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## Hepatitis E in Italy: A silent presence

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### ABSTRACT

Hepatitis E virus (HEV) was discovered in the 1980s and has been considered as being confined to developing countries. The purpose of this critical review was to determine the reported HEV seroprevalence rates in Italy, to identify predisposing factors and individuals at risk and to assess possible importation of HEV by immigrants. A critical review of 159 articles published in PubMed from 1994 to date was done. Only 27 original reports of 50 or more subjects, written in the English or Italian language, were included. Over three decades, the HEV seroprevalence varied from 0.12% to 49%, with the highest rates being reported from the central region of Italy. Risk factors included ingestion of raw pork or potentially contaminated food. The seroprevalence among immigrants ranged from 15.3% to 19.7% in Apulia. Italy has a population of 60 656 000; the total number of individuals surveyed was only 21.882 (0.036%). A national epidemiological survey program is needed to capture more comprehensive seroprevalence data.

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### Introduction

Hepatitis E virus (HEV) is the ubiquitous etiological agent of enteric non-A viral hepatitis and it represents an ongoing internationally challenging issue for public health. Annually, HEV is responsible for 3.3 million new symptomatic infections with fatal outcomes in 56 600 individuals worldwide [1,2]. Three decades after its discovery during an outbreak of unexplained hepatitis in Afghanistan [3], not only is its origin unknown but the modes of transmission remain far from being clearly understood in the industrialized world. HEV is a small hepatotropic single-stranded RNA virus, the sole member of the Hepeviridae family, belonging to the

*Abbreviation:* Assay-1, Dia.Pro; Assay-2, Abbott; Assay-3, Wantai; Assay-4, Adaltis; HEV, Hepatitis E virus.

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Hepevirus genus [4]. The genetic variability of HEV, its host range, as well as its classification, has been in constant evolution [5]. Previous genomic sequence analysis had revealed the existence of four well-defined mammalian genotypes and at least 24 sub-genotypes, with a specific geographic distribution [6]. Indeed, the epidemiology and pathogenicity of HEV observes a bimodal pattern that differs in emerging nations and occidental countries. Genotypes 1 and 2 cause large outbreaks and epidemics mainly among young adults in Africa, Central and Southern Asia, Central America and the Middle East [7–12]. The infection is acquired predominately through a fecal–oral route and it is associated with an unusually high mortality rate during pregnancy [13]. Poor sanitation and contaminated water sources are precipitating factors. An increasing number of sporadic and small locally acquired outbreaks have been reported in Northern America, Australia, Europe, China and Japan [14–19]. Genotypes 3 and 4 are less virulent strains identified as the causative agents of subclinical and clinical infection in the elderly population. HEV is mostly transmitted zoonotically with the ingestion of raw and undercooked food. To date, eight genotypes have been detected and 4 of which are confined to animal species: genotype 5 and 6 in Japanese wild boar (*Scrofa scrofa leucomystax*) [20] and genotype 7 and 8 respectively in dromedary camels (*Camelus dromedaries*) and Bactrian camels (*Camelus bactrianus*) [21].

In Europe, HEV seroprevalence estimates ranged in the general population from 7.5% to 31.9% with the average rate being 19.16%; rates increase with age [22]. However, the real prevalence could be underestimated due to the difference in test sensitivity and the frequently asymptomatic course of the disease. Overall, it is likely that current geopolitical instability and the consequent massive immigration would lead towards the local introduction of new pathogenic variants and modify the known epidemiology in Western countries.

## Methods

The critical review is based on a literature search on PubMed, using the keywords “hepatitis E in Italy” and “hepatitis E seroprevalence in Italy”. Studies published from January 1994 and May 2017 were included according to the following criteria: studies provided clear information regarding the seroprevalence rate at the regional or national level and included at least 50 samples in the cohort (Fig. 1). No age restriction was observed and all studies were written in the English or Italian language. The statistical analyses of the reported regional seroprevalences have been done. We used the screening methods to adjust the prevalence value according to the sensitivity and specificity of the assay. Only estimated seroprevalence rates with a lower positive value for C.I. at 95% have been considered statistically significant.

According to the data available, we focused on fourteen study cohorts: general population, blood donors, pregnant women, the pediatric population, acute hepatitis patients, chronic liver disease patients, hemodialysis patients, immigrants, prisoners, intravenous drug users, HIV co-infected individuals, HIV-exposed and/or infected individuals and workers with contact with potential zoonotic reservoirs (abattoir workers, laboratory workers exposed to biological swine material, animal breeders, veterinarians and farmers) and recipients of renal transplants. Studies that did not meet the above-mentioned criteria, provided duplicate data, personal opinion or international reviews, were excluded from the critical review.

## Results

159 publications were identified by title and abstract through a PubMed search and 27 articles were included in the final data

analysis. Based on data published in these articles, we calculated that a total of 21,882 individuals have been tested for anti-HEV IgG and/or anti-HEV IgM, representing only 0,036% of the current Italian population [23]. The seroprevalence rates ranged from 0,12% to 49% among the study cohort [24,25]. The Abruzzi region was found to be a hyper-endemic region with a seroprevalence rate of 49% among blood donors [25]. A seroprevalence study of 132 blood donor residents in Tuscany has reported rates of 9.1% [26], which is similar to the 9% rate of the same cohort of individuals in the Latium region in 2009 (further data not shown). [25]. A seroprevalence of 9% was also reported in the general population of Abbiategrosso, in Lombardy; the highest assessed among the northern regions of Italy [27]. Conversely, the lowest seroprevalence of 1.3% and 2.7% was reported in Piedmont and Apulia among the open population, respectively in the north and south of Italy [28,29]. The highest rate among the southern regions was reported in Calabria (Casanova) with a seroprevalence of 17.8% [27]. Based on the data on age reported by 17 of the 27 studies, we calculated a mean age of 42.28 years for the HEV positive subjects. Moreover, 59,26% were males, according to the information provided by 21 studies. Overall, the seroprevalence increased in association with age and no relevant variation related to gender has emerged from any study. However, only one pediatric study with a prevalence of 0.4% was found in Molise [30].

The study included: 10,527 individuals from the general population cohort, 2776 blood donors, 352 pregnant woman, 264 individuals at pediatric age, 2,609 patients affected by acute hepatitis, 800 individuals in hemodialysis, 118 renal transplant recipients, 430 chronic liver disease patients, 371 at zoonotic risk workers, 510 immigrants and 3,125 at high-risk individuals (100 HIV infected and 1116 with sexual or occupational exposure, 936 intravenous drug users and 973 prisoners).

The selected articles were from 13 different regional areas: Abruzzi (n = 1), Apulia (n = 2), Calabria (n = 2), Latium (n = 2), Lombardy (n = 3), Marche (n = 1), Molise (n = 1), Piedmont (1), Sardinia (n = 1), Sicily (n = 3), Republic of San Marino (n = 1), Tuscany (n = 1), and Veneto (n = 2) (Fig. 2).

The remaining 7 studies provided information at a national level only. Over three decades, 169 cases of hepatitis E were linked to travel in high endemic countries. Nearly 90% of them occurred in travelers returning from Bangladesh, India and Pakistan. The remaining cases were diagnosed in patients who traveled in Angola, Somalia, Morocco and Green Cape. Secondary and intra-familial infection has been described by two studies with a rate of 2.6% and 4.5% respectively [31,32]. Generally, a higher probability to be positive for anti-HEV antibodies has been associated with immigrants by the different studies focusing on socio-economic and demographic variables (healthy population, prisoners and at-risk categories). Genotype 1 (G1), subtype 1a and 1c, has been isolated in all imported cases of HEV. Genotype 3 (G3), subtype 3e, 3f and 3h, has been associated with a local source of infection. No significant differences in the clinical course of the disease caused by the G1 and G3 subtypes have been observed in immunocompetent individuals. Potential risk factors for HEV transmission included poor sanitation, person to person contact, family with more than 4 members, parenteral blood contact, male to male contact, professional long exposure with zoonotic reservoirs and raw and undercooked pork meat and shellfish.

In order to assess the seroprevalence of hepatitis E, different enzyme immunoassays (EIA) have been used to detect class G and M immunoglobulins against HEV. The commercially available assays were based on two methodologies: ELISA and Western Blot. The majority of studies (22 over 27) used one or more Elisa assays [25–28,30–47], while in 5 articles were used both serological assay types [24,29,48–50]. HEV RNA was detected if samples were positive for IgM and/or IgG in 12 of the selected studies [25,28,29,32,36,37,39,42,44,46,47,50].

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