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# Epidemiological and clinical features of HEV infection: a survey in the district of Foggia (Apulia, Southern Italy)

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## SUMMARY

In this study we assessed the seroprevalence of hepatitis E virus (HEV) infection in both the Italian population and immigrants from developing countries in Foggia (Apulia, Southern Italy). The seroprevalence of HEV was determined in 1217 subjects [412 (34%) immigrants and 805 Italian subjects (blood donors, general population, HIV-positive, haemodialysis patients)]. Serum samples were tested for anti-HEV and confirmed by Western blot assay; in positive patients HEV RNA and genotype were also determined. There were 8·8% of patients that were positive to anti-HEV, confirmed by Western blot. The prevalence in immigrants was 19·7%, and in Italians 3·9% (blood donors 1·3%, general population 2·7%, HIV-positive patients 2·0%, haemodialysis patients 9·6%). Anti-HEV IgM was found in 38/107 (35·5%) of the anti-HEV-positive serum samples (34 immigrants, four Italians). This study indicates a higher circulation of HEV in immigrants and Italian haemodialysis patients, whereas a low prevalence of HEV antibodies was seen in the remaining Italian population.

**Key words**: HEV, seroepidemiological survey, Southern Italy, viral hepatitis.

## INTRODUCTION

Hepatitis E virus (HEV) represents the major aetiological agent of enteric non-A hepatitis and it presents four different genotypes (genotypes 1–4): genotypes 1 and 2 are mainly human genotypes, while genotypes 3 and 4 are also animal genotypes. Once believed to be an infection confined to developing countries, HEV is now recognized as a widespread geographically distributed disease. It is associated with large epidemic outbreaks, particularly in Asia, the Middle East and North Africa, where the disease is endemic [1]; HEV IgG antibodies, which are indicative of past infections, have been detected in 5–60% of the general population of these countries [2].

Recently seroprevalence studies in industrialized countries have reported variable rates of anti-HEV antibodies in healthy populations: 2·5% in the USA [3] and 0·4–3% in Western Europe [4, 5], with peaks in the Mediterranean European countries (Italy, Spain, France, Greece) where there is a high level of immigration [6, 7]. Sporadic acute cases of HEV

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hepatitis have also been described in industrialized countries [8, 9]; in a recent Italian long-term prospective study, the prevalence of acute hepatitis E was 20·6% in a cohort of 651 patients with acute viral non-A/non-C hepatitis.

Several of these cases could be traced to travel to developing countries and/or immigration, but others occurred in autochthonous individuals who had not travelled abroad or had at-risk contacts [10].

Higher rates of hepatitis E antibodies were found in drug users in Denmark [11] and Sweden [12]: this may indicate parenteral transmission by needle sharing within this group. Furthermore, HEV was found in sewage samples collected in some Western countries (France, Spain, USA), with evidence of autochthonous HEV infection in these areas [13].

Zoonotic transmission should also be mentioned. People having occupational contact with swine or wild animals in industrialized countries often show a high seroprevalence of anti-HEV antibodies [14–16]. Autochthonous cases of hepatitis E in industrialized countries are generally caused by genotypes 3 and 4 [17, 18], whereas in travellers and immigrants infection is primarily associated with HEV genotypes 1 and 2.

In addition to causing occasional cases of human disease, genotypes 3 and 4 also widely circulate in swine populations; these findings strengthen the view that some cases of autochthonous hepatitis E in developed countries could reflect zoonotic transmission [19].

Furthermore, several studies – unexpectedly – showed a high prevalence of antibodies to HEV in haemodialysis patients [20–22] and blood donors in developed countries [23–25]; the mode of exposure and clinical significance of these infections are not well understood.

In order to better understand the profile of this infection in a developed country with a high number of immigrants arriving from HEV-endemic areas, this observational study aimed to assess the seroprevalence and conduct a clinical survey of HEV infection in both the autochthonous Italian population and in immigrants living in the province of Foggia.

## PATIENTS AND METHODS

This observational study was performed in 2010–2011. HEV seroprevalence was determined in a cohort of 1217 subjects, 412 (34%) were immigrants (mostly from countries in sub-Saharan Africa) who had recently arrived in Italy (<2 months) and 805 were Italians divided into four different groups (151 volunteer blood donors, 450 subjects from the general population, 100 HIV-positive patients, 104 haemodialysis patients) (Table 1).

Blood samples ($n = 412$) were collected from immigrant study cases, 57·8% were male, who were temporarily housed in an open refugee camp managed by the Italian Red Cross, located in Foggia (Apulia, Southern Italy). Two-hundred and eighty-six (69·4%) participants enrolled in the study came from sub-Saharan African countries (54·3% from East Africa, 35·9% from West Africa, 10·8% from Central Africa), 86 (20·8%) from Asia, mainly from the Indian subcontinent, and 40 (9·7%) from Eastern Europe; the subjects were in Italy for a mean period of 54 days (range 19–121 days).

All guests of the camp were orally informed about the purpose of the study and invited to participate. Subsequent recruitment was on a voluntary basis with no special inclusion criteria. The study was reviewed and approved by the local Chief of the Red Cross and written informed consent was obtained from each study subject before enrolment into the study. All study procedures were in agreement with the Declaration of Helsinki (Edinburgh, 2000). At baseline, all study participants were interviewed using a questionnaire to obtain demographic, clinical, and socioeconomic information and to assess their previous exposure to viral hepatitis. All enrolled subjects also received a full clinical examination and were treated accordingly.

Since this was an observational study, for the Italian subjects all the procedures were similar, even though the assent of the local Ethics Committee was not mandatory.

The samples were investigated for the detection of anti-HEV immunoglobulin (IgG/IgM) using a commercially available enzyme immunoassay (EIA) based on recombinant proteins (HEV IgG; Dia.Pro, Diagnostic BioProbes, Italy). If repeatedly positive, results were confirmed by Western-blot (WB) assay (HEV-Recomblot, Nuclear Laser Medicine, Italy). In order to determine HEV RNA, a commercially available assay was used (Qiamp viral RNA mini kit, Qiagen, USA). After RT-nested PCR, genotyping was performed using restriction endonuclease analysis [26].

HBsAg was assayed by a commercially available immunoassay (Abbott-Auszyme Mc, Abbott Laboratories, USA). The presence of antibodies to HCV

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Table 1. *Distribution of subjects screened for group, sex and average age*

| | Females | | Men | | | Age | |
|---|---|---|---|---|---|---|---|
| Groups | *N* | (%) | *N* | (%) | Total | Mean | (S.D.) |
| General population | 272 | (60·4) | 178 | (39·6) | 450 | 40·1 | (18·6) |
| Donors | 43 | (28·5) | 108 | (71·5) | 151 | 37·0 | (10·4) |
| HIV positive | 38 | (38·0) | 62 | (62·0) | 100 | 39·1 | (9·2) |
| Immigrants recently arrived | 174 | (42·2) | 238 | (57·8) | 412 | 28·7 | (6·4) |
| Dialysis patients | 40 | (38·5) | 64 | (61·5) | 104 | 65·1 | (16·2) |

was determined through a third-generation enzyme-linked immunoabsorbent assay (HCV ELISA, Ortho Diagnostic System, USA) and confirmed by a third-generation recombinant immunoblot assay (RIBA, Ortho Diagnostic Systems). Antibodies to HAV IgG/IgM were assayed by a commercially available immunoassay (Dia-Sorin Diagnostics, Italy). Serum alanine aminotransferase (ALT) was quantified by ultraviolet enzymatic assay (normal range 0–40 IU/l).

### Statistical analysis

The $\chi^2$ test was used to compare categorical variables (sex, positivity for anti-HEV IgM, WB test for antibodies to HEV, antibodies to HCV, HBsAg, antibodies to HAV IgG/IgM. When possible, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Continuous variables (age, ALT level) were compared by Student's *t* test for independent samples and ANOVA. Logistic regression models were used to account for the confounding effects of patient demographics. *P* values <0·05 were considered significant. Data were analysed by Stata 10 MP software (StataCorp., USA) for Mac OS X.

## RESULTS

A total of 107/1217 (8·8%) serum samples examined were reactive to anti-HEV IgG and confirmed by WB. The prevalence was 19·7% in immigrants and 3·9% in Italians (blood donors 1·3%, general population 2·7%, HIV-positive patients 2·0%, haemodialysis patients 9·6%). Immigrants had the highest rates of positivity for anti-HEV IgM and WB. A total of 81 (19·7%) of the 412 serum samples of immigrants were reactive to anti-HEV IgG, and confirmed by WB. The prevalence of anti-HEV IgG positivity was 51 (63·0%) cases in immigrants arriving from sub-Saharan Africa, 21 (25·9%) from Asia and nine (11·1%) from Eastern Europe. In comparison to Asian and Easern European population subjects, African immigrants had a significantly greater likelihood of being HEV positive (Asian: OR 7·87, 95% CI 4·41–14·9, $P<0·001$; Eastern Europeans: OR 3·78, 95% CI 1·5–8·9, $P<0·001$). Compared to the general population, blood donors and HIV-positive patients, immigrants and haemodialysis patients had a significantly greater likelihood of being HEV positive (immigrants: OR 7·87, 95% CI 4·41–14·9, $P<0·001$; haemodialysis patients: OR 3·78, 95% CI 1·5–8·9, $P<0·001$) and WB positive (immigrants: OR 8·9, 95% CI 4·7–18·3, $P<0·001$; haemodialysis patients: OR 3·9, 95% CI 1·4–10·1, $P<0·05$). Anti-HEV IgM was found in 38/107 (35·5%) of the anti-HEV IgG-positive serum samples [34 in immigrants and four in Italians (two in haemodialysis patients, one in the general population and one in a HIV-positive patient)]. Regarding the prevalence of anti-HEV IgM, an increased risk was observed only for immigrants (OR 40·4, 95% CI 6·7–1644·7, $P<0·001$) (Table 2).

Anti-HEV IgM was found in 34/81 (41·9%) of the anti-HEV IgG-positive immigrants. The risk of being anti-HEV IgM positive was greater in immigrants from the Horn of Africa (Eritrea 15, Somalia 7, Ethiopia 6) (OR 65·4, 95% CI 7·2–592·7, $P<0·001$) than in subjects from Asia or Eastern Europe (Table 3). HEV RNA determination was positive for all IgM-positive patients; of the immigrants 28 carried genotype 1, two presented mixed genotypes (1 and 2) and four presented genotype 2; of the Italians one haemodialysis patient presented genotype 1, while the other presented genotype 3; the patient screened in the free population presented genotype 1 and the HIV-positive subject presented genotype 3.

There was no correlation between sex and positivity for anti-HEV IgG/IgM and WB test ($P>0·05$). The mean age, both in the general population and immigrant subjects, was significantly higher in subjects who were HEV positive (general population:

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Table 2. *Number of subjects and prevalence (%) of total HEV positive, HEV IgM positive and Western blot positive, for the group*

| | Total HEV positive | | HEV IgM positive | | Western blot positive | |
|---|---|---|---|---|---|---|
| Groups | *N* | Prevalence (%) | *N* | Prevalence (%) | *N* | Prevalence (%) |
| General population | 15 | (3·33) | 1 | (0·22) | 12 | (2·67) |
| Donors | 2 | (1·32) | 0 | (0·00) | 2 | (1·32) |
| HIV positive | 3 | (3·00) | 1 | (1·00) | 2 | (2·00) |
| Immigrants recently arrived | 88 | (21·36) | 34 | (8·25) | 81 | (19·66) |
| Dialysis patients | 12 | (11·54) | 2 | (1·92) | 10 | (9·62) |

Table 3. *Number of immigrant subjects and prevalence (%) of total HEV positive, HEV IgM positive and Western blot positive, by continent of origin*

| | Total HEV positive | | HEV IgM positive | | Western blot positive | |
|---|---|---|---|---|---|---|
| Continent of origin | *N* | Prevalence (%) | *N* | Prevalence (%) | *N* | Prevalence (%) |
| Europe | 10 | (18·9) | 1 | (1·9) | 9 | (17·0) |
| Africa | 71 | (25·0) | 32 | (11·3) | 67 | (23·6) |
| Asia | 7 | (9·3) | 1 | (1·3) | 5 | (6·7) |

49·8 ± 12·1 years; immigrants: 29·7 ± 6·7 years) *vs.* HEV negative (general population: 39·7 ± 18·9 years, $t = 2{\cdot}06$, $P < 0{\cdot}05$; immigrants: 28·4 ± 6·3, $t = 1{\cdot}69$, $P < 0{\cdot}05$). In logistic regression models adjusted for age, sex and group, the risk of being HEV positive was related to age (OR 1·02, 95% CI 1·007–1·04, $P < 0{\cdot}05$) and it was higher in immigrants (OR 11·7, 95% CI 5·9–23·2, $P < 0{\cdot}001$); the >35 years age group was more frequently HEV positive than the other groups (1–18 and 19–35 years). The risk of being anti-HEV IgM positive was greater in immigrants (OR 65·4, 95% CI 7·2–592·7, $P < 0{\cdot}001$); the risk of being WB-positive was related to age (OR 1·02, 95% CI 1·001–1·04, $P < 0{\cdot}05$) and it was greater for immigrants (OR 12·3, 95% CI 5·9–25·5, $P < 0{\cdot}001$).

For the most part, anti-HEV-positive patients were asymptomatic. Only 14 (17·3%) reported moderate asthenia, whereas 11/34 (32·3%) IgM-positive patients presented jaundice, and in 19/34 (55·8%) patients we observed physical signs, e.g. hepatomegaly and distended abdomen.

Evaluating all the patients, about 54% of individuals with positive anti-HEV antibodies (~82% in IgM positive) had higher ALT values than normal; higher ALT levels were found in anti-HEV IgM-positive subjects compared to anti-HEV IgM-negative subjects (208·8 ± 131·1 *vs.* 33·7 ± 14·5, $P < 0{\cdot}001$). ALT levels were high in only 16/38 patients (42·1%) (15 immigrants and in one haemodialysis patient who was anti-HEV IgM-positive). Of the blood donors, subjects who were HEV positive had ALT levels significantly lower compared to HEV negative (22·5 ± 0·7 *vs.* 28·24 ± 4·4, $P < 0{\cdot}05$) subjects; conversely, ALT levels in HEV-positive immigrants were higher than those in HEV-negative immigrants (101·59 ± 118·05 *vs.* 33·72 ± 14·7, $P < 0{\cdot}001$). In immigrants and haemodialysis patients, higher ALT levels were found in anti-HEV IgM-positive subjects compared to anti-HEV IgM-negative subjects (immigrants: 208·8 ± 131·1 *vs.* 33·7 ± 14·5, $P < 0{\cdot}001$; haemodialysis patients: 59 ± 42·4 *vs.* 32·8 ± 13·5, $P < 0{\cdot}05$).

Of the HEV-positive subjects, immigrants had the highest ALT levels (101·59 ± 118·05), followed by HIV-positive patients (84 ± 60). Similarly, immigrants (208·8 ± 131·1) and HIV-positive patients ($n = 148$) had the highest ALT levels when anti-HEV IgM-positive subjects were considered.

WB-positive patients had higher ALT levels compared to WB-negative patients (107·8 ± 121·05 *vs.* 33·6 ± 14·6, $P < 0{\cdot}001$). WB-positive blood donors

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had ALT levels lower than WB-negative donors (22·5 ± 0·7 *vs.* 28·24 ± 4·4, $P < 0·05$); by contrast, WB-positive immigrants had ALT levels higher than WB-negative immigrants (107·8 ± 121·05 *vs.* 33·6 ± 14·6, $P < 0·001$).

Of the WB-positive subjects, HIV-positive patients had the highest ALT level (111·5 ± 51·6), followed by immigrants (107·8 ± 121·05). Of the immigrants, Africans were most frequently positive with HEV, anti-HEV IgM and WB ($P < 0·05$, Table 3). Moreover, Africans had the highest ALT levels in HEV-positive immigrants (108·9 ± 120·7, $P < 0·05$), in those anti-HEV IgM-positive (205·1 ± 131·2, $P > 0·05$), and in WB-positive immigrants (113·5 ± 122·5, $P < 0·05$).

Co-infection with another hepatitis virus was present in 71/81 (87·6%) of anti-HEV-positive patients, a co-infection with HAV was present in 69·1% of cases, in 26·0% of cases there was a co-infection with HBV, and in 7·4% with HCV.

It was not possible to correlate any stage of chronic hepatitis to HEV infection in all patients; only one subject with HIV/HEV infection presented advanced fibrosis.

## DISCUSSION

There is little data on the prevalence of HEV infection and/or prevalence of circulating HEV antibodies in Italy. Previous studies have shown that anti-HEV antibodies are detectable in around 1–3% of the individuals tested in the Northern and Central regions and approximately in 3–6% of those tested in the South or in the main islands [10, 27]. In our survey we studied five cohorts of patients (general population, immigrants, haemodialysis patients, blood donors, HIV-positive subjects); the overall prevalence of circulating HEV antibodies was 8·8% with great deviations in the different groups, ranging from 1·3% in blood donors to 19·7% in immigrants recently arrived in Italy. The prevalence in the general population (2·7%) indicated a low circulation rate of HEV in the province of Foggia; only one of the HEV-positive subjects presented HEV IgM positivity, and only 1/12 reported previous travel in an HEV-endemic area. Thus, this result could reflect only a cohort effect: in the recent past HEV infections might have occurred in Foggia, imported by immigrants (in the 1990s) [28], and become present as sporadic cases owing to faecal contamination of drinking water. Anti-HEV IgG can persist for a long time, and it is possible that some waterborne outbreaks that occurred earlier in the 20th century were hepatitis E and not A. It is noteworthy that in the general population the positivity rate for HEV increases with age, varying from 0·5% in subjects aged <18 years to 6·3% in subjects aged >65 years.

The 1·3% seroprevalence of anti-HEV IgG observed in blood donors in Foggia is lower than in other industrialized countries (Brazil 2·3% [29], France 3·2% [23], Switzerland 4·9% [24]) and is consistent with data of HEV seroprevalence in the USA (1·2%) [30]. A higher rate of HEV infection was present in two other countries: China (32·6%) [25] and Denmark (20·6%) [15]. In China sanitation might have played a prominent role in urban and rural areas. In Denmark, because of the high rate in farmers, the main hypothesis is that HEV infection, in blood donors, is a zoonotic infection transmitted by cattle. Data on work activities were not available for all our donors, but both the anti-HEV-positive subjects were not employed in occupations related to animals. Although HAV and HEV are both transmitted by the faecal–oral route, in this study no association between these two infections was found, thus suggesting different patterns of transmission in these patients. Both the two positive donors did not have a recent history of travel in HEV-endemic countries, but a previous trip in high-prevalence regions and a possible exposure to HEV cannot be excluded.

We observed a high rate of HEV infection (19·7%) in immigrants recently living in the same refugee camp, as already shown in previous studies on immigrants arriving in Italy from developing countries [31]. A higher prevalence was significantly present in Asian and Eastern European subjects [32]. These data were partly in contrast with the results observed in their regions of origin, but it should be borne in mind that in Asian and Eastern European immigrants there is a high proportion of farmers (about 20%), thus the main hypothesis is that HEV infection, in this population, can be a zoonotic infection. On the contrary, in our study, Africans had a significantly greater likelihood of being HEV-positive compared to Asian and Eastern European subjects. For the most part, our patients presented only as anti-HEV IgG positive without other signs or a history of a previous disease; in fact HEV infection most commonly manifests as a self-limiting, acute jaundiced hepatitis, indistinguishable from that caused by other hepatotropic viruses [1].

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The rate of HEV IgM-positive immigrants was about 42% and the higher prevalence of acute hepatitis concerned mainly subjects arriving in Italy during the same period, coming from the same countries (Eritrea, Ethiopia, Somalia) and living in the same areas of the camp. The route of transmission of their infection was not available. Unlike many other enterically transmitted infections, person-to-person transmission of HEV appears to be uncommon [33]. Even if multiple cases may occur in a family or a group, the time interval between cases is usually short, indicating a shared primary waterborne infection rather than person-to-person spread [34]. Nevertheless, in an epidemiological setting characterized by an active circulation of HEV, inter-group transmission (person-to-person), even though inefficient, could have played an important role in the spread of HEV during the period in which this infection peaked [35, 36]. This hypothesis is stimulating and could be strengthened by the findings of our study, because only 4/34 patients with acute HEV hepatitis were not from the Horn of Africa and lived in other areas of the camp, and none of the healthcare personnel presented HEV hepatitis.

Our study shows that chronic HEV co-infection has been reported in only two patients with HIV infection, in one case it was associated with advanced fibrosis and the other case presented with HCV cirrhosis. The prevalence of HIV/HEV chronic co-infection is uncertain, in fact previous studies have shown conflicting results; our data partly concur with those of a similar study from Spain that found no evidence of HEV viraemia in 50 HIV-infected patients [37] and a study from the USA that also found a low rate of prevalence of chronic HEV co-infection in 194 HIV-infected patients [38]. Thus, current evidence could indicate that chronic HEV/HIV co-infection is not a common problem, at least in Western countries. There are two factors that may have influenced the low rate of HEV/HIV co-infection and the degree of hepatic disease in our cohort of patients. First, compared to some regions in developing countries where HEV is endemic, Italy has a modest anti-HEV seroprevalence with a low incidence of circulating HEV in the community, possibly resulting in a reduced risk of chronic co-infection with HIV. Second, most of our patients were receiving antiretroviral therapy and had low HIV viral loads and most had CD4 counts >750 cells/ml. This indicates that, although they were infected with HIV, the immunosuppressive consequences in our cohort of patients were, on the whole, mitigated by effective antiretroviral therapy. Chronic HEV infection occurs as a severe disease in the immunosuppressed, and it appears that the degree of immunosuppression is one of the key factors that determines the failure of HEV clearance. The two previously documented cases of chronic HIV/HEV co-infection have two important similarities. Both patients had a low CD4 count (<200 cells/ml) and both had abnormal liver function tests. In both patients, there was no relationship between any of the sexual risk factors examined, IDU or probable mode of HIV acquisition and anti-HEV seropositivity.

A prevalence of anti-HEV IgG of 9·6% in chronic haemodialysis patients attending a single dialysis unit of our hospital was observed; this rate was considerably higher than in the healthy population (2·7%). Studies concerning HEV epidemiology in chronic haemodialysis patients are few and give conflicting results. Difference of HEV prevalence in the general population, the criteria for inclusion of patients, and the routes of HEV transmission could partially explain the different findings [20–22]. On the basis of the high prevalence of anti-HEV found in haemodialysis patients, it was suggested that in these patients oral–faecal transmission may not be the only route of transmission of HEV and that patients with a high risk for B and C virus infections could also be infected by HEV. In fact, experimental transmission of HEV to humans showed a transient phase of viraemia preceding the onset of clinical symptoms, and prolonged viraemia has been observed in some patients [39]. Therefore, the theoretical possibility of HEV transmission via a parenteral route has been suggested, mainly in endemic areas [1, 18]. A logistic regression analysis showed that neither duration of haemodialysis, nor other variables related with haemodialysis were associated with HEV, while a significant association was found between the presence of anti-HEV IgG and older age (>70 years). The correlation of HEV with age may reflect, also in haemodialysis patients, a cohort phenomenon due to infection acquired decades ago. In our patients, no important association between HEV and HCV was found.

Acute hepatitis in haemodialysis patients is not uncommon and a probable under-diagnosis in many units could be considered. A total of 1·9% (2/104) of the haemodialysis patients were positive for anti-HEV IgM; none of the patients had any clinical event suspected or diagnosed as acute hepatitis at the time of the study. The symptoms usually

associated with acute hepatitis are often less pronounced in these patients (low grade or subclinical hepatitis), this factor might have contributed to the failure to recognize and document any clinical episodes of hepatitis in our patients. The ALT levels in the two anti-HEV IgM-positive patients showed only mild abnormalities, the highest levels being less than twice the upper limit of normal level. Baseline ALT levels are low in patients on dialysis and ALT elevations are usually less pronounced in haemodialysis patients, even in the presence of acute hepatic injury. The peak elevation of ALT in acute HEV indicates that the mean ALT levels were highest within 1–3 days of the onset of illness and declined thereafter; it is possible that in these patients the ALT serum value was estimated later.

In conclusion, the findings of this study show a remarkable circulation of HEV in the district of Foggia, but this high prevalence is related mainly to the immigrant population and haemodialysis patients, with a high percentage of acute hepatitis in a cohort of immigrants. However, this high rate of HEV infection does not seem to represent a possible risk for the local population; in fact a low prevalence of HEV infection both in the general population, blood donors and in HIV-positive patients was observed. Currently, HEV infection is not a major problem in Western European countries, but the increasing number of travellers to HEV-endemic regions, the high number of immigrants arriving in Italy and the new zoonotic aspect of the infection could change this epidemiological situation in the future.

## DECLARATION OF INTEREST

None.

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