The objective of the study was to investigate the prevalence of immunoglobulin G (IgG) antibodies to hepatitis E virus (HEV) infection in a population sample from Catalonia and to analyze the demographic and clinical variables associated with the presence of these antibodies. A total of 1,280 subjects between 15 and 74 years of age were selected randomly from urban and rural areas. Data for sociodemographic and clinical variables were collected by using a questionnaire. IgG antibodies to HEV were determined by an immunoenzymatic method. The odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated for studied variables. Multiple logistic regression analysis was used to determine which variables were independently associated with the prevalence of HEV infection. Anti-HEV antibodies were detected in 96 (7.3%) of the 1,280 samples analyzed. The prevalence of antibodies was greater among males (7.8%) than among women (7%) and increased with age for both sexes, from 3% among subjects 15 to 24 years of age to 12% among subjects ≥65 years of age. Bivariate analysis of the sociodemographic and clinical variables showed an association between the prevalence of hepatitis E virus infection and minor surgery (OR, 1.96; 95% CI, 1.24 to 3.11), abdominal surgery (OR, 1.74; 95% CI, 1.12 to 2.73), and, for women, being uniparous or multiparous (OR, 2.84; 95% CI, 1.19 to 6.79). The multivariate analysis showed an association with minor surgery only (OR, 1.68; 95% CI, 1.03 to 2.70). In conclusion, anti-HEV antibodies were detected in 7.3% of the Catalan population. The seroprevalence of anti-HEV antibodies increased with age and was associated with previous minor surgery.

Hepatitis E virus (HEV) infection is a major cause of epidemic and acute sporadic hepatitis in many nonindustrialized countries, such as Mexico, India, and some parts of Asia and Africa, which are considered areas of endemicity (2, 3, 11, 18). Sporadic cases, among migrant laborers and travelers returning from areas of endemicity, have been observed in developed countries (13).

HEV is an enterically transmitted RNA virus that principally affects young adults and, in countries where the disease is endemic, is associated with more than 50% of the cases of sporadic acute hepatitis. The disease is self-limiting but sometimes has severe complications and a high case fatality rate, particularly among pregnant women (about 20%) (11, 18, 24). Traditionally, North America and Europe have been considered areas of nonendemicity where most HEV infections were thought to be imported, although the seroprevalences in these areas range from 1 to 5% (11, 18).

The availability of diagnostic serologic tests has permitted the epidemiology of the infection to be better known. It is estimated that the prevalence of infection in regions of endemicity ranges between 3 and 26%, and the estimates suppose that this infection accounts for more than 50% of sporadic cases of acute hepatitis. In regions of nonendemicity, prevalences of infection range between 1 and 3% (11, 14, 15, 16, 18, 19, 24, 25, 30).

Infections are more frequent in countries with deficient hygienic conditions and may present as waterborne or foodborne outbreaks (1, 7, 26, 29) or as sporadic cases. The highest disease incidence rates are observed for young and middle-aged adults, and anicteric and subclinical forms are more frequent in children and adolescents (7). In developed countries, most cases are detected in travelers coming from regions where the disease is endemic.

At present, no risk factors associated with sporadic cases have been identified, although person-to-person transmission seems to be infrequent (29).

Although initial evidence suggested that HEV was an enterically transmitted virus with transmission mechanisms similar to those of the hepatitis A virus (HAV), the differences in the prevalences of infection of the two viruses and their differential distributions in specific population groups have led to a search for risk factors associated with HEV infection (1, 10). The fact that other enterically transmitted viruses, such as the hepatitis A virus, can occasionally be transmitted parenterally has led to the suggestion that HEV could also be transmitted by this route. Some studies have shown a prevalence among hemodialyzed patients higher than that among blood donors or the general population (1, 6). However, there are no conclusive studies for this transmission mechanism and it seems that the risk, if it exists, would be low (1, 8, 28).

The objective of this study was to study the prevalence of HEV infection in a representative sample of the adult popu-
loration of Catalonia and to determine the associated demo-
graphic and behavioral factors.

MATERIALS AND METHODS

Sample. The study was carried out in 2002 in Catalonia, a region in the
northeast of Spain with a population of more than six million. A representative
sample of the adult population of Catalonia that was ≥15 years of age was
obtained by a two-stage procedure. In the first stage, 97 municipalities were
randomly selected. In the second stage, participants were selected randomly
from municipal censuses. The number of participants selected in each municipality
was proportional to its classification as urban (≥10,000 inhabitants) or rural
(<10,000 inhabitants).

The sample size calculated for an expected prevalence of 50%, an alpha error
of 5%, and a precision of ±0.025 was 1,536 people. Informed consent was
obtained from all participants.

Serological tests. Blood samples were obtained from all participants by veni-
puncture, and the sera obtained were frozen at −20°C until serologic testing.
Anti-HEV antibodies were determined by an immunoenzymatic method (Bio-
elisa HEV IgG; BIOKIT, Barcelona, Spain) in which immunoglobulin G (IgG)
antibodies to HEV are captured by three recombinant antigens, derivatives of a
Burma strain and a Mexico strain, that correspond to the structural region of
HEV. A goat anti-human IgG combined with a peroxidase that unites with the
antigen-antibody complex was used as the secondary antibody. Anti-HEV antibo-
dies were detected by incubating the complex with an enzymatic substrate and
a chromogen. The intensity of the resulting color is proportional to the amount
of anti-HEV IgG content. A sample was considered positive if the absorbance
was superior to a cutoff value calculated by adding 0.500 to the average absor-
bance of the negative control. A repeatedly positive result indicated the presence
of antibodies in the sample.

Sociodemographic, behavioral, and clinical variables. Data for sociodemog-
ographic and clinical variables were obtained from all participants by use of a
questionnaire. The sociodemographic variables studied were age, sex, place of
birth, place of residence, and occupation. Places of residence were classified as
rural (<10,000 inhabitants) or urban (≥10,000 inhabitants). Socioeconomic lev-
els were determined by occupation and classified into six sociodemographic
groups (I to VI) (23). The questionnaire was also used to obtain information on
risk factors for parenteral and sexual infection.

Statistical analysis. The prevalence of anti-HEV antibodies and their 95%
confidence intervals (95% CIs) for different age and sex groups, the sociodemo-
graphic variables, and the prevalence of risk factors were calculated. The chi-
square test was used to analyze the differences. A P < 0.05 was considered
statistically significant.

The odds ratios (ORs) of the statistically significant variables in the univariate
analysis and their 95% CIs were calculated. Multiple logistic regression analysis
was carried out to adjust the odds ratios and to determine which variables were
independently associated with the prevalence of HEV infection.

The statistical analyses were carried out using the SPSS statistical program
(SPSS Inc., Chicago, Ill.).

RESULTS

The number of people included in the sample was 1,280,
which represented a participation of 83%. IgG antibodies to
HEV were detected in 96 (7.3%) of the patient samples ana-
yzed. The presence of antibodies in males (7.8%) was greater
than that in women (7%). Figure 1 shows the distributions
according to age and sex. Antibody positivities increased with
age, both for women and men, ranging between 1.2 and 5.9%,
respectively, in the 15- to 24-year age group, and 11.1 and
13.2%, respectively, in the ≥65-year age group.

With respect to the sociodemographic behavioral and cli-
cial variables studied, the bivariate analysis showed an associ-
ation between the prevalence of anti-HEV antibodies and a
history of minor surgery, abdominal surgery, and, for women,
being uniparous or multiparous (Table 1). No differences in
the prevalences of anti-HEV antibodies were observed with
respect to place of birth, urban or rural habitat, or risk factors,
such as injecting-drug use or blood transfusions. The only
variable statistically associated with the presence of anti-HEV
antibodies in the multivariate analysis was minor surgery (OR,
1.68; 95% CI, 1.03 to 2.70).

DISCUSSION

This is the first large Spanish study of the prevalence of IgG
antibodies to HEV, which reveal a past infection or exposure
to HEV. The prevalence of anti-HEV antibodies was lower
than 10%, but this is substantially higher than the 1 to 3%
prevalence found in a Spanish study analyzing blood donors,
although that study had a smaller sample size (22).

In patients with acute hepatitis of unknown etiology, the
prevalence of IgM anti-HEV antibodies or HEV RNA, mark-
ers associated with acute hepatitis E, is also very low. In a study
carried out by our group, anti-HEV antibodies were detected
in only 5.6% of cases of non-A, non-B, and non-C acute hep-
atitis and in 4% of cases of acute hepatitis A (5, 16, 30). These
data contrast with the 43% prevalence of HEV detected in
sewage in different years, a prevalence considered high for a
region where HEV infection is nonendemic (30). The discrep-
ancies between the low seroprevalence of HEV in the general
population and cases of acute hepatitis and the high level of
HEV in sewage water may be due to various reasons.

Most of the existing assays for the detection of antibodies to
HEV are enzyme immunoassays which use recombinantly ex-
pressed proteins or synthetic peptides representing antigenic
domains from Orf2 and Orf3, commonly from strains of at
least two geographically distinct HEV strains (4, 12, 17, 20, 21,
27). The HEV strains used in these tests are representative of
those from countries of endemicity and show some differences
with recently identified strains in the amino acid sequence of
some of the major epitopes, such as the region near the car-
boxyl ends of Orf2 and Orf3. This diversity could be producing
a lower level of sensitivity in the serological assays for these
infections. A study by the Hepatitis E Virus Antibody Serum
Panel Evaluation Group (21) concluded that differing results
with blood donor sera indicate that anti-HEV seroprevalence
data in countries of nonendemicity may be unreliable and
should be interpreted with caution.

Another explanation could be the reduction of IgG HEV
antibodies to undetectable levels (17). The humoral response

FIG. 1. Prevalence of antibodies to the hepatitis E virus in the adult
population of Catalonia in 2002.
### TABLE 1. Variables associated with the prevalence of antibodies to the hepatitis E virus in the adult population of Catalonia

| Risk factor parameter                        | Prevalence (%) (95% CI) | No. of people | OR (95% CI), OR a. (95% CI) | p^c |
|----------------------------------------------|-------------------------|---------------|----------------------------|-----|
| Minor surgery                               |                         |               |                            |     |
| Yes                                         | 11.6 (7.7–15.5)         | 259           | 1.96 (1.24–3.11), 1.68 (1.03–2.70) | 0.003 |
| No                                          | 6.3 (4.8–7.8)           | 1,008         |                            | 0.055 |
| Abdominal surgery                           |                         |               |                            |     |
| Yes                                         | 10.4 (7.0–13.8)         | 317           | 1.74 (1.12–2.73), 1.38 (0.86–2.20) | 0.013 |
| No                                          | 6.2 (4.7–7.7)           | 947           |                            | 0.183 |
| Uniparous or multiparous woman              |                         |               |                            |     |
| Yes                                         | 8.3 (5.9–10.7)          | 517           | 2.84 (1.19–6.79), 1.81 (0.76–4.33) | 0.014 |
| No                                          | 3.1 (0.7–5.5)           | 194           |                            | 0.177 |
| Sex                                          |                         |               |                            |     |
| Male                                         | 7.8 (5.6–10.0)          | 567           |                            |     |
| Female                                       | 7.0 (5.1–8.9)           | 713           |                            | NS   |
| Habitat                                      |                         |               |                            |     |
| Urban                                        | 7.5 (5.9–9.1)           | 1,060         |                            |     |
| Rural                                        | 6.4 (3.2–9.6)           | 220           |                            | NS   |
| Social class^c                               |                         |               |                            |     |
| I to III                                     | 6.5 (4.3–8.7)           | 489           |                            | NS   |
| IV to V                                      | 7.0 (5.0–9.0)           | 610           |                            | NS   |
| Place of birth                               |                         |               |                            |     |
| Spain                                        | 7.1 (5.7–8.5)           | 1,220         |                            | NS   |
| Other                                        | 8.3 (0–17.3)            | 36            |                            | NS   |
| Injecting-drug user                         |                         |               |                            |     |
| Yes                                         | 0.0                     | 5             |                            |     |
| No                                          | 7.4 (5.9–8.9)           | 1,233         |                            | NS   |
| Tattoos                                      |                         |               |                            |     |
| Yes                                         | 6.0 (0–12.6)            | 50            |                            | NS   |
| No                                          | 7.4 (5.9–8.9)           | 1,222         |                            | NS   |
| Transfusions                                 |                         |               |                            |     |
| Yes                                         | 7.8 (2.6–13.0)          | 102           |                            | NS   |
| No                                          | 7.2 (5.7–8.7)           | 1,167         |                            | NS   |
| Injections                                   |                         |               |                            |     |
| Yes                                         | 8.2 (5.8–10.6)          | 524           |                            | NS   |
| No                                          | 7.0 (5.1–8.9)           | 697           |                            | NS   |
| Hospitalizations                             |                         |               |                            |     |
| Yes                                         | 8.6 (5.9–11.2)          | 429           |                            | NS   |
| No                                          | 6.8 (5.1–8.5)           | 838           |                            | NS   |
| Accidents causing bleeding wounds           |                         |               |                            |     |
| Yes                                         | 6.0 (4.0–8.0)           | 550           |                            | NS   |
| No                                          | 8.2 (6.2–10.2)          | 720           |                            | NS   |
| Health professional                          |                         |               |                            |     |
| Yes                                         | 4.3 (0–10.1)            | 47            |                            | NS   |
| No                                          | 7.4 (5.9–8.9)           | 1,222         |                            | NS   |
| Endoscopy(ies)                               |                         |               |                            |     |
| Yes                                         | 7.8 (4.1–11.5)          | 205           |                            | NS   |
| No                                          | 7.2 (5.6–8.7)           | 1,068         |                            | NS   |
| Hemodialysis                                 |                         |               |                            |     |
| Yes                                         | 0.0                     | 6             |                            | NS   |
| No                                          | 7.3 (5.9–8.7)           | 1,266         |                            | NS   |
| Administration of gamma globulins            |                         |               |                            |     |
| Yes                                         | 4.6 (1.0–8.2)           | 130           |                            | NS   |
| No                                          | 7.8 (6.2–9.4)           | 1,083         |                            | NS   |

*Continued on facing page*
generated against HEV infection has a variable duration. During the acute HEV infection phase, IgM anti-HEV antibodies appear in the early phase of clinical illness, preceding IgG anti-HEV by a few days, and disappear over a 4- to 5-month period (13). In one study, 100%, 50%, and 40% of sera collected from patients during hepatitis outbreaks 1 to 40 days, 3 to 4 months, and 6 to 12 months after the onset of jaundice, respectively, tested positive for IgM anti-HEV (4). The IgG response appears shortly after the IgM response, and its titer increases throughout the acute phase and into the convalescence phase and remains high from 1 to 4.5 years after the acute phase (9, 13). In one study, anti-HEV was detected in 47% of individuals 14 years after acute HEV infection (17), but the exact duration of persistence of anti-HEV is not known. In a previous study, our group demonstrated that IgG antibodies are reduced in 64% of cases a few years after infection (5). In some cases, this occurs after only 3 to 4 months, which makes the diagnosis of hepatitis E virus infection extremely difficult, particularly if HEV RNA or IgM anti-HEV antibodies are not used (5, 17).

In addition, reports suggest that some people may not produce a detectable antibody response and that the prevalence of anti-HEV in areas where the disease is endemic is much lower than expected, at a rate of 2.8 to 20.2%, with a very high proportion of HAV-seropositive individuals (3, 8). In industrialized countries, anti-HEV antibodies have regularly been found at a rate below 5%, and in Spain, a level of 1 to 3% is reported in blood donors (22). The low prevalence of IgG antibodies to HEV in patients with acute hepatitis during the study period probably indicates that some cases of acute hepatitis E are asymptomatic and that the serological tests currently applied may not have adequate sensitivity for the strains circulating in industrialized countries.

### Table 1—Continued

| Risk factor parameter          | Prevalence (%) (95% CI) | No. of people | OR (95% CI), OR aj, (95% CI) | \( \rho^c \) |
|-------------------------------|------------------------|--------------|-----------------------------|---------|
| Blood diseases                |                        |              |                             |         |
| Yes                           | 2.6 (0.0–5.1)          | 39           |                             | NS      |
| No                            | 7.8 (5.8–9.8)          | 691          |                             |         |
| Surgical interventions        |                        |              |                             |         |
| Yes                           | 7.9 (6.0–9.8)          | 783          |                             | NS      |
| No                            | 6.4 (4.2–8.5)          | 497          |                             |         |
| Dental extractions            |                        |              |                             |         |
| Yes                           | 7.9 (6.2–9.5)          | 1,032        |                             | NS      |
| No                            | 4.6 (1.9–7.2)          | 240          |                             |         |
| Abortions                     |                        |              |                             |         |
| Yes                           | 9.2 (0–18.9)           | 153          |                             | NS      |
| No                            | 6.3 (4.3–8.3)          | 556          |                             |         |
| Acupuncture                   |                        |              |                             |         |
| Yes                           | 7.6 (3.6–11.6)         | 170          |                             | NS      |
| No                            | 7.3 (5.8–8.8)          | 1,103        |                             |         |
| Piercing                      |                        |              |                             |         |
| Yes                           | 4.8 (0–11.3)           | 42           |                             | NS      |
| No                            | 7.5 (6.0–9.0)          | 1,228        |                             |         |
| Multiple sexual partners      |                        |              |                             |         |
| Yes                           | 11.8 (1.0–22.6)        | 34           |                             | NS      |
| No                            | 7.3 (5.8–8.8)          | 1,154        |                             |         |
| Sex-worker client             |                        |              |                             |         |
| Yes                           | 10.0 (0–28.6)          | 10           |                             | NS      |
| No                            | 7.3 (5.8–8.8)          | 1,161        |                             |         |
| Condom use                    |                        |              |                             |         |
| Yes                           | 5.5 (3.2–7.8)          | 382          |                             | NS      |
| No                            | 8.4 (6.5–10.2)         | 862          |                             |         |
| Hepatitis in spouse/partner   |                        |              |                             |         |
| Yes                           | 7.6 (1.2–14.0)         | 66           |                             | NS      |
| No                            | 7.4 (5.9–8.9)          | 1,150        |                             |         |
| HIV infection                 |                        |              |                             |         |
| Yes                           | 6.5 (1.8–11.2)         | 107          |                             | NS      |
| No                            | 4.4 (0.2–8.6)          | 90           |                             |         |

\( ^a \) OR aj., odds ratio adjusted by multiple logistic regression analysis including significant variables in the univariate analysis.

\( ^b \) NS, not significant.

\( ^c \) Social classes include professional (I), managerial and technical (II), skilled (III), partly skilled (IV), and unskilled (V) occupations.
HEV is transmitted by fecal-oral routes in a way similar to that of hepatitis A virus. However, the seroprevalence of anti-HEV antibodies in Spain is much higher (67.8%) than that detected for HEV, and the presence of HAV in sewage samples collected from 1994 to 2001 was 57.4%, suggesting that a similar relationship with HEV would occur.

Finally, our cross-sectional study demonstrated that the only variable associated with a risk of HEV was minor surgery. It is difficult to explain the role of this factor and the lack of a relationship with rural habitat or low levels of education, variables usually found in developing countries associated with HEV infection. Hygienic and health conditions are probably important factors in the reduction of the prevalence of HEV infection, but a prospective study of the risk of infection in people undergoing this type of operation would be necessary to determine their true relevance.

In conclusion, this study found a prevalence of anti-HEV antibodies of 7.3% in the adult Catalan population, which would be necessary to people undergoing this type of operation if HEV infection. Hygienic and health conditions are probably associated with a risk of HEV was minor surgery. It is likely that a similar relationship with HEV would occur.

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