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a series of fact sheets written  
by experts in the field of liver  
disease

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# Hepatitis E (HEV)

Alan Franciscus, Editor-in-Chief

*In the past, it was believed that hepatitis E was only a problem in developing countries due to contaminated water supplies. It was also believed that in industrialized countries the majority of HEV infections were among people who had visited countries where HEV infection was widespread.*

*However, over the last few years, studies and news reports have surfaced that are painting a different picture on HEV infections in industrialized countries such as the United States. In the U.S., there is little information about the prevalence of HEV mainly because of the lack of surveillance and testing even though there have been small studies that have hinted that the prevalence of HEV is more widespread than previously believed. Recently, a large study on the prevalence of HEV was published that will give us a better picture of the estimated number of people in the U.S. who have been infected with HEV. The study results are somewhat alarming and should, at the very least, promote more dialogue about the need for more strategies for testing and educating the public about the risk factors and ways to prevent the transmission of HEV. The higher prevalence should also help to support the development of an effective vaccine to prevent HEV infection.*

The hepatitis E virus is a hepatotropic, single stranded RNA virus. The main transmission route of HEV is fecal-oral due to HEV contaminated water supplies, but other sources of infection have been identified. The largest outbreaks of HEV usually occur in developing countries, but less severe disease outbreaks also occur in industrialized countries.

HEV has 4 genotypes numbered 1 through 4 and 24 subtypes. HEV has been found in humans, and animals—genotype 1 and 2 is found only in humans whereas genotypes 3 and 4 have been found in humans and animals (pigs, boar, and deer). Genotypes 1 and 2 are mainly found in the subtropical and tropical areas of Asia, Africa, and the Americas. Genotype 3 is found worldwide and genotype 4 is confined mostly to Asia.

Genotype distribution is indicative of transmission modes. For instance, genotypes 1 and 2 are mainly from contaminated water, whereas genotypes 3 and 4 can be transmitted from pigs or other animals to humans.

## **Transmission**

HEV is transmitted by the fecal-oral route – by drinking or eating contaminated food or water especially in countries that do not have sanitized sewage and water systems. It can also be transmitted from person-to-person but this is uncommon.

The incubation period is usually 40 days, but it can range from 15 to 60 days.

## **Prevention**

Since there is no vaccine to protect against HEV the following steps should be taken:

- Always follow basic food safety guidelines for washing and cooking food.
- Avoid eating animal parts or organs that could possibly transmit HEV.
- In areas where there is a high prevalence of HEV avoid the drinking water (unless bottled), uncooked shellfish, unpeeled fruit and vegetables (unless personally prepared).

## Symptoms

The most common symptoms of HEV are the typical hepatitis symptoms – jaundice (yellowing of the skin and whites of the eyes), malaise (out of sorts), loss of appetite, fever, diarrhea, abdominal pain, and muscle and joint pain. However, most people who become infected with HEV do not develop symptoms.

Normally, infection with acute HEV will resolve and the infected individual will develop antibodies that are protective against future infection. However, one study found that eight organ transplanted patients (HEV genotype 3 with severely compromised immune systems) had elevated liver enzymes and HEV RNA (viral load) over time, which would mean that HEV could lead to chronic

infection. But it is unclear if this is a true chronic infection or just due to a weakened immune system that can't resolve the infection. Deaths associated with HEV are uncommon except that pregnant women and their unborn babies are at risk of death especially during the third trimester of pregnancy – although this is mostly confined to developing nations. In industrialized nations deaths related to HEV are rare and mostly occur in people who have received organ transplants and who have severely suppressed immune systems. Having another hepatitis virus could also lead to a more severe form of disease.

There are no vaccines to protect against HEV but there are many that are in phase I and phase II clinical trials.

**Table 1. Prevalence of antibody to hepatitis E virus (anti-HEV) for selected demographic variables among participants (age ≥6 years) in the Third National Health and Nutrition Examination Survey, 1988–1994.**

Variable	Samples tested, no. (n p 18,695)	Positive for anti-HEV, <sup>a</sup> % (95% CI)
<b>Sex</b>		
Female	10,124	20.4 (18.3–22.5)
Male	8571	21.6 (19.3–23.9)
<b>Race/ethnicity</b>		
Non-Hispanic		
White (reference)	7052	22.1 (19.8–24.4)
Black	5312	14.5 (13.1–15.9) <sup>b</sup>
Mexican American	5527	20.3 (18.3–22.3)
Other	804	20.2 (16.5–23.9)
<b>Country of birth<sup>c</sup></b>		
United States (reference)	15,051	20.1 (18.1–22.0)
Mexico	2357	30.9 (28.9–32.9) <sup>b</sup>
Other	1233	26.2 (22.9–29.5) <sup>b</sup>
<b>Region of residence</b>		
South (reference)	8168	14.7 (12.3–17.0)
Northeast	2372	20.8 (16.5–25.1) <sup>b</sup>
Midwest	3655	26.6 (22.4–30.8) <sup>b</sup>
West	4500	25.0 (20.9–29.1) <sup>b</sup>

**NOTE.** Seroprevalence estimates were weighted (1) to denote the total civilian noninstitutionalized US household population in the age groups covered, (2) to account for oversampling, and (3) to account for nonresponse to the household interview and physical examination but not for nonresponse to phlebotomy. CI, confidence interval; reference, reference group.

<sup>a</sup> Of 18,695 samples tested, the percentage (95% CI) of samples that were anti-HEV positive was 21.0% (19.0%–22.9%).

<sup>b</sup> P<.05, compared with the reference group.

<sup>c</sup> The total no. of samples shown is <18,695, because of incomplete reporting.

### The key findings of the study:

- HEV infection was uncommon among children, but became more common as people aged.
- People in the Midwest had the highest regional estimates and interestingly the Midwestern region of the U.S. has the largest swine population (pigs, hogs, and boar).
- The highest incidence of HEV was found in the metropolitan areas.

### Risk factors for HEV included:

- Having a well as a source of tap water.
- Having HAV antibodies was associated with significantly **lower** odds of having HEV antibodies.
- Having a pet in the household.
- Having a dog in the household.
- Consuming liver or other organ meats more than once per month.
- Having HCV.

### U.S. Prevalence

In a current study,<sup>1</sup> 18,695 participants in the Third National Health and Nutrition Examination Survey (NHANES III) were tested for HEV antibodies. Participants were 6 years of age or older. The study period was 1988 through 1994. **The overall prevalence of HEV antibodies in the non-institutionalized U.S. population was 21%.** The breakdown of the prevalence of HEV by race, sex, race/ethnicity, country of birth, and geographic region is shown in **Table 1**.

The authors concluded that their study suggests that HEV is common in the general U.S. population. Previous studies in the U.S. suggested that the prevalence of antibodies to HEV was mostly due to people who traveled or who were from developing countries with a high prevalence of HEV. But in this study the authors theorized that many of the infections may have originated in the U.S. and may have been spread

by exposure to swine. In this study and in previous studies the association between eating liver or other organ meats has been found to be a highly plausible route of infection. It is also interesting to note that this would explain why acute infection of HEV is rarely reported because HEV from genotype 3 (from swine) is believed to be less severe and acute symptoms may not necessitate a trip to a medical provider for testing and treatment. Another reason it goes undetected in the U.S. is that there are no FDA approved hepatitis E antibody tests available for general use.

**Of note:** HEV has been found in pig livers sold in U.S. grocery stores. Another possible reason is that there is currently no HEV antibody test licensed in the U.S.; so even if HEV is suspected there is little in the way of diagnostic tests that medical providers have at their disposal.

### Source:

<sup>1</sup>Epidemiology of Hepatitis E Virus in the United States: Results from the Third National Health and Nutrition Examination Survey, 1988–1994. Mark H. Kuniholm, Robert H. Purcell, Geraldine M. McQuillan, Ronald E. Engle, Annemarie Wasley, and Kenrad E. Nelson

**For more information about hepatitis C, hepatitis B and HCV coinfections, please visit [www.hcvadvocate.org](http://www.hcvadvocate.org).**

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