

RESEARCH PAPER

## Serological survey of hepatitis B immunity in healthcare workers in Catalonia (Spain)

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### ABSTRACT

Healthcare workers (HCW) are exposed to preventable infectious diseases, notably hepatitis B (HB). The aim of this study was to determine the immunity of HCW against hepatitis B. We made a seroprevalence study using a self-administered survey and obtained blood samples. Antibodies against the HB surface antigen (anti-HBs) and against the HB core antigen (anti-HBc) were studied. The odds ratio (OR) and 95% confidence intervals (CI) were calculated. The adjusted OR were calculated using logistic regression.

Of the 644 HCW who participated (29.7% physicians, 38.7% nurses, 13.4% other clinical workers and 18.3% non-clinical workers), 46.4% were primary care workers and 53.6% hospital workers. The overall prevalence of anti-HBs was 64.4%. HCW aged <25 y had a significantly higher prevalence (86.7%) than those aged 35–44 y (adjusted OR 3.40; 95% CI 1.06–10.90). The prevalence of anti-HBc was 4.1%, and increased with age. Significant differences were found for HCW aged >44 y with respect to those aged 25–34 y. 75.6% of HCW stated they were vaccinated, but only 39.3% had a vaccination card. In HCW who stated they were unvaccinated, 10.8% had a vaccinated serological pattern (anti-HBc-negative and anti-HBs -positive). Written, updated vaccination records are essential to reliably determine the vaccination status.

### KEYWORDS

hepatitis B; healthcare workers; nosocomial transmission; seroprevalence; vaccination

### Introduction

Hepatitis B (HB) infection is caused by the HB virus, which is transmitted through percutaneous or mucosal contact with infected blood or other body fluids. The HB virus is very stable in the external environment and may remain viable in contaminated surfaces for at least 7 days<sup>1</sup> or even months under appropriate conditions.<sup>2</sup> Of the blood-borne viruses, including hepatitis C virus and human immunodeficiency virus, HB is the most efficiently transmitted after percutaneous exposure. The risk of unvaccinated health workers acquiring HB infection in a percutaneous accident depends on the infectiousness of the person the blood or bodily fluid comes from. Studies in healthcare workers with percutaneous exposure to blood contaminated by HB virus suggest the risk of transmission is <30% if the source patient is HB surface antigen (HBsAg) and HB e antigen (HBeAg) positive, and < 6% if HBeAg is negative.<sup>3</sup>

Healthcare workers (HCW) are one of the main groups at risk of HB infection. The risk is particularly high in HCW with greater exposure to accidental inoculation at work and is related to the duration of professional activity (although it is higher during training), the characteristics of the healthcare center and the type of population served.<sup>2,4</sup> Infected HCW are also a potential source of infection of the patients they care for. Hepatitis B vaccination is the

best tool for the primary prevention of HB infection. For these reasons, HCW were one of the first risk groups in whom vaccination was recommended.<sup>5</sup>

HB vaccination of HCW began in Catalonia with the appearance of the first vaccines in the 1980s, with good acceptance, especially of recombinant vaccines.<sup>6</sup> In 1992, HB vaccination was incorporated into the immunization schedule of Catalonia at 12 y of age, and high vaccination coverages were obtained.<sup>7</sup> Therefore, most people born after 1980 in Catalonia are vaccinated, including HCW. Although most HCW in Catalonia have had the opportunity to be vaccinated, either in the workplace or through routine vaccination, a percentage of HCW may be susceptible to HB because they have not been vaccinated or do not respond to vaccination.

The aim of this study was to determine the history of HB vaccination or infection and the state of susceptibility or protection against HB infection in HCW in Catalonia in order to implement appropriate strategies for the detection of susceptible HCW and minimize their risk of contracting hepatitis B and infecting the susceptible patients they care for.

### Results

Five of the 10 primary healthcare occupational risk prevention services (ORPS) of Catalonia and 6 of the 9 hospital ORPS

invited to participate in the study accepted. The participating centers were located in 5 of the 7 Catalan health regions, representing 87.6% of the population.

A total of 644 HCW participated in the study, of whom 151 (23.4%) were male and 493 (76.6%) female. The median age was 42 y (range 22–67). The distribution according to professional category was: nurses (249; 38.7%), physicians (191; 29.7%) other clinical workers (86; 13.4%) and non-clinical workers (118; 18.3%). According to type of center, 345 workers (53.6%) came from hospitals and 299 (46.4%) from primary healthcare centers. Less than 5% of HCW in participating ORPS refused to take part in the study.

The overall prevalence of protective HB surface antigen antibodies (anti-HBs) was 64.4%, (95% CI 60.6–68.1), and was higher in HCW born after 1985 and lower in HCW born in 1975 and before. The prevalence of anti-HBs was higher in women, nurses and physicians and in hospital workers. In the multivariate analyses, significant differences were found for HCW aged <25 y (born after 1985) with respect to those aged 35–44 y (born between 1964 and 1975), in physicians, nurses and clinical workers versus non-clinical workers, and in hospital workers vs. primary care workers (Table 1).

Anti-core antibodies (anti-HBc) were determined in 633 HCW (in 18 subjects no sample was available), of whom 26 (4.1%) were positive. The prevalence of anti-HBc increased with age. In the multivariate analyses, significant differences were found for HCW aged >44 y (born before 1964) with respect to those aged 25–34 y (born between 1985 and 1975). No significant differences between the prevalence of anti-HBc were found according to sex, type of occupation or type of center (Table 2).

Of the 633 HCW with anti-HBc and anti-HBs analyzed, 385 (60.8%) had a serological pattern corresponding to vaccination (anti-HBc negative and anti-HBs positive). The prevalence of HCW with markers compatible with vaccination showed a downward trend with increasing age. Differences were also observed with respect to sex (lower prevalence in men), professional status (lower prevalence in non-clinical workers) and type of center (lower prevalence in primary healthcare centers). In the multivariate analyses, significant differences were found for HCW aged < 35 y (born after 1985) with respect to those

aged > 54 y (born between 1964 and 1975), in women with respect to men, in physicians, nurses and clinical workers with respect to non-clinical workers, and in hospital workers vs. primary care workers (Table 3).

Of the participants, 487 stated they were vaccinated, 112 that they were unvaccinated, and 45 were unaware of their vaccination status: 415 had a vaccination card, which confirmed HB vaccination in 253. In HCW who stated they were vaccinated, the prevalence of anti-HBs was 76.2% (95% CI 72.1–79.9) and was 74.3% (95% CI 68.4–79.6) in those for whom the vaccination card was available. The difference between HCW who stated they were vaccinated and those who stated they were not was statistically significant ( $p < 0.001$ ). In HCW who stated they were not vaccinated, the prevalence of anti-HBs was 23.2% (95% CI 15.8–32.1), and in HCW who stated they were not vaccinated and were anti-HBc negative, the prevalence of anti-HBs was 10.8% (95% CI 5.7–18.1).

## Discussion

The most important result of this study is that the proportion of HCW showing a serological history of HB infection (anti-HBc-positive) is low, especially in younger HCW, without differences according to type of professional activity. This contrasts with the results of a 1993 study of Barcelona HCW, which found a prevalence of markers for HB infection of 16.07%,<sup>8</sup> similar to the 15.6% (95% CI 13.9–17.3) in the general population found in a 1989 seroprevalence study.<sup>9</sup> This is probably due to the implementation of preventive measures in the health care setting (standard precautions practices against bloodborne pathogens and vaccination) and to the success of HB vaccination programs performed in Catalonia, both those specifically aimed at HCW and at routine vaccination. This is similar to the results observed in the USA, where the decrease in acute HB infection among HCW probably resulted from routine pre-exposure to HB vaccination and reduced the risk of exposure through improvements in infection-control practices.<sup>10</sup>

Nearly two-thirds (64.4%) of the HCW in our study had protective anti-HBs titres (anti-HBs  $\geq 10$  mIU/mL) and most of these were anti-HBc negative, indicating that protection was

**Table 1.** Prevalence of antibodies against the hepatitis B surface antigen (anti-HBs).

Variable	n	Prevalence (95% CI)	OR (95% CI)	p	aOR (95% CI)	p
Age (in years)						
<25	30	86.7 (69.3–96.2)	4.25 (1.42–12.73)	0.010	3.40 (1.06–10.90)	0.040
25–34	186	68.8 (61.6–75.4)	1.44 (0.93–2.24)	0.102	1.41 (0.87–2.27)	0.162
35–44	167	60.5 (52.6–67.9)	Reference		Reference	
45–54	170	61.2 (53.4–68.5)	1.03 (0.67–1.60)	0.896	0.94 (0.58–1.51)	0.790
$\geq 55$	91	61.5 (50.8–71.6)	1.05 (0.62–1.77)	0.868	0.89 (0.51–1.57)	0.692
Sex						
Male	151	57.6 (49.3–65.6)	Reference		Reference	
Female	493	66.5 (62.2–70.7)	1.46 (1.01–2.12)	0.046	1.52 (0.99–2.33)	0.054
Professional category						
Physicians	191	69.1 (62–75.6)	3.90 (2.40–6.34)	<0.001	4.15 (2.49–6.90)	<0.001
Nurses	249	77.1 (71.4–82.2)	5.88 (3.65–9.47)	<0.001	5.84 (3.56–9.58)	<0.001
Other clinical workers	86	55.8 (44.7–66.5)	2.20 (1.25–3.89)	0.006	1.95 (1.08–3.52)	0.027
Non-clinical workers	118	36.4 (27.8–45.8)	Reference		Reference	
Type of centre						
Primary healthcare	299	56.2 (50.4–61.9)	Reference		Reference	
Hospital	345	71.6 (66.5–76.3)	1.97 (1.42–2.73)	<0.001	1.83 (1.28–2.62)	0.001
All	644	64.4 (60.6–68.1)				

**Table 2.** Prevalence of antibodies against the hepatitis B core antigen (anti-HBc).

Variable	n	Prevalence (95% CI)	OR (95% CI)	p	aOR (95% CI)	p
Age (in years)						
<25	30	0 (0–11.6)	0	0.998	0	0.998
25 – 34	183	0.5 (0–3.0)	Reference		Reference	
35 – 44	161	3.7 (1.4–7.9)	7.05 (0.84–59.16)	0.072	7.19 (0.85–61.16)	0.071
45 – 54	168	4.8 (2.1–9.2)	9.10 (1.13–73.55)	0.038	8.58 (1.04–70.99)	0.046
≥55	91	12.1 (6.2–20.6)	25.03 (3.18–197.12)	0.002	23.24 (2.9–186.36)	0.003
Sex						
Male	148	5.4 (2.4–10.4)	1.48 (0.63–3.48)	0.366	2.03 (0.75–5.47)	0.161
Female	485	3.7 (2.2–5.8)	Reference		Reference	
Professional category						
Physicians	186	3.2 (1.2–6.9)	Reference		Reference	
Nurses	248	4.8 (2.5–8.3)	1.53 (0.56–4.14)	0.407	1.81 (0.59–5.56)	0.298
Other clinical workers	85	3.5 (0.7–10)	1.10 (0.27–4.50)	0.897	1.71 (0.39–7.47)	0.475
Non-clinical workers	114	4.4 (1.4–9.9)	1.38 (0.41–4.62)	0.605	1.69 (0.47–6.00)	0.421
Type of centre						
Primary healthcare	299	5.7 (3.3–8.9)	2.18 (0.96–4.96)	0.064	1.73 (0.73–4.09)	0.212
Hospital	334	2.7 (1.2–5.1)	Reference		Reference	
All	633	4.1 (2.7–6.0)				

due to vaccination. In any case, an anti-HBs level <10 mIU/mL is equivalent to not being vaccinated, as some vaccinated subjects will not respond to vaccination and, in responders, anti-HBs titres diminish over time, becoming negative in many cases.<sup>11,12</sup>

The highest proportion of HCW with serological markers of vaccination was found in younger subjects (86.7%). This may be explained by the fact that they belonged to cohorts receiving routine vaccination in childhood, where there is a better response to vaccination anti-HBs. In a study in dental students from the University of Granada with a mean age of 20 y who had been vaccinated at 10–12 y of age, over 70% had anti-HBs levels ≥ 10 mIU/mL.<sup>13</sup>

The percentage of HCW with serological markers of vaccination differed according to sex (higher in women), and job characteristics (higher in hospital workers and lower in those with non-clinical jobs). The greater protection in hospital workers may be due to the fact that these workers are continuously engaged in activities aimed at determining the HB immune status and the promotion of vaccination. By contrast, the lower level of immunity in non-clinical workers may be explained by a low

level of coverage as they are not considered priority targets for vaccination due to the low risk activities they carry out.

More than 3-quarters of the study participants stated they had received HB vaccination but this was recorded in the vaccination card in only 39.3%. Although the proportion of anti-HBs-positive subjects was much higher and statistically significant in HCW who stated being vaccinated compared with those who stated they were not, 10.8% of the latter group had serological markers of vaccination, emphasizing the need for written information and updated immunization records that reliably record the vaccination status.

HB vaccination coverage in HCWs is not uniform in all countries: according to a WHO estimate, coverages in 2005 ranged from 18% in Africa to 77% in Australia and New Zealand.<sup>14</sup> The 2011 National Health Interview survey (NHIS) found a coverage of 63.8% in the USA HCW (10), and a 2004 study found a coverage of 85% in Belgium.<sup>15</sup>

The prevalence of serological markers of infection (anti-HBc positive) is not uniform in all countries, reflecting the prevalence of infection in the general population.<sup>2</sup> In highly endemic countries, the percentage of HCW who have markers of immunity

**Table 3.** Prevalence of HCW with serological markers of vaccination (anti-HBc negative and anti-HBs positive).

Variable	n	Prevalence (95% CI)	OR (95% CI)	p	aOR (95% CI)	p
Age (in years)						
<25	30	86.7 (69.3–96.2)	5.82 (1.88–18.03)	0.002	5.67 (1.67–19.21)	0.005
25 – 34	183	67.8 (60.5–74.5)	1.88 (1.12–3.15)	0.016	2.25 (1.27–3.97)	0.005
35 – 44	161	56.5 (48.5–64.3)	1.17 (0.70–1.95)	0.563	1.37 (0.78–2.40)	0.272
45 – 54	168	57.1 (49.3–64.7)	1.19 (0.72–1.99)	0.497	1.34 (0.77–2.31)	0.300
≥55	91	52.7 (42.0–63.3)				
Sex						
Male	148	53.4 (45.0–61.6)				
Female	485	63.1 (58.6–67.4)	1.49 (1.03–2.17)	0.035	1.60 (1.04–2.47)	0.033
Professional category						
Physicians	186	66.1 (58.8–72.9)	4.41 (2.67–7.27)	<0.001	4.87 (2.86–8.28)	<0.001
Nurses	248	73.4 (67.4–78.8)	6.22 (3.82–10.14)	<0.001	6.39 (3.83–10.64)	<0.001
Other clinical workers	85	52.9 (41.8–63.9)	2.54 (1.42–4.55)	0.002	2.17 (1.17–4.00)	0.014
Non-clinical workers	114	30.7 (22.4–40.0)				
Type of centre						
Primary healthcare	299	51.2 (45.4–57.0)				
Hospital	334	69.5 (64.2–74.4)	2.17 (1.57–3)	<0.001	1.96 (1.37–2.81)	<0.001
All	633	60.8 (56.9–64.6)				

acquired due to HB infection is high: 36.5% in a hospital in Tanzania,<sup>16</sup> 41% in Kenya,<sup>17</sup> 48.8% in Laos (Lao PDR),<sup>18</sup> 73.4% in hospital HCW and 91% in rural Cameroon HCW.<sup>19-20</sup>

Paradoxically, a study performed in a Polish university hospital found that 15.7% of HCW had anti-HBc, almost 3-fold higher than the rate observed in young Polish military recruits: the authors attributed these results to infections acquired before hepatitis B vaccination.<sup>21</sup>

Our results show a very low level of HB infection in HCW in Catalonia and a high vaccination coverage, especially in younger people. The current situation is probably due to the introduction of the vaccination of HCW as a risk group and the adoption of standard precautions for infection control since the 1980s. However, the reduction in the risk of infection in the healthcare setting was probably decisively influenced by the changes in HB epidemiology caused by the inclusion of the HB vaccine in the routine immunization schedule in the early 1990s, as occurred in the USA.<sup>1,7,9,22</sup>

One limitation of this study is that, as a convenience sample was used, the results may not be generalizable to all Catalan HCW. Likewise, the serological study was made in HCW who voluntarily attended ORPS health examinations. Therefore, the prevalence of anti-HBs and anti-HBc in the study subjects may differ from that of HCW who did not attend these examinations. However, the large sample size, including hospital and primary healthcare workers from 5 of the 7 Catalan health regions, and the fact that less than 5% of HCW invited to participate refused, suggest that our results may reflect the true situation in many Catalan healthcare centers.

In conclusion, although HB infections have declined substantially since the introduction of HB vaccination, the risk of exposure to HB persists in the healthcare setting. Therefore, there is a need to improve vaccination programs in HCW, in order to protect them from infected persons and vice versa. Since not all vaccinated subjects respond to vaccination, the serological response should be checked one to 2 months after vaccination.<sup>2,10,23,24</sup> Non-responders should receive a new round of vaccination and, if there is no response, should be fully informed of the risk of infection. Some guidelines recommend annual monitoring of non-responding HCW to detect possible infection.<sup>22</sup> It is essential to have easily-accessible records of the immune status of HCW against HB and other vaccine-preventable diseases.<sup>25</sup> In the case of accidental exposure, it may be necessary to have information on the previous immune status, as many vaccinated subjects who responded to the vaccine may have negative anti-HBs at the time of the accident, and this affects post-exposure prophylaxis. Accessing information systems on the immune status of HCW might decrease unnecessary passive post-exposure prophylaxis with hepatitis B immune globulin (HBIG) and revaccination among responder HCW, and also reduce the cost and inconvenience of repeat anti-HBs testing.<sup>10</sup>

## Material and methods

The study was performed using a convenience sample. ORPS from 10 primary healthcare areas and 9 of the leading tertiary hospitals in Catalonia were asked to recruit patients. HCW

were defined as all persons, paid and unpaid, working in health-care settings potentially exposed to patients and/or infectious materials. HCW included physicians, nurses, other clinical workers (nursing assistants, therapists, technicians, emergency medical service personnel, pharmacists, laboratory personnel, students and trainees) and non-clinical workers (clerical, house-keeping, laundry, security, maintenance, administrative staff and billing). HCW attending voluntary periodic health examinations between June 2008 and December 2010 were informed of the study and were recruited after written informed consent was obtained. The study was approved by the Ethics Committee of the University of Barcelona. Blood samples were obtained and demographic and epidemiological variables were collected using a questionnaire (age, sex, type of HCW, type of center, history of having had hepatitis B disease and vaccination history) and completed by ORPS physicians and nurses. If available, the vaccination card was also reviewed.

To determine HB immunity, antibodies against the HB surface antigen (anti-HBs) and antibodies against the HB core antigen (anti-HBc) were studied. Anti-HBs were determined using the ADVIA Centaur anti-HBs2 Assay (Siemens Healthcare Diagnostics Inc. Tarrytown, New York 10591-5097 USA). According to the manufacturer, the sensitivity and specificity of the method are 100% and 99.4%, respectively. Values  $\geq 10$  mIU/mL were considered protective. Anti-HBc were determined using the ADVIA Centaur HBc Total Assay (Siemens Healthcare Diagnostics Inc. Tarrytown, New York 10591-5097 USA). According to the manufacturer, the sensitivity and specificity of the method are 99.8% and 98.9%, respectively. Index values  $\geq 0.5$  were considered positive.

The prevalence of anti-HBs and anti-HBc and the 95% confidence intervals (CI) were calculated using the exact binomial method. The relationship between the dependent variables (anti-HBs and anti-HBc) and the independent variables (age, sex, professional category and type of center) was assessed using the odds ratios (OR) and 95% CI. Odds ratios were adjusted using logistic regression. Statistical significance was established assuming an  $\alpha$  error of 0.05.

Data processing and analysis were performed using the SPSS v19.0 for Windows and R 2.13.0 (R Development Core Team 2011) programs.

## Abbreviations

anti-HBc	antibody to hepatitis B core antigen
anti-HBe	antibody to hepatitis e antigen
anti-HBs	antibody to hepatitis B surface antigen
aOR	adjusted odds ratio
CI	confidence interval
HB	hepatitis B
HBcAg	hepatitis B core antigen
HBcAg	hepatitis B e antigen
HBIG	hepatitis B immune globulin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCW	health care workers
OR	odds ratio
ORPS	occupational risk prevention service

## Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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