Hepatitis E in Southeast Asia

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ABSTRACT

Hepatitis E is a major cause of acute viral hepatitis in the world. The causative agent of hepatitis E is hepatitis E virus (HEV). In Southeast Asia, the seroprevalence of HEV and the most prevalent genotype of HEV are largely unclear and the available data is either limited or outdated. After a systematic review of literature, we found the seroprevalence of HEV and the most prevalent genotype of HEV appear to vary greatly by countries. The seroprevalence is likely between 17% to 42% and the prevalent genotypes across Southeast Asia are likely 1, 3, and 4, but not 2 as no cases of genotype 2 have been reported in this region. As HEV remains widespread in Southeast Asia and the clinical implications of HEV can be severe, surveillance programs for HEV should be implemented.

Keywords: Epidemiology; genotype; seroepidemiologic studies; vaccination; swine (Siriraj Med J 2020; 72: 259-264)

INTRODUCTION

Hepatitis E virus

Globally, hepatitis E is a major cause of acute viral hepatitis.[1,2] The causative agent of this liver disease is the hepatitis E virus (HEV).[3] HEV is a non-enveloped, single-stranded, positive-sense RNA virus with similar physical characteristics to the hepatitis A virus.[4,5] Similar to the hepatitis A virus, HEV is transmitted via the oral-fecal route through contaminated water and it can also be transmitted via zoonosis.[6,7] There are five genotypes of HEV known to infect humans, genotypes 1-4 and recently genotype 7 however, for those five genotypes, there is only one serotype.[8,9] HEV appears to have genotype-specific complications. Infection by genotype 1 and 2 can result in severe complications such as death and stillbirth while infection by genotype 3 typically results in mild to non-existent complications in immunocompetent individuals.[10-14]

Genotypes 1 and 2 have only been reported in humans while genotypes 3 and 4 are zoonotic and are known to be carried by swine and other animals depending on the regions. Transmission of HEV from infected swine can be due to direct contact with the swine, consumption of undercooked swine meat, or exposure to swine feces. Exposure to the swine feces can be either directly through contact or indirectly through contaminated water or contaminated shellfish.[6,7,15] Although swine are the most commonly reported source of zoonotic transmission, deer and other animal species have been reported to transmit genotype 3 to humans as well.[16]

Review methodology

We conducted a systematic search on PubMed and Google Scholars for research articles with the main keywords "hepatitis E," "genotype," and "seroprevalence." These keywords were supplemented with the "Southeast Asia,"

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"Brunei," "Burma," "Myanmar," "Cambodia," "Timor-Leste," "Indonesia," "Laos," "Malaysia," "Philippines," "Singapore," "Thailand," and "Vietnam." Non-English research articles without English translations were not reviewed. All relevant research articles found in the search were reviewed. Recent publications were favored; however, publication dates were not used as an exclusion factor.

Epidemiology

In Southeast Asia, previous studies have reported genotype 1 and 4 to be prevalent in humans.[17,18] However, recent evidence found conflicting results suggesting that those previous studies may be outdated.[19-24] The prevalent genotype of HEV is largely unclear and varies greatly by countries.

In Thailand, multiple studies have found that the local swine carry HEV genotype 3, exclusively.[25-28] And in humans, genotype 3 have also been found.[19-24] The seroprevalence of HEV, defined in this paper as the presence of anti-HEV immunoglobin G, was found to be 14% nationally in 2007-2008, but the seroprevalence was not homogenous, varying greatly within the country.[29] The study found lower HEV seroprevalence in Muslim dominated regions where pork consumption is relatively scarce.[29,30] A decade later, a recently published study found that the seroprevalence of HEV to be much higher, 29.7% in the general Thai population.[31] This study also found lower HEV seroprevalence in Muslim dominated region.[31] Recent reports, including a recently published national study, have only found genotype 3 in Thailand.[20,21] Because of these consistent reports, the prevalent HEV genotype that is circulating in Thailand is almost certainly genotype.[3]

In Cambodia, studies have reported various genotypes circulating in the country. In humans, genotypes 3 and 4 have been found.[22,32] And swine have been found to carry HEV genotype 1, 3, and 4.[32,33] Genotype 3 has also been found in the river water.[34] In a study in 2015, the seroprevalence of HEV was found to be 18.4% in the general population.[22]

In Laos, the swine population has been found to carry genotype 4.[35-37] However, there are currently no genotyping studies of HEV in humans in Laos. The seroprevalence in humans may be 17% based on controls used in a study by Bounlu et al.[38]

In Malaysia, a 1999 study reported the seroprevalence of HEV to be only 2% in the general population, strangely low.[39] Another study around the same time found the seroprevalence to be 10% in a population of patients infected by the human immunodeficiency virus.[40] This suggests that seroprevalence of HEV used to be very low, however, these studies are outdated. Genotype information for both humans and swine have not been reported in the literature.

In Myanmar (previous known as Burma), the predominant genotype appears to be genotype 1. A few studies have reported finding genotype 1 in humans.[4,41] The statuses of other genotypes are unknown and swine genotypes have not been studied. A study in 2001 found the seroprevalence of HEV in Myanmar to be 31.5% in humans and 24% in swine.[42]

In Vietnam, studies have reported genotype 4 in humans.[43,44] Genotype 1 has been suspected of being prevalent in Vietnam due to waterborne outbreaks of HEV, however, genotypic analysis to explicitly confirm the presence of genotype 1 HEV does not exist.[45] Animal reservoirs for HEV in Vietnam have not been reported in the literature. This seroprevalence is unknown in the whole country, but in the capital city of Ho Chi Minh City, it is very high at 42%.[46]

In Indonesia, genotype 4 has been found in humans.[47] Genotype 4 has also been reported in swine.[47,48] A study in 2005 of 2,450 pregnant women found that the seroprevalence of HEV was 18% in this population nationally, and that in Muslim dominated areas, where pork consumption is relatively scarce, the seroprevalence was much lower at 2%.[49] There have been no reports of genotype 1, 2, or 3 in Indonesia suggesting that the prevalent genotype may be genotype 4, likely due to zoonotic transmission from swine.

In Singapore, studies on the seroprevalence or genotype of HEV do not exist based on our search criteria. However, the incidence rate of cases is very low at 0.92 per 100,000 people between 2009-2011.[50] Such a low incidence rate is likely related to the fact that Singapore is the most developed country in Southeast Asia, which typically comes with good hygiene and well-funded public health programs.

In the Philippines, a recent study found that the swine carry genotype 3 exclusively.[51] In the river water, HEV RNA was detected and samples were all found to be genotype 3.[23] However, we could not find any seroprevalence or genotype reports on HEV in humans.

There were no or very limited HEV epidemiology data from Brunei and Timor-Leste. However, in Timor-Leste, HEV is likely still endemic.[52]

The seroprevalence of HEV in humans is still unknown in most areas of Southeast Asian countries. The seroprevalence in the region may be between 17% in Laos to 42% in Ho Chi Minh City, Vietnam (Figs 1, 2, and 3).

Fig 1. Map of hepatitis E virus genotype distribution found in humans in Southeast Asia.

Fig 2. Map of hepatitis E virus genotype distribution found in swine in Southeast Asia.

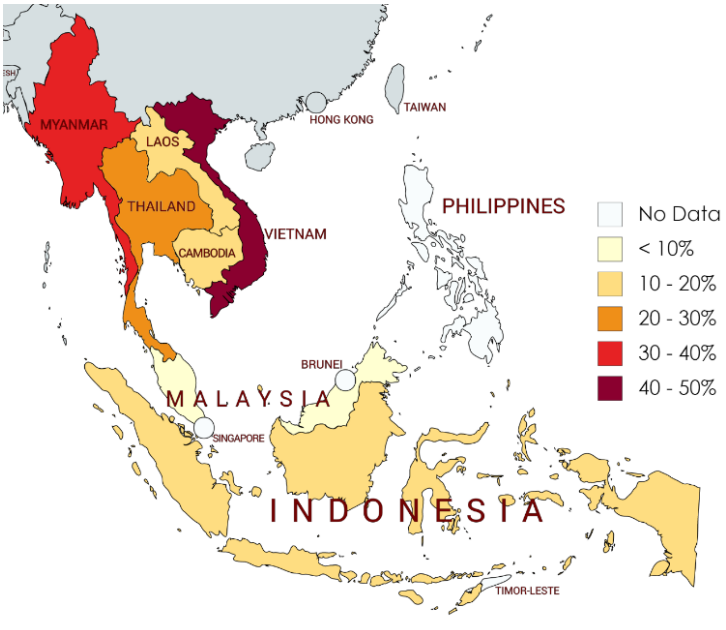

Fig 3. Seroprevalence of hepatitis E virus in humans in Southeast Asia.

Complications and consequences

In the general population, the complications of HEV are typically moderate such as fatigue, vomiting, and jaundice.[53] However, in certain groups, the complications can be severe. In people with chronic liver diseases, acute-on-chronic liver failure, a serious condition with high short-term mortality, can occur as a result of genotype 1 HEV infection.[11] In pregnant women, high morbidity and mortality for both the mother and the fetus have been reported. A study in 2007 on pregnant women in India reported a mortality rate of 41% of those infected with HEV compared to 7% of those non-infected.[10] That study also reported 54% of births from women infected with HEV were stillbirths compared to 1% in non-infected women.[10] Hepatitis E is generally an acute disease, however, in populations with a compromised immune system such as organ transplant recipients or HIV populations, the disease can become chronic.[54-56] In Southeast Asia, studies on the effects of HEV on these vulnerable groups are lacking. A study by Rein et al. estimated the burden of HEV in one year, 2005, in Southeast Asia to be 1,984,235 incident infections, 357,086 symptomatic cases, 7,347 deaths, and 148 stillbirths.[57] Rein et al., however, only explored genotypes 1 and 2 of HEV, thus, their report of burden are likely underestimates.[57]

Diagnosis

Clinically, hepatitis E is practically indistinguishable from infection from other hepatitis virus such as hepatitis B and C. Thus, confident diagnosis of hepatitis E requires serological tests. Antibody assays for anti-HEV immunoglobin M and anti-HEV immunoglobin G and nucleic acid assays for HEV RNA in blood are commonly used in hepatitis E diagnosis.[58] Ideally, all three tests are done for a comprehensive evaluation, however, resources in many Southeast Asian countries may be too scarce to permit this. The reverse transcriptase polymerase chain reaction for HEV RNA is the most resource intensive, but it is a direct method for detecting HEV and can provide information on whether a patient has a current infection. HEV RNA can be detected in feces as well, but this method is not commonly used. Antibody assays for anti-HEV immunoglobin M and anti-HEV immunoglobin G, such as the Wantai assays by Beijing Wantai Pharmacy Enterprise Co., Ltd. (Beijing, China), are relatively inexpensive, simple to use, and both high in sensitivity and specificity.[59,60] Anti-HEV immunoglobin M and anti-HEV immunoglobin G are indirect methods for detecting HEV. The presence of anti-HEV immunoglobin M indicates either current or recent infection of up to approximately 5 months prior.[61,62] The presence of anti-HEV immunoglobin G indicates a distant past infection of up to 14 years prior in some reports.[63] One of the facilities able to test for HEV, both the antibody and the RNA, is the Armed Forces Research Institute of Medical Sciences (AFRIMS) which have centers in many Southeast Asian countries, especially Thailand.

Recently, new assays were developed by Pisanic et al. for detecting anti-HEV immunoglobin A (for current or recent infection) and anti-HEV immunoglobin G in saliva. The study showed high sensitivity and specificity for anti-HEV immunoglobin G and low sensitivity but high specificity for anti-HEV immunoglobin A.[64] Because these assays are non-invasive and also inexpensive and rapid like the Wantai assays, they have the potential to be useful for HEV screening.

Vaccination

Since 2012, there exists an approved recombinant HEV vaccine called HEV 239 or Hecolin developed by Xiamen Innovax Biotech in China.[65] However, it is currently only approved for use in China. The vaccine was designed to protect against HEV genotype 1; however, a phase 3 clinical trial demonstrated its effectiveness in protecting against genotype 4 as well.[65] The study reported an efficacy of 100% against HEV genotypes 1 and 4 over a 12-month period.[65] However, there is no data on Hecolin's effectiveness in protecting against genotypes 2 and 3. The vaccine has been shown to be effective for at least 4.5 years for 87% of healthy adults.[66] Because the burden of HEV across Southeast Asia is unclear, the need to evaluate Hecolin for domestic use is also unclear.

CONCLUSION

HEV genotype 1, which has been typically associated with South Asian countries, does not appear to be prevalent in Southeast Asia based on genotyping studies. All genotypes except for genotype 2 have been reported in Southeast Asia. However, this data and the data on seroprevalences were not ideal as the studies were often outdated or had limited populations of study. Large, national studies or surveillance programs are few. As the seroprevalence of HEV remains high throughout Southeast Asia and the impact of HEV could be significant, surveillance programs for HEV should be implemented.

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