PREVALENCE OF ENTERIC HEPATITIS A AND E VIRUSES IN THE MEKONG RIVER DELTA REGION OF VIETNAM

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Abstract. A study of antibody prevalence for hepatitis A virus (HAV) and hepatitis E virus (HEV) was carried out in southwestern Vietnam in an area adjacent to a known focus of epidemic HEV transmission. The purpose of this investigation was first to provide a prevalence measure of hepatitis infections, and second to determine the outbreak potential of HEV as a function of the susceptible population. Blood specimens collected from 646 persons in randomly selected village hamlets were examined by an ELISA for anti-HEV IgG and anti-HAV IgG. The prevalences of anti-HEV IgG and anti-HAV IgG were 9% and 97%, respectively. There was a significant increase \( P < 0.01 \) in age-specific anti-HEV IgG. A notable increase in anti-HAV IgG prevalence \( P < 0.0001 \) occurred between child populations 0–4 (64%) and 5–9 (95%) years of age. No evidence of familial clustering of anti-HEV IgG-positive individuals was detected, and household crowding was not associated with the spread of HEV. Boiling of water was found to be of protective value against HEV transmission. A relatively low prevalence of anti-HEV indicates considerable HEV outbreak potential, against a background of 1) poor, water-related hygiene/sanitation, 2) dependence on a (likely human/animal waste)–contaminated Mekong riverine system, and 3) periodic river flooding.

Epidemic and sporadic hepatitis E virus (HEV) transmission has been documented throughout the developing world1 (Balayan MS, unpublished data). In southeast Asia (in contrast to other geographic regions), HEV occurrence is generally reported as a rural rather than urban phenomenon.2 The proportion of (sporadic) acute hepatitis cases attributed to HEV reported in cities such as Jakarta (Indonesia) and Hanoi (Vietnam) has been found to be very low: 3% and < 1%, respectively3 (Persahabatan Hospital, Jakarta, Indonesia, unpublished data). Conversely, foci of epidemic HEV transmission have been recognized in jungle/riverine areas of Indonesian Borneo (Kalimantan)4,5 and the Mekong River delta region of Vietnam.6 Transmission determinants associated with worldwide spread of enteric HEV are principally water-related.4 In developing areas, the spread of hepatitis A virus (HAV) is also related to waterborne transmission, whereas in more developed settings, infections are predominately acquired through contact with an infected person, usually a child with inapparent infection, and occasionally from contaminated food or drink. Dependence on a (contaminated) water source for drinking/hygiene/sanitary purposes has been implicated in both epidemic and sporadic (community-acquired) spread of HEV and HAV. Epidemic HEV infections were attributed to well water in Somalia4 and river water in Indonesia4,5 and Vietnam.6 However, unlike HAV transmission, there is little evidence of person-to-person spread of HEV. Also, HEV infections, when compared with HAV, are characterized by 1) a longer incubation period, 2) case-fatality in pregnant women (10–24%), and 3) poor protection by gamma globulin.7–9 An investigation of anti-HEV IgG prevalence was conducted in an area contiguous to that where epidemic HEV transmission was first documented in Indochina. The purpose of this study was to determine the epidemic potential of HEV as reflected in the proportion of susceptible individuals in the population.

METHODS

Epidemiology. A cross-sectional study of hepatitis A and E prevalence was carried out in the Tan Chau District, An Giang Province, Vietnam from January through March 1994. The communities surveyed are located along the Mekong River and its tributaries, (otherwise referred to as the Mekong delta), a wet-rice (controlled irrigated flooding of rice fields as opposed to dry-rice cultivation)–producing agricultural area situated along the Cambodian border. Work and leisure in this tropical, lushly vegetated area revolves around the many rivers and streams that crisscross the landscape. The population of Tan Chau District (151,771 persons, based on 1990 projected census estimates) is universally dependent on the rivers(streams) for water-related hygiene and sanitation and drinking water; area communities are strategically located along the river banks to take full advantage of this resource, in the general absence of other water supplies, e.g., treated municipal water. Cyclic flooding conditions in the Mekong delta region contribute to the overall human/animal/industrial contamination of water resources.

There are 10 communes located in Tan Chau District. Each commune is composed of 15–50 village hamlets. A systematic sampling of village hamlets (three in each commune) were selected for study purposes; this covered an area of approximately 60 km². After obtaining a list of villages in each commune, an appropriate systematic ratio was determined to ensure the random selection of three hamlets, e.g., every fifth village hamlet. All households within selected hamlets were targeted for enrollment. The family household served as the principal sampling unit. All persons living in study households were targeted for study inclusion to ensure cross-sectional age/sex representation of the general population. Participation was predicated on informed voluntary consent; parents or the principal care provider provided signed approval for children ≤ 12 years of age. Study activities were undertaken only after review and approval by the Committee for the Protection of Human Subjects at the
U.S. Naval Medical Research Unit No. 2 (Jakarta), the Committee for Human Use at the Pasteur Institute (Ho Chi Minh City), and the Committee for Research Ethics in An Giang Province, Vietnam. A standardized questionnaire providing for demographic and environmental, risk-related information was first pretested and then administered to study subjects by trained interviewers.

Laboratory analysis. A 10-ml blood sample was collected from subjects (5 ml from children ≤ 12 years) using disposable syringes and with a butterfly apparatus for infants. Specimens were centrifuged, separated from the clots, disposable syringes and with a butterfly apparatus for in-

Six hundred forty-six persons (266 males and 380 females) representing 263 households (mean = 2.45 persons/household) from 30 hamlets were enrolled into the study. The mean ± SD number of study participants/community cluster was 23 ± 6.07 (range = 9–37). The ages of the study population ranged from less than one to 87 years (mean ± SD = 20.45 ± 20.36). The mean ± SD age of females (30 ± 20.153 years) did not vary significantly (P > 0.065) when compared with that of males (28 ± 20.605 years).

Overall prevalences were 9% (95% CI for proportion = 7–12%) for anti-HEV IgG and 97% (95% CI = 95–98%) for anti-HAV IgG. The prevalence of anti-HEV IgG significantly increased with age, ranging from a low of 3% in young children (< 5 years old) to 16% among older adults (≥ 50 years old). Notable was the dramatic increase in anti-HEV IgG prevalence in the population 5–9 years of age (95%), compared with children < 5 years of age (64%) (Table 1). Also, the mean ages of anti-HEV IgG- and anti-HAV IgG-positive individuals were significantly higher compared with negative individuals: 39 versus 29 years (P < 0.001, 95% CI for the difference between means = 10–16) and 30 versus 11 years (P < 0.0001, 95% CI = 10–28), respectively.

The results in Table 1 show that the proportion of anti-HEV IgG-positive individuals did not differ significantly between males (7%) and females (11%). However, the prevalence of anti-HEV IgG in females ≥ 40 years of age was significantly higher (P < 0.001) than for males: 17% versus 3%. The difference in prevalence of anti-HAV IgG between male (95%) and female (98%) subjects, although statistically significant (P < 0.05), was quite modest (95% CI for the difference between proportions = 0.5–5%). There was no significant difference in the mean ages of female (41 years) and male (34 years) anti-HEV IgG reactors. Also, no difference was detected in mean ages between male and female anti-HAV IgG (20 years old)–positive individuals.

There was significant variability (\(\chi^2 = 20.262, P = 0.01\)) in anti-HEV IgG prevalence by community (30 hamlets), ranging from < 1% to 23%. Prevalence of anti-HAV IgG between communities did not vary significantly (86–100%). Lastly, there was no observable geographic clustering of hamlets on the basis of high or low hepatitis prevalence, regardless of the marker (anti-HEV IgG and anti-HAV IgG).

There was no apparent familial (household) clustering of anti-HEV IgG reactors (Table 2). Only 2% (95% CI for proportion = 0.4–4%) of the households had more than one anti-HEV IgG-positive family member. In comparison, 66% (95% CI for proportion = 60–72%) of the households contained more than one anti-HAV IgG-positive member.

There was no difference in proportional use of the river as a principal source of drinking/bathing water between anti-HEV IgG-positive individuals (78%) and anti-HEV IgG-negative individuals (79%). However, the practice of boiling water for drinking purposes was significantly (P < 0.01) associated with the absence anti-HEV IgG: 30% of those who were anti-HEV IgG positive boiled water compared

### Table 1

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>No. of males</th>
<th>No. of females</th>
<th>Total no.</th>
<th>Males positive (%)</th>
<th>Females positive (%)</th>
<th>Total (%)</th>
<th>Males positive (%)</th>
<th>Females positive (%)</th>
<th>Total (%)</th>
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<td>18</td>
<td>33</td>
<td>7</td>
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<td>5–9</td>
<td>27</td>
<td>32</td>
<td>59</td>
<td>4</td>
<td>6</td>
<td>5</td>
<td>96</td>
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<td>80</td>
<td>98</td>
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<td>5</td>
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<td>40–49</td>
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<td>37</td>
<td>67</td>
<td>0</td>
<td>11</td>
<td>6</td>
<td>93</td>
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<td>16</td>
<td>100</td>
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<tr>
<td>Total</td>
<td>266</td>
<td>380</td>
<td>646</td>
<td>7</td>
<td>11</td>
<td>9</td>
<td>95</td>
<td>98</td>
<td>97</td>
</tr>
</tbody>
</table>

\(\chi^2 = 19.799; P < 0.01\)

\(\chi^2 = 132.916; P < 0.0001\)

*HEV = hepatitis E virus; HAV = hepatitis A virus.

†P refers to the level of significance as determined by the chi-square test for trend generally denoting an increasing trend.
with 47% of those who were anti-HEV IgG negative (95% CI for the difference between proportions = 5–30%). There was no correlation between household crowding conditions and anti-HEV IgG-positive (mean = six persons/household) or -negative (mean = five persons/household) antibody status.

**DISCUSSION**

Low prevalence of anti-HEV IgG in the study population (9%), particularly when compared with anti-HAV IgG (97%), likely reflects more sporadic than epidemic type occurrence. Transmission in Southeast Asia involving epidemic spread of HEV generally overwhelms a population, as reflected in high area prevalence. In the neighboring district of Tan Chau, anti-HEV IgG prevalence among healthy study controls examined during a 1994 outbreak investigation was 33%. Similarly, in Indonesia, high anti-HEV IgG prevalence (50%, range = 40–55%) was found in outbreak-affected populations seven years following epidemic spread. In contrast, background HEV infections in adjacent non-outbreak areas (surveyed for comparative purposes) were recognized in only 23% (range = 15–32%) of the population.5

The increase in anti-HEV IgG prevalence with age, although not as dramatic as observed for anti-HAV IgG, is nevertheless pronounced. This feature, which was also observed in Indonesia and Nepal, may indicate an occupational and/or age-dependent risk associated with HEV exposure, i.e., wet-rice farming, fish farming, washing of farm animals, drinking untreated water, etc.4,5,10 Young children have also been under-represented among acute, clinically recognized HEV cases resulting from either epidemic or community-acquired (sporadic) infections. The low prevalence of anti-HEV IgG in pediatric populations suggests that this is more likely due to a lack of childhood exposures rather than to asymptomatic, acute HEV infections.5

The lack of familial clustering of anti-HEV IgG-positive individuals indicates the absence of person-to-person spread. Additionally, household crowding was not associated with HEV antibody status. These findings are consistent with what has been described in Indonesia, albeit pertaining to epidemic transmission, where there was no evidence of anti-HEV IgG clustering by household.4

Boiling water for drinking was found to be of protective value against HEV infection in this study. The practice of boiling water in Indonesia was also significantly associated with the absence of both epidemic and sporadic HEV infections. Conversely, drinking, defecating, and bathing in river water (sole source of water) was shown to increase the relative risk of HEV infections.4,5 The observation in this investigation that drinking from and bathing in river water was not related to HEV infections may reflect the added value of boiling water in minimizing exposure risk. Also, the type of exposure opportunities associated with drinking and bathing, e.g., frequency, location on river, direct immersion versus water drawn in a bucket, zoonosis, and/or cultural influences, may have contributed to the lack of significance assigned these two activities in enhancing risk. Nevertheless, these results support the notion of waterborne spread as the principal mechanism in HEV transmission. Periodic flooding of the Mekong River and tributaries probably contributes to the contamination of water sources with human and/or animal waste material, adding to the risk of exposure. In Nepal, flooding conditions have been linked with increases in HEV infections.10

In conclusion, the large percentage of people who remain susceptible in the population with conditions that include 1) poor, water-related sanitation/hygiene; 2) sporadic infections; and 3) regular flooding, favors the epidemic potential of HEV spread. Finally, the fact that > 95% of the population has been exposed to HAV by adolescence suggests that HEV will be the culprit in future outbreaks of enteric hepatitis.

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**REFERENCES**


