

# Carriers of hepatitis C: should they all be vaccinated for hepatitis A?

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**Aim.** To investigate the prevalence of immunization against hepatitis A virus (HAV) in persons with hepatitis C virus (HCV) infection, in order to determine who should be vaccinated for the former.

**Design.** Descriptive, cross-sectional study.

**Setting.** Urban health center serving 12 000 inhabitants.

**Participants.** Patients older than 14 years positive for HCV infection.

**Main measures.** Variables: presence of chronic liver disease, serological indications of hepatitis B, A, and immune deficiency virus (HIV) infection, vaccination for hepatitis B.

**Results.** A total of 134 persons (70.9% men and 29.1% women) comprised the sample of patients positive for HCV infection. Mean age was 41.75 years (SD, 16.55 years). Nearly all patients (93.3%) had chronic liver disease, 56.7% were intravenous drug users, 56% were positive for Hbc antibodies and 32.8% were positive for HIV. Serological testing for HAV was done in 75 patients (56%); the result was positive in 86.7%. Mean age in this subgroup was 50.4 years (SD, 17.8 years). In the HAV-negative subgroup, mean age was 36.6 years (SD, 15 years;  $P=0.02$ ). Serological testing for HAV could not be done in 44% of the patients: 33.6% did not respond to attempts to contact them by telephone or in writing, 6% were temporarily away from home, and 1 patient declined to be tested. The response to requests to obtain blood samples was better in women (66.7%), HIV-negative patients (34.7%), persons who were not intravenous drug users (43.3%) and persons with chronic liver disease (60%).

**Conclusions.** In persons younger than 40 years, the proportion of seronegative individuals is similar to that in the general population. Vaccination should be considered for all patients positive for HCV infection. In persons older than 40 years with chronic liver disease, the decision to vaccinate for HAV should be made in the light of serological findings.

**Key words:** Hepatitis C. Hepatitis A. Vaccination.

PORTADORES DE HEPATITIS C: ¿TENEMOS QUE VACUNARLOS A TODOS FRENTE A LA HEPATITIS A?

**Objetivo.** Estudiar la prevalencia de inmunización frente al virus de la hepatitis A (VHA) en personas infectadas por el virus de la hepatitis C (VHC), con el fin de indicar la vacunación.

**Diseño.** Estudio descriptivo transversal.

**Emplazamiento.** Centro urbano (12.000 habitantes).

**Participantes.** Pacientes positivos para el VHC mayores de 14 años.

**Mediciones principales.** Variables: presencia de hepatopatía crónica, serologías de hepatitis B y A e inmunodeficiencia humana (VIH), vacunación de hepatitis B.

**Resultados.** La muestra de pacientes positivos para el VHC se componía de 134 personas, el 70,9% varones y el 29,1% mujeres. Edad media: 41,75 (DE, 16,55) años. El 93,3% presentaba hepatopatía crónica, el 56,7% era usuario de drogas por vía parenteral (UDVP), el 56% era HBcAc positivo y el 32,8% VIH positivo. La serología del VHA se realizó a 75 pacientes (56%), y fue positiva en el 86,7%. La edad media en los pacientes VHA+ era de 50,4 (DE, 17,8) años, y en VHA- de 36,6 (DE, 15) años ( $p = 0,02$ ).

Al 44% de los pacientes no se pudo determinar la serología VHA: un 33,6% no respondió a los mensajes telefónicos ni a las cartas enviadas, un 6% estaba ausente temporalmente y un caso no aceptó hacerse la analítica.

La respuesta a la realización de la prueba fue mejor en las mujeres (66,7%), en pacientes VIH-(34,7%), en no UDVP (43,3%) y en hepatópatas crónicos (60%).

**Conclusiones.** En menores de 40 años, la proporción de seronegativos es similar a la de la población general y se debería considerar la vacunación en todos los pacientes VHC+.

En mayores de 40 años y en los pacientes con hepatopatía crónica se debería investigar el estado serológico para vacunar contra la hepatitis A.

**Palabras clave:** Hepatitis C. Hepatitis A. Vacunas.

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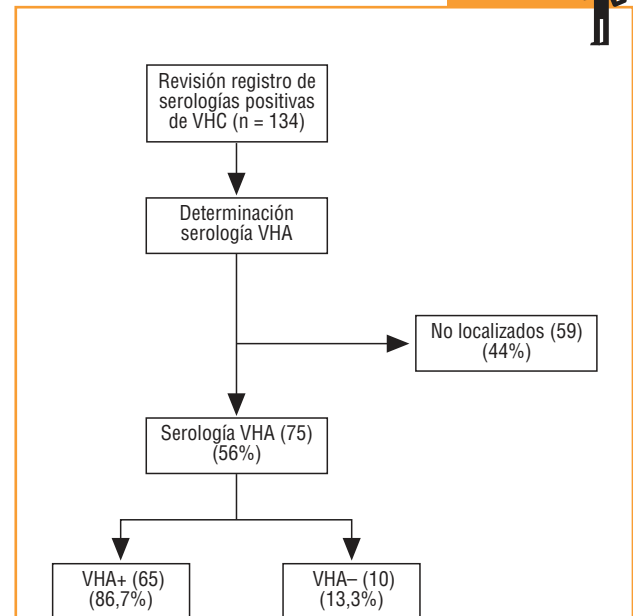
## Introduction

Recent years have seen a change in the epidemiological pattern of hepatitis A (HA). Epidemiological studies in Spain based on serological analyses carried out between 1977 and 1996 have shown a significant decrease in the prevalence of anti-HA antibodies in younger age groups. In persons aged 11-14 years, the prevalence declined from 49% in 1977 to 30% in 1985, and to 4.6% in 1996. In persons aged 21-30 years the prevalence declined from 73% in 1977 to 58.5% in 1985. In 1996 the figure was 29.1% for persons 20-24 years old, and 42% for those aged 25-30 years. These data reflect a reduction in the incidence of HA in younger persons, and an increase in the number of persons susceptible to infection in older age groups, in which the disease is known to course with more, and more severe, symptoms.<sup>1-9</sup> This change in the epidemiological pattern is also of relevance because of its implications for patients with chronic liver disease, mainly that caused by hepatitis C virus (HCV), as in these patients, superinfection or coinfection with hepatitis A virus (HAV) implies an increased risk of fulminant hepatitis or death.<sup>10-13</sup> In these groups of patients vaccination against HAV is recommended as a preventive measure, and has been shown to be effective in preventing infection.<sup>14-18</sup> The aim of this study was to investigate the prevalence of immunization against HAV in persons with HCV infection, in order to identify susceptible individuals who could potentially benefit from HAV vaccination.

## Material and methods

The study was done at the Dr. Pujol y Capsada Health Center, an urban center located in El Prat de Llobregat (Barcelona province, Spain) serving a population of 12 000. The socioeconomic level of most inhabitants is low, and approximately 20% of the inhabitants are members of the Gypsy ethnic group. This descriptive, cross-sectional study was done between May 1999 and March 2000 and involved the population of individuals older than 14 years who were seen at this health center. Patients were initially identified from a computerized register of cases of chronic liver disease, persons with human immunodeficiency virus (HIV) infection or intravenous drug users (IVDU), and from the register of serological laboratory tests ordered during the previous 2 years to detect persons positive for HCV infection. The medical records of these patients were reviewed, and HAV serological testing was requested for those patients who had not undergone such testing. These patients were contacted in the course of a visit to the health center, by telephone or in writing. The variables analyzed in this study were age, sex, presence of chronic liver disease, laboratory results for hepatitis B (HBcAb), hepatitis A (IgG, classified as positive or negative on the basis of the laboratory reference value), antecedents of vaccination for HB, intravenous drug use, and the results of serological testing for HIV (if such testing had been done).

## Material and methods



## Esquema general del estudio

Descriptive, cross-sectional study of patients older than 14 years with hepatitis C virus infection, followed at an urban health center since before April 2000.

The prevalence of immunization against HAV was analyzed in patients with HCV infection diagnosed at any time during their life.

The SPSS-PC software was used to generate descriptive statistics for the variables, with  $P < .05$  used to indicate statistical significance. 95% confidence intervals were calculated for the main findings. Chi-squared and Student's  $t$  tests were used for the bivariate analysis.

## Results

Of the patients we studied, 134 were HCV-positive. Men made up 70.9% of this group (95% CI, 63.2%-78.6%), and 29.1% were women (95% CI, 21.4%-36.8%). Mean age was 41.75 years (SD, 16.55 years). Chronic liver disease was present in 93.3% (95% CI, 89%-97.5%), IVDU was recorded in 56.7% (95% CI, 48.3%-65.1%), HBcAb positivity was found in 56% (95% CI, 47.6%-64.4%), and HIV positivity was found in 32.8% (95% CI, 24.9%-40.8%) (Table 1).

Immunity to HA was tested in 75 patients (56%). The response to the request for testing was better in wo-

**TABLE 1** Characteristics of the population in subgroups of patients who were and were not tested for hepatitis A infection

|                         | Hepatitis A serology | No hepatitis serology | Total       | Significance |
|-------------------------|----------------------|-----------------------|-------------|--------------|
| Sex                     |                      |                       |             |              |
| Women                   | 31 (41.3%)           | 8 (13.6%)             | 39 (29.1%)  | .0004        |
| Men                     | 44 (58.7%)           | 51 (86.4%)            | 95 (70.9%)  |              |
| HBcAb                   |                      |                       |             |              |
| Positive                | 43 (57.3%)           | 32 (54.2%)            | 75 (56%)    |              |
| Negative                | 25 (33.3%)           | 18 (30.5%)            | 43 (32.1%)  | .5745        |
| Unknown                 | 7 (9.4%)             | 9 (15.3%)             | 16 (11.9%)  |              |
| Hepatitis B vaccination |                      |                       |             |              |
| Yes                     | 2 (2.7%)             | 3 (5.1%)              | 5 (3.7%)    |              |
| No                      | 2 (2.7%)             | 2 (3.4%)              | 4 (3%)      | .7370        |
| Unknown                 | 71 (94.6%)           | 54 (91.5%)            | 125 (93.3%) |              |
| HIV                     |                      |                       |             |              |
| Positive                | 15 (20.0%)           | 29 (49.2%)            | 44 (32.8%)  |              |
| Negative                | 26 (34.7%)           | 20 (33.9%)            | 46 (34.4%)  | .0002        |
| Unknown                 | 34 (45.3%)           | 10 (16.9%)            | 44 (32.8%)  |              |
| IVDU                    |                      |                       |             |              |
| Current history         | 13 (17.3%)           | 31 (52.6%)            | 44 (32.8%)  |              |
| Past history            | 15 (20.0%)           | 17 (28.8%)            | 32 (23.9%)  | .0001        |
| No                      | 47 (62.7%)           | 11 (18.6%)            | 58 (43.3%)  |              |
| Chronic liver disease   |                      |                       |             |              |
| Yes                     | 75 (100%)            | 50 (84.7%)            | 125 (93.4%) |              |
| No                      | 0                    | 7 (11.9%)             | 7 (5.2%)    | .0065        |
| Unknown                 | 0                    | 2 (3.4%)              | 2 (1.4%)    |              |

HBcAb indicates antibody to hepatitis B core antigen; HIV, human immunodeficiency virus; IVDU, intravenous drug use.

men, HIV-negative persons, persons with no history of IVDU, and persons with chronic liver disease (Table 1).

Of the 59 patients (44%) in whom HA immunity could not be tested, 84.7% (95% CI, 75.6%-93.9%) did not respond to attempts to contact them by phone or in writing, 13.6% (95% CI, 4.8%-22.3%) were temporarily absent from their home (in prison or in a detoxification center, or away on holiday), and 1 patient (1.7%; 95% CI, 0%-5%) declined to be tested.

Mean age of the patients who were tested for HA immunity was 48.4 years (SD, 18 years); mean age in the group who did not undergo serological testing was 33.3 years (SD, 9.3 years;  $P<.0001$ ). Of patients with a current or previous history of IVDU, or who were positive for HIV, 37.8% agreed to be tested, vs. 84.6% of the patients with neither of these antecedents ( $P=.0001$ ). There were no significant differences in the prevalence of HAV infection between these groups (83.9% in the former group vs. 88.6% in all other patients).

**TABLE 2** Characteristics of the sample in subgroups of patients who tested positive and negative for hepatitis A infection

|                         | Positive HA serology | Negative HA serology | Significance |
|-------------------------|----------------------|----------------------|--------------|
| Sex                     |                      |                      |              |
| Women                   | 26 (40%)             | 5 (50%)              | .5499        |
| Men                     | 39 (60%)             | 5 (50%)              |              |
| HBcAb                   |                      |                      |              |
| Positive                | 40 (61.6%)           | 3 (30%)              |              |
| Negative                | 19 (29.2%)           | 6 (60%)              | .1374        |
| Unknown                 | 6 (9.2%)             | 1 (10%)              |              |
| Hepatitis B vaccination |                      |                      |              |
| Yes                     | 2 (3.1%)             | 0                    |              |
| No                      | 1 (1.5%)             | 1 (10%)              | .2643        |
| Unknown                 | 62 (95.4%)           | 9 (90%)              |              |
| HIV                     |                      |                      |              |
| Positive                | 13 (20%)             | 2 (20%)              |              |
| Negative                | 22 (33.8%)           | 4 (40%)              | .9199        |
| Unknown                 | 30 (46.2%)           | 4 (40%)              |              |
| IVDU                    |                      |                      |              |
| Current history         | 11 (16.9%)           | 2 (20%)              |              |
| Past history            | 13 (20%)             | 2 (20%)              | .9702        |
| No                      | 41 (63.1%)           | 6 (60%)              |              |
| Chronic liver disease   |                      |                      |              |
| Yes                     | 65 (100%)            | 10 (100%)            |              |
| No                      | 0                    | 0                    |              |
| Unknown                 | 0                    |                      |              |

HBcAb indicates antibody to hepatitis B core antigen; HIV, human immunodeficiency virus; IVDU, intravenous drug use.

Serological tests for HA were positive in 86.7% (95% CI, 79.0%-94.4%) and negative in 13.3% (95% CI, 6.0%-21.0%). Mean age in the former group was 50.17 years (SD, 17.8 years), and mean age in the latter was 36.6 years (SD, 15.0 years;  $P=.02$ ). The prevalence of seropositivity among patients younger than 40 years was 75.7% (95% CI, 61.9%-89.5%), vs. 97.5% (95% CI, 92.3%-100%) in older patients ( $P=.006$ ). Table 2 summarizes the characteristics in patients who were positive and negative for HAV; no statistically significant differences were found.

## Discussion

La prevalencia de inmunización frente al VHA en pacientes infectados por el VHC es de un 86,5% en la muestra. The prevalence of immunization against HAV in patients with HCV infection was 86.5% in the sample of persons we studied. This figure is similar to that reported in 1998

Discussion  
Key points



### What is known about the subject

- The change in the epidemiological pattern of hepatitis A (HA) in recent years has led to a reduction in the incidence of HA among younger persons, and an increase in the number of older individuals susceptible to the infection.
- Hepatitis A courses with more, and more severe, symptoms in adults.
- Patients with chronic liver disease, especially those caused by hepatitis C virus (HCV) infection, superinfection or coinfection with hepatitis A virus (HAV) are at greater risk for fulminating hepatitis and death.
- Chronic liver disease is an indication for HA vaccination.

### What this study contributes

- We report data on the seroprevalence of HAV infection in patients with HCV infection.
- In patients younger than 40 years the proportion of seronegative persons is similar to that in the general population. All HCV-positive patients should be considered candidates for vaccination.
- In persons older than 40 years with chronic liver disease, the decision to vaccinate against HAV should be based on serological findings.

by Diago et al for a Valencian population. These authors studied patients hospitalized with chronic liver disease caused by HBV and HCV, who were similar in age to the population we studied. The prevalence of HAV infection in their study ranged from 75% to 90%<sup>1</sup>.

Our sample did not differ in terms of sex, age or seroprevalence of HB in comparison to other studies<sup>1,10</sup>, although the percentage of patients with a history of IVDU was higher in our sample than in the study by Diago et al.<sup>1</sup> Coinfection with HIV could not be compared with earlier studies, as we found none that had investigated this factor. In the present study, most of the patients who declined HAV testing were HIV carriers or had a history of IVDU (62.2% of these patients refused testing), as compared to a refusal rate of 15.4% among all remaining patients. This response may reflect problems in locating the patients, and the tendency of these patients to reject preventive health interventions.

The population we studied contained a high percentage of persons who were positive for HIV infection or who had a current or prior history of IVDU, and the prevalence of HAV infection might be expected to be higher in this group. However, we found no difference in the rate of HAV infection between the patients with these two antecedents and those without them.

Vaccination against HA is indicated for patients with chronic liver disease, and vaccination should be given systematically if the patient is seronegative.<sup>14-19</sup>

In the present study we found a higher proportion of HAV seronegative patients among those younger than 40 years, in whom seroprevalence was similar to that reported for patients aged 30-39 years in the general population (77.3%; 95% CI, 72.9%-81.8%).<sup>4,5</sup> These figures mean that vaccination against HA should be recommended for all HCV-positive patients younger than 40 years, and for patients of any age with chronic liver disease who are seronegative.

Cost-benefit studies will be needed to determine whether serological testing should be done before vaccination in different age groups.

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## COMMENTARY

# Carriers of hepatitis C: should they be vaccinated against hepatitis A?

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Nearly 1.5 million new cases of hepatitis A (HA) are reported annually throughout the world, although the actual figure is estimated to be 3-fold to 4-fold higher. Mortality from HA is low (1.4 per 1000 symptomatic cases), and is due, in most cases, to fulminant disease (60% mortality), which is most frequent in adolescents and adults. In Spain, as noted in the article by Sans et al., the epidemiological pattern of HA has changed; the importance of this change lies in the fact that more symptomatic (hence more severe) forms of the disease are seen much more frequently in adults.<sup>1-4</sup>

An estimated 300 million persons world wide are infected with the hepatitis C virus (HCV); of these, 5 million live in Europe. The number of HCV carriers in Spain is estimated at 800 000, with an estimated prevalence of 2% for the entire population. Infection by HCV is the main cause of chronic liver disease. Between 75% and 80% of all persons infected with HCV develop chronic liver disease, and more than 25% develop liver cirrhosis in the ensuing 30 to 40 years. Moreover, 70% of all hepatocellular carcinomas are linked to HCV.<sup>1-3,5</sup>

Superinfection by other hepatitis viruses (in addition to HA) in patients with chronic hepatitis from HCV infection can lead to significant morbidity and mortality. In some patients with chronic liver disease, superinfection

- Superinfection or coinfection with hepatitis B virus in patients with hepatitis C virus infection increases morbidity and mortality.
- In patients with hepatitis C who are candidates for vaccination, prior testing for hepatitis A and B antibodies is not necessary.
- Patients with hepatitis C should be vaccinated against hepatitis A and B before they develop chronic liver disease.

with hepatitis A or B virus can lead to acute liver failure.<sup>5</sup>

Strong evidence supports the benefits of vaccination against hepatitis A and B virus in patients with chronic liver disease.<sup>6</sup> All patients with chronic liver disease should be studied to determine whether antibodies to hepatitis B core antigen are present. If immunity is not detected, these patients should be vaccinated against hepatitis A and B. It should be noted, however, that in populations with a low incidence and prior exposure, it may be more cost-effective

ve to forego antibody studies and vaccinate all susceptible individuals. In patients with and without of chronic liver disease, the rates of post-vaccination seroconversion are 94% for hepatitis A and close to 100% for hepatitis B.

Some organisms that issue recommendations on vaccination policies insist that vaccination for hepatitis A should be considered only for patients with chronic hepatitis. Moreover, these organisms emphasize that there are no data to indicate the need for routine vaccination for hepatitis A in carriers of hepatitis B or C virus in the absence of chronic liver disease.<sup>5</sup> In Spain, some working groups on vaccination policies include HCV infection as an indication for vaccination against hepatitis A.<sup>1</sup>

However, in view of the data indicating that 75%-80% of all patients with HCV infection will develop chronic liver disease, it would be good preventive strategy to vaccinate them against hepatitis A and B before chronic liver disease ensues. Because it is clear that superinfection with hepatitis A or B virus in patients with HCV infection increases morbidity and mortality, vaccination as soon as

possible for hepatitis A and B are advisable. In our setting, it is more cost-effective to forego prior testing for antibodies and to simply vaccinate all susceptible individuals.

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