Seroprevalence of hepatitis A and cost evaluation of different vaccination strategies against hepatitis A virus in patients with chronic hepatitis C in France

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SUMMARY

Objectives — To prospectively determine the prevalence of total hepatitis virus A antibodies in patients with chronic hepatitis C and to evaluate the direct costs of several vaccination strategies against hepatitis A virus in these patients.

Methods — From April 1 to July the 31 1998, 219 patients with hepatitis C virus antibodies underwent a systematic testing for total hepatitis virus A antibodies (MEIA-AXSYM, Abbott laboratories). The prevalence of hepatitis A virus antibodies was evaluated according to age and suspected way of hepatitis C contamination. This prevalence has been compared to that in individuals undergoing a check-up provided by the national health insurance system stratified by age. Direct costs of 2 vaccination strategies “A” and “B” were evaluated according to age (< 40 vs > 40 years) and number of vaccine doses (1 or 2). “A” strategy included the systematic vaccination of all patients without determining the presence of total hepatitis A antibodies. “B” strategy included testing for total hepatitis A antibodies and vaccination of seronegative patients. The costs of these two strategies (A and B) were calculated with one and two vaccine doses.

Results — The prevalence of total hepatitis A antibodies was 76% in the entire population. It increased after the age of 35 and was statistically higher in patients who were older than 40 than in patients younger than 40. This prevalence was not significantly different from that in individuals who underwent a check-up provided by the national health insurance system stratified according to age. “B” strategy with 2 vaccine doses was less expensive that A strategy in the whole population and in patients younger than 40. This strategy was less expensive with 1 vaccine dose except in patients who had recently screened positive for hepatitis C antibodies younger than 40 when it induced an increased in direct cost due to the low prevalence of total hepatitis A antibodies in these patients.

Conclusions — In patients with hepatitis C antibodies with a high prevalence of total hepatitis A antibodies, testing for the prevalence of these antibodies before vaccination decreases the direct cost of this vaccination.


Improved health conditions have been associated with a reduction in the seroprevalence of total anti-hepatitis A virus (HAV) antibodies in France [1, 2]. In non-vaccinated subjects, presence of anti-HAV antibodies results from naturally acquired immunity. In 1991, seroprevalence was 40% among subjects under 35 years of age attending national health insurance check-up clinics in the Center-West region of France [2]. In North-America, the risk of severe HAV infection in patients with chronic hepatitis C [3, 4] has led health authorities to recommend anti-HAV vaccination in non-immunized people [5, 6]. The seroprevalence of HAV antibodies in patients with hepatitis C is unknown in France and optimal anti-HAV vaccination strategies remain to be determined for hepatitis C virus (HCV) positive subjects. The aims of this prospective study in HCV-positive subjects was to: 1) determine the seroprevalence of total anti-HAV antibodies in comparison with the seroprevalence observed in subjects attending check-up clinics provided by the national health insurance, and 2) evaluate the direct cost of different vaccination strategies in light of this seroprevalence.

Patients and methods

Patients

The study population included 219 patients with HCV infection who attended the hepatology clinic at Creil Hospital (n = 174) or who were screened positive for HCV initially at the hospital’s hematology-immunology laboratory (n = 45) between April 1st and July 31st 1998 and who had total HAV antibody tests. This population included 130 men and 89 women, mean age 47.1 ± 17 years. Two groups were identified: group 1 = patients who screened HCV-positive for the first time (45 patients, mean age 45 ± 19 years (67% men); group 2 = 174 patients followed at Creil Hospital for chronic hepatitis C, mean age 17 ± 16 years (58% men). HCV RNA was detected in 150 (90%) of the subjects in group 2.

Methods

Virology

Anti-HCV antibodies were detected using 3rd generation methods: firstly the MONOLISA anti-HCV test (Sanofi Diagnostics Pasteur) and...
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Screen for total anti-HAV antibodies

**STRATEGY A**
No screen
Systematic vaccination

- All patients
- Patients 18-40 yrs

**STRATEGY B**
Systematic screen
Vaccination if antibody-negative

- ALL patients HAV-
- Patients HAV-18-40 ans

1 or 2 vaccine doses

Fig. 1 – Vaccination strategies A and B.

secondly the HCV 3.0 ELISA test (Ortho Diagnostic System). ELISA-
reproducible positive tests were validated by immunoblot (Deciscon HCV
Sanofi Diagnostics Pasteur), that detects antibodies directed against C,
NS3, and NS4 antigen regions. Immunoblots were considered positive
when two antibody activities were detected, in accordance with the
manufacturer’s criteria. HCV RNA was detected with qualitative PCR
(Amplicor, Roche®) with a detection threshold of 1,000 copies per ml.
Total anti-HAV antibodies were determined using the MEIA AXSYM
(Abbot) technique.

**SEROPREVALENCE OF TOTAL ANTI-HAV ANTIBODIES**

Seroprevalence of HAV infection was determined first in the overall
study population then by group. Seroprevalence of total anti-HAV
antibodies was studied by age: 18-40 years versus > 40 years. In
the patients in group 2, who attended hepatology consultations, seropreva-
ience of anti-HAV antibodies was classified by presumed route of HCV
contamination: intravenous drug use versus transfusion. The control
population for comparing HAV prevalence in HCV-positive patients was
taken from a prospective survey of subject attending check-up clinics
provided by the national health insurance system [2]. This survey provides
HAV seroprevalence data, independently of HCV serology, for the
general French population which is similar to the population residing in
the urban community around our center in Creil.

**PROSPECTIVE EVALUATION OF VACCINATION COST**

The direct cost of different vaccination strategies (figure 1) were
determined in groups 1 and 2. Two strategies, A and B, were evaluated.
Strategy A consisted of vaccination of all HCV-positive patients irrespec-
tive of prior HAV immunization. The cost of strategy A was evaluated for
all patients in the study population and for groups 1 and 2, as well as in
the subset of patients aged under 40 years. Cost was calculated using a
1-dose and a 2-dose vaccination scheme. Strategy B consisted of first
determining HAV serology status then vaccinating HAV-negative sub-
cost. Cost of this strategy was calculated in the same way as for strategy
A, again with 1-dose and 2-dose schemes. The number of persons to
vaccination was taken as “n”, i.e. the total number of persons in the study
population for strategy A and N × (1-P) for strategy B, where P is the
number of HAV-positive patients. The cost of determining anti-HAV total
antibody status (D) (which is reimbursed by the national health insurance)
was 19.2 euros (€) at the time of the study. The cost of a single dose of
Havrix® (V) adult 1440 (not reimbursed by the national health insurance)
was 44.2 €. The direct cost of strategy A was N × V and the direct cost of
strategy B was N × D + N × (1-P) × V. In order for strategy B to be cost
effective, the seroprevalence (P = prevalence of HAV-positive patients) of
HAV infection would have to be at least P = D/V, all items costs being
equivalent. This calculation was performed before determining the
seroprevalence in our study population and led to the conclusion that
seroprevalence of total anti-HAV antibodies would have to be at least
43% for strategy B to reach cost effectiveness for a 1-dose scheme
(maximum number of patients to vaccinate = 57%) and at least 22% for a
2-dose scheme (maximum number of patients to vaccinate = 78%). The
model applied used a single dose of vaccine (Havrix® adult 1440) with
one initial injection and a booster six months later for the 2-dose scheme.

**STATISTICS**

Chi-square test or Fisher exact test as appropriate were used for
qualitative variables and Student’s t test or Mann-Whitney test as
appropriate for quantitative variables. Results are expressed as
mean ± SD and in percentage with P < 0.05 considered as significant.

**Results**

**Seroprevalence**

Seroprevalence of total anti-HAV antibodies, reflecting
immunization, was 76% (166 patients) in the study population.
There was no difference in seroprevalence by gender. Seropreva-
ience was higher in patients older than 40 years than in patients
aged 18-40 years (97% versus 96%, P < 10⁻¹⁰). Seroprevalence in
patients in group 2 contaminated by transfusion (n = 64) was
higher than in patients contaminated by intravenous drug use
(n = 68) (89% versus 69%, P < 10⁻³), but this difference was no
longer significant after adjustment for age. The seroprevalence of
total anti-HAV antibodies in the entire study population and in
groups 1 and 2 are presented in table I. For a given age range,
seroprevalence of HAV infection was higher in group 1 than in
strategy B was N × V and the direct cost of
strategy A was N × D + N × (1-P) × V. In order for strategy B to be cost
effective, the seroprevalence (P = prevalence of HAV-positive patients) of
HAV infection would have to be at least P = D/V, all items costs being
equivalent. This calculation was performed before determining the
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appropriate for quantitative variables. Results are expressed as
mean ± SD and in percentage with P < 0.05 considered as significant.

Table I. – Prevalence of total hepatitis A antibodies in patients with
hepatitis C antibodies.

<table>
<thead>
<tr>
<th>All</th>
<th>18-40 yrs</th>
<th>&gt; 40 yrs</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n = 219)</td>
<td>76 %</td>
<td>50 %</td>
<td>95 %</td>
</tr>
<tr>
<td>Group 1 (n = 43)</td>
<td>60 %</td>
<td>37 %</td>
<td>85 %</td>
</tr>
<tr>
<td>Group 2 (n = 174)</td>
<td>80 %</td>
<td>56 %</td>
<td>97 %</td>
</tr>
</tbody>
</table>

*Difference between patients aged 18-40 years and > 40 years.
Group 1: recently screened HCV+ patients; Group 2: patients attending hepatology
consultations for chronic hepatitis C.

Among group 1 patients recently screened positive for HCV, 18 (40%) would be vaccinated according to strategy B (60% HAV seroreprevalece, table I). The gain in direct cost (for 100 patients) for this population would be 731 and 3387 euros for 1- and 2-dose schemes respectively. Conversely, due to the low HAV seroreprevalece in the 18-40 age range (37), the 2-dose scheme still produces a gain while the 1-dose scheme would lead to an extra cost of 285 euros for 100 patients (table III). In group 2 patients followed for chronic hepatitis C, the HAV antibody seroprevalence was high, 56% and 97% for patients below and above 40 years of age respectively, resulting in cost effectiveness strategy B for all ages and for both dose schemes (table IV). Thus the gain for the 2-dose scheme for 100 patients was 5143 euros for the entire population and 3047 euros for patients under 40 years.

**Discussion**

The results of this study demonstrate that total anti-HAV antibody seroreprevalece in an urban population in France with chronic hepatitis C (mean age 47 years) is 76%. This seroreprevalece is not different from that observed in the general population and study periods were different, respectively, resulting in cost effectiveness strategy B for all ages and for both dose schemes (table IV). Thus the gain for the 2-dose scheme for 100 patients was 5143 euros for the entire population and 3047 euros for patients under 40 years.

**Table II.** – Comparaison of total hepatitis A antibodies in patients with hepatitis C antibodies in patients undergoing a medical check-up provided by the national health insurance system.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Observed (check-up)</th>
<th>Expected (general population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>15-24</td>
<td>8 (50)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>25-34</td>
<td>56 (43)</td>
<td>26 (47)</td>
</tr>
<tr>
<td>35-46</td>
<td>49 (36)</td>
<td>36 (74)</td>
</tr>
<tr>
<td>45-60</td>
<td>45 (42)</td>
<td>42 (91)</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>60 (60)</td>
<td>56 (95)</td>
</tr>
</tbody>
</table>

*HAV: hepatitis A virus.*

**Table III.** – Evaluation of direct costs of virus A vaccination in patients recently screened positive for hepatitis C antibodies (group 1; n = 45).

<table>
<thead>
<tr>
<th>Budget line</th>
<th>All patients</th>
<th>Patients aged 18-40 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>N screening tests</td>
<td>0  45</td>
<td>0  27</td>
</tr>
<tr>
<td>Cost</td>
<td>0  864</td>
<td>0  519</td>
</tr>
<tr>
<td>N vaccinated</td>
<td>45  18</td>
<td>27  17</td>
</tr>
<tr>
<td>1 vaccination</td>
<td>1 989  796</td>
<td>1 194  752</td>
</tr>
<tr>
<td>2 vaccinations</td>
<td>3 979  1 591</td>
<td>2 397  1 503</td>
</tr>
</tbody>
</table>

Gain for 100 patients (strategy B vs A)

| 1 vaccination | 731  285 |
| 2 vaccinations | 3 387  1 352 |

**Table IV.** – Evaluation of direct costs of virus A vaccination in patients followed for chronic hepatitis C (group 2; n = 174).

<table>
<thead>
<tr>
<th>Budget line</th>
<th>All patients</th>
<th>Patients aged 18-40 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>N screening tests</td>
<td>0  174</td>
<td>0  73</td>
</tr>
<tr>
<td>Cost</td>
<td>0  3 342</td>
<td>0  1 402</td>
</tr>
<tr>
<td>N vaccinated</td>
<td>174  35</td>
<td>73  32</td>
</tr>
<tr>
<td>1 vaccination</td>
<td>7 693  1 547</td>
<td>3 277  1 415</td>
</tr>
<tr>
<td>2 vaccinations</td>
<td>15 385  3 095</td>
<td>6 455  2 829</td>
</tr>
</tbody>
</table>

Gain for 100 patients (strategy B vs A)

| 1 vaccination | 1 611  562 |
| 2 vaccinations | 5 143  3 047 |

Increased HAV infection is not higher in HCV-infected subjects than in the general population [7]. The seroprevalence of HAV in our population of HCV-positive patients increased strongly with age, commencing at 45-46 years, as is observed in the general population. It was significantly higher in patients over 40 (95%) than in those under 40. Thus, in our population, 50% under 40 were not immunized against HAV, raising the theoretical risk of acute hepatitis A.

The potential gravity of hepatitis A in patients with chronic hepatitis C remains controversial [3, 4]. This study was designed after the publication by Vento et al. [3] of the high prevalence of fulminant hepatitis A in HCV-positive patients. In that Italian study, 7 out of 17 patients (45%) with acute hepatitis A developed fulminant disease which was fatal in 6 [3]. Four of these patients had a HLA haplotype frequently found in autoimmune hepatitis (A1B8DRI3) suggesting HAV superinfection induced a dysimmunization phenomenon in these patients [8]. The highly debated observations of this prospective study [9-11] were not found in other retrospective studies [11, 12]. Nonetheless, other prospective studies have confirmed the potential gravity of hepatitis A in patients with chronic liver disease [13]. Hepatitis A-related mortality increased from 3.4% to 27.5% in case of chronic liver disease and it was also noted that 60% of patients with chronic liver disease had cirrhosis [13]. In another study conducted in the United States [14], mortality from acute hepatitis A was 1.5% in patients free from chronic liver disease and reached 4.6% in patients with chronic liver disease [14]. These different studies have led United States health authorities to recommend anti-HAV vaccination for patients with chronic liver disease [5]. Apart from over mortality and independently of chronic liver disease, hepatitis A in adults frequently results in severe symptoms and often presents with prolonged cholestasis [13, 14].

Our model does not allow us to draw conclusions concerning the effect of HAV vaccination of non-immunized patients with chronic liver disease. Similarly, French or European health authorities have not provided precise recommendations. In the absence of such recommendations, French experts recently opted for an “intuitive principle of precaution” [17] proposing anti-HAV vaccination for HCV-positive and/or HBV-positive persons [17, 18]. In our opinion, anti-HAV vaccination should be proposed for all non-immunized patients with chronic liver disease caused by the hepatitis B or C virus, irrespective of the severity. There exists a cost problem however since HAV vaccination is not reimbursed by the national health insurance system. Future discussions with the health authorities should thus focus on this point.

The efficacy and safety of the anti-HAV vaccine ( Havrix®) has been recently demonstrated in patients with chronic hepatitis C [19]. However, while 93% of the healthy subjects exhibited a
seroconversion with total anti-HAV antibodies after a single dose, this percentage was only 73.7% in patients with chronic hepatitis C. A 9.4% immunization rate is however obtained after complete vaccination, emphasizing the usefulness of two doses for these subjects [19]. In addition, the geometric antibody titer was lower in patients with chronic liver disease perhaps an expression of less effective protection. The duration of immunization after anti-HAV vaccination is approximately 20 years [in patients other than chronic liver disease] [18]. No data is available for patients with chronic liver disease [20]. Prospective studies are required to determine whether the level of immunization provided by anti-HAV vaccination is the same in patients with chronic liver disease as in healthy subjects.

We evaluated direct cost of different vaccination strategies by age group and number of vaccine doses (one or two). Of patients with a mean age of 47 years attending a general hospital located in an essentially urban community (group 2), seroprevalence of total anti-HAV antibodies was 80% for the overall population and 56% for patients under 40 years. Using equivalent item costs, strategy B (screening for antibodies then vaccinating negative subjects) is more economical for all ages and for both dose schemes. In a population of patients recently screened positive for HCV, our small sample showed that 60% of the population was immunized against HAV. Here using strategy B with a single vaccine dose induces an extra cost. These results should however be balanced against data concerning vaccination in HCV-positive patients which have demonstrated less efficacy of a single dose compared with complete vaccination [19]. Cost simulations for single-dose strategies would thus be less pertinent. The impact of HAV infection epidemiology on cost-effectiveness of anti-HAV vaccination in HCV-positive patients was recently demonstrated by Myers et al. [21]. In Canada, the economical strategy is abstention from vaccination. However the screening-vaccination strategy becomes cost effective when the seroprevalence of anti-HAV antibodies is in the 50-70% range [21]. If, after a few years the seroprevalence of anti-HAV antibodies should fall significantly, the vaccination strategy we propose on the basis of our results could become obsolete. Indeed, in a recent North American study [7] where the study population had a lower HAV seroprevalence than ours, the authors proposed systematic vaccination without prior screening for antibodies in all subjects under 40 years of age and systematic screening before vaccination in Afro-American patients and patients aged over 60 years, where the HAV seroprevalence is high [7].

In conclusion, the results of this study show that the seroprevalence of total anti-HAV antibodies in HCV-positive patients is about 76% and is comparable with the seroprevalence observed in the age-stratified general population. The cost-effective vaccination strategy in this population with a high anti-HAV seroprevalence would be screening first for the presence of total anti-HAV antibodies followed by complete vaccination in seronegative subjects. An evaluation of the overall costs of this vaccination is currently under way in a larger population.

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Références


