was developed, its structure replicating that of the Framework Document on Population Screening (13); each and every criterion has been developed with their corresponding literature supportive references. Point 8 criteria (criteria for selecting the mutations to be included) have not been addressed as the screening test does not aim at detecting gene mutations; this is also the case with program-related criteria (criteria 12-18) as these deal with the program's practical implementation (13).

**CRITERIA FOR STRATEGIC DECISION-MAKING REGARDING POPULATION SCREENING PROGRAMS IN SPAIN – THE HEPATITIS C CASE**
I. Criteria related to the health problem

1. Important health problem
According to most recent data in the PC setting, among the Spanish population aged 20 to 80 years in 2018 there were 337,107 individuals positive for anti-HCV and 76,839 with hepatitis C; of these, 29.4% were unaware of their condition. With some models it was estimated that should the current policy and practice of hepatitis C management in Spain continue, the number of viremic patients would go from 314,000 in 2014 to 128,000 in 2030 (1).

The high cost of management for these patients, including liver cirrhosis, HCC, and liver transplantation since they develop during the course of disease, represents a huge burden for the health system. Hepatitis C also has extrahepatic manifestations and significantly impacts quality of life (19). In addition to health system costs, hepatitis C results in a high social cost. One study estimated that the loss of productivity attributable to early death from hepatitis C in Spain during the 2007-2011 period amounted to €1,054.7 million. Of this amount, 30.1% was associated with cirrhosis and 24.6% with HCC (20).

2. A well-defined disease with a well-known natural history
There are four primary routes of HCV transmission: in association with health care, use of injection drugs, from mother to child, and sexual contagion (21). In mid- to high-income countries most infections occur among IDUs via the intravenous route. IDUs have a high prevalence of infection, estimated to be 67% worldwide. Mother-to-child transmission has a moderate risk, higher for mothers with HIV coinfection (10-20%). The risk of HCV sexual transmission is higher in HIV-positive individuals, particularly among MSM. Other blood-borne transmission routes include contagion in health workers, cosmetic procedures (tattoos, piercings), scarification and circumcision, and use of intranasal drugs (22). The immigrant population from high-prevalence countries should also qualify as a special-focus group (23).
Anti-HCV antibodies persist for life. In people with anti-HCV antibodies a test is needed to detect HCV-RNA, which thus identifies the virus presence and confirms the diagnosis with hepatitis C (22). Spontaneous HCV clearing occurs within six months after infection in 15%-45% of infected individuals in the absence of treatment (22,24). The remaining 55%-85% will remain infected with HCV for life (if untreated), and will be considered hepatitis C patients, often with a paucisymptomatic course. When untreated, hepatitis C may progress to liver cirrhosis, liver failure, and HCC; the estimated risk of liver cirrhosis is 15%-30% at 20 years. The annual incidence of HCC in cirrhotic patients is approximately 2% to 4% (22,25).

3. Detectable latency period
The detectable latency period may be considered to begin at six months after acute infection, and remains for life in untreated patients (see section I.2). Avoiding HCV propagation is a key challenge in controlling hepatitis C progression as the condition is usually identified in a late stage. Even in developed countries the rate of diagnosis does not exceed 40% of cases given the asymptomatic nature of the disease for protracted periods of time, and the extant weakness of the surveillance system for HCV (26). However, this undetectable phase because of absent symptoms may be shortened by detecting anti-HCV antibodies, and when positive by measuring HCV-RNA (27).

4. Implemented cost-effective primary prevention interventions
Since no hepatitis C vaccine is available, the prevention of HCV infection relies on reducing the risk for viral exposure. This represents a significant challenge for health systems because of the various transmission routes and populations involved. Because of all this, the WHO recommends an integrated intervention package including, for example, damage reduction with IDU-specific activities, with provision of sterile injection equipment, together with education on how to prevent viral hepatitis transmission among IDUs (22). Although these necessary measures are already implemented in Spain, they are inadequate for the elimination of hepatitis C in a specific region. Therefore, is is necessary
that the unknown population with hepatitis C be treated in order to reduce the numbers of affected individuals and prevent the condition's transmission and reinfection (28). The efficiency of screening programs will be discussed in section II.6.

II. Criteria related to the initial screening test

5. A simple, safe test

The screening test for hepatitis C is based on the detection of anti-HCV antibodies. Most of the commercially available tests are enzyme immunoassays (EIAs) to be performed in a laboratory, and assess the presence of said antibodies in venous blood, hence a venipuncture is required to draw blood and then process the serum and plasma. Rapid diagnostic tests (RDTs) are also available that use several matrices, including serum or plasma but also capillary blood (finger puncturing) or gingival crevicular fluid, which facilitates detection with no need for venipunction, centrifugation, freezing, or certified personnel (22,29). At any rate, bearing in mind the infrastructure and professional training of the Spanish health system, these are simple tests with no associated risk for the patient. Screening should be supplemented with HCV-RNA testing only for anti-HCV-positive individuals. The test must be performed on the same biological sample used for antibody measurement, which is referred to as one-step diagnosis (OSD).

6. A valid, reliable, efficient test

EIAs have a sensitivity of nearly 100% (30), hence they detect anti-HCV antibodies in the vast majority of patients with resolved or active infection with HCV. However, the result may be negative (false negative) in recently infected patients and deeply immunodepressed individuals (29). EIA specificity is again nearly 100% (30), hence the likelihood of false positive results is very low. Considering the above sensitivity and specificity, as well as the prevalence of HCV in Spain (3), predictive values (PPV and NPV) also approach 100%. When a OSD is performed (see section III.9), PPV is 100% (no false positives) and NPV is higher than 99.95% (30). RDTs have sensitivity and specificity values
slightly lower than EIAs but remain acceptable (> 97%) (31,32), hence they may be of use for some specific groups (see section II.9).

Population screening strategies, while costlier than those focused on high-risk populations, may allow early diagnosis and treatment for asymptomatic patients, preventing new disease transmission and complications (27). A study performed in 2017 estimated that, with a screening strategy for the adult population (20 to 80 years) in Spain, the screening cost for the identification of one case of hepatitis C would be €8,418, and the cost per quality-adjusted life year (QALY) gained would be €1,900. Regarding a screening strategy for the high-risk population, the incremental cost-utility ratio would be €8,900/QALY (28). Furthermore, a study in Andalusia concluded that OSD is more efficient than traditional diagnosis (increases the number of diagnosed patients and their access to treatment, and saves costs) (33).

7. An acceptable test
In the pilot study carried out in the Valencian Autonomous Community of a population screening program (adults aged 25 to 70 years), where participants were invited by mail, the participation rate was 46% (27).

People may decide to undergo a HCV screening test or otherwise according to their context (including HCV awareness, psychologic health, lifestyle, and relationships with others) and the perceived consequences and implications of getting a positive result, including the availability and effectiveness of HCV treatment, and their concern for potentially transmitting the condition. Overall, they prefer that the testing be done confidentially, in a comfortable environment where they may receive adequate information on the HCV and the test being performed (34,35). In the Spanish context, it is to be expected that the screening test will be highly accepted by the population if adequate information is provided (access to effective treatment, avoidance of further transmission and progression, etc.).

Most IDUs visiting syringe exchange venues and mobile testing units consider these places adequate for HCV detection (35). Also, the high-risk population (IDUs, MSM) places great
importance on obtaining results fast, hence RDTs enjoy higher acceptability and their use is appropriate for these populations in settings other than the health system.

III. Criteria related to confirmation diagnosis and treatment

9. Scientific evidence on the diagnostic process and treatment
When a positive anti-HCV value is obtained the viral load should be measured (RNA by PCR) to establish a diagnosis of hepatitis C (22,36-38). The AEEH, SEPD (Sociedad Española de Patología Digestiva) and SEIMC-GEHEP (Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica) recommend using a OSD (39,40).

DAAs are indicated for patients with active infection, and are highly effective against HCV, with most treated patients being cured (22,29,38,41,42).

10. Availability of a more effective therapy in the presymptomatic stage
Treatment during an asymptomatic stage is more effective than when symptoms are present. Treatment clears the infection, thus preventing both hepatic complications (liver necroinflammation, fibrosis, cirrhosis, decompensated cirrhosis, HCC) and the extrahepatic disorders associated with HCV. Furthermore, it reduces mortality rates and improves patient quality of life. It also prevents infection transmission, thus reducing the incidence of the disease (11,29,38,41,44,45).

Hepatitis C treatment is acceptable and accessible in Spain. The Plan Estratégico para el Abordaje de la Hepatitis C (PEAHC) within the national health system establishes that all patients with hepatitis C, whether or not coinfected with HIV, whether treatment-naïve or failing to respond to a prior therapy, must be considered candidates to antiviral therapy, regardless of fibrosis grade (46). Several economic assessment studies conclude that in Spain the use of DAA-based regimens is efficient, and treatment cost is mostly balanced out by savings in long-term health care expenditure (47,48). Furthermore, they represent a health opportunity for vulnerable groups with limited access to health care resources.
11. Optimized health care as usual

The means required for the confirmation diagnosis of infection with HCV are available in Spain. Diagnostic laboratories have the infrastructure and human resources necessary to assume the diagnostic testing derived from the establishment of universal screening. Once a screening test yields a positive result, the NHS warrants equity in both the diagnosis and treatment of hepatitis C all across the nation (46,49,50).

DAA therapy is available for all patients in Spain, hence health outcomes could be optimized by treating all patients in need. For instance, once virological cure is attained, treatment with DAAs reduces HCV-attributable mortality thereafter (51,52); decreases hospitalization rates (53); improves the condition of patients on the waitlist for liver transplantation, and even allows to take some patients off the waitlist, which in turn improves organ availability for other patients (54); improves survival post-transplant (55); reduces the incidence of hepatocellular carcinoma (56,57); decreases extrahepatic manifestations (58), and finally lowers cardiovascular risk (59).

DISCUSSION

In Spain, the incidence and prevalence of hepatitis C have decreased, particularly since the PEAHC implementation, which allows treating all patients regardless of fibrosis grade (44). However, hepatitis C remains a significant health problem in Spain. According to some estimates, depending on the health policies that might be developed in Spain, the number of prevalent hepatitis C cases might go down from around 400,000 in 2015 to 15,000-300,000 by 2024. The most effective strategy for prevalence reduction is the one that most increases identification of undiagnosed individuals (43), and could be developed with some sort of screening program.

General population screening programs are costlier than those focused on populations at risk, but allow early diagnosis and treatment of asymptomatic patients, which prevents further transmission and complications (26). According to our review, hepatitis C meets the criteria laid down by the Spanish Health Ministry for a condition qualifying for a population screening plan (12).
In Spain’s current situation, the efficiency of population screening has acceptable ratios to be considered as fundable by the NHS; its incremental cost-utility rate (cost per QALY gained) versus an at-risk population screening approach in the adult population would be €8,900/QALY (27). This figure is lower than considered in Spain as efficient technology (60). Furthermore, SNS structure and organization allow implementation of a population screening program with a small incremental cost if utilization of available resources improves. For instance, 81% of hospitals have the means for OSD, but only 31% use them (39). The OSD approach, followed by effective communication of results and shared alerts, would provide diagnosed patients with access to treatment without unnecessary delays. Plausibly, the efficiency of any population screening strategy will shortly increase if OSD increases (32), if diagnostic testing is simplified (32,61), and if the tendency to lower drug prices persists (62).

In summary, hepatitis C meets all the requirements laid down by the Health Ministry for consideration as a disease qualifying for a population screening strategy, which is the best, most efficient approach to achieve the elimination of hepatitis C, and would also be beneficial both to patients and the NHS.
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