衞生防護中心
Centre for Health Protection

Scientific Committee on Enteric Infections and Foodborne Diseases

Epidemiology and Prevention of Hepatitis E

Purpose

This paper reviews the latest global and local epidemiology of hepatitis E and examines the public health measures in order to prevent and control the disease.

The Pathogen and the Disease

The Pathogen

2. Hepatitis E virus (HEV) is a spherical, non-enveloped, positive-sense single-stranded RNA virus of approximately 32 to 34 nanometers in diameter. It was recognized as a new disease in 1980 and was originally classified within the family of Caliciviridae because of the morphological similarity. However, its genome was cloned and characterized in 1991 and it became the only member of the genus *Hepevirus* in the family of *Hepeviridae.*

3. The genomes of several HEV strains from different parts of the world have been sequenced and compared. They can be generally distinguished into four major groups, namely genotype 1, 2, 3 and 4 respectively. All HEV strains appear to comprise a single serotype. No serologic or hybridizing cross-reactivity between HEV and other viral hepatitis agents, including hepatitis A virus (HAV) has been observed.[1]

Clinical Presentation and Course of the Disease

4. The clinical features of acute hepatitis E resemble those of other types of acute viral hepatitis, i.e. initially presenting with non-specific symptoms such as fever, malaise, anorexia and vomiting, followed by jaundice, tea-coloured urine and hepatomegaly. Other less common symptoms include arthralgia, diarrhoea, pruritus and urticarial rash. Nevertheless, some subtle differences were noted between Hepatitis A Virus (HAV) and HEV infection. Table 1 summarizes the major characteristics between the two infections. Both diseases present with acute, self-limiting infection that may vary in severity from inapparent to fulminant disease. However, HEV has a slightly longer incubation period (on average 10 days) than HAV.[2] In a local study,[3] jaundice was found to be slightly more common in HEV infection (96%) than HAV infection (80%) and the bilirubin level was higher in HEV infection than HAV infection. Coagulopathy and protracted cholestasis were also more common in HEV infection than HAV infection. Bimodal or relapsing symptoms over 6 to 9 months are relatively common in hepatitis A but rare in hepatitis E infection. In general, neither type of hepatitis progresses to chronicity. However, chronic hepatitis E infection has been rarely reported in organ-transplant recipients or immunocompromised hosts.[4,5] The mortality rate of hepatitis E is higher than that of hepatitis A, especially in the pregnant women (approximately 20%) although the reason is not known.[6] The mortality rate of hepatitis A is approximately the same in pregnant and non-pregnant women.

Table 1. Comparison of major characteristics between hepatitis A and E

	HAV	**HEV**
Occurrence	Worldwide	Worldwide, epidemics in some parts of Asia, Africa & Mexico
Route of transmission	Usually via contaminated water or food; person-to-person spread more common	Usually via contaminated water & occasionally food; probably zoonotic; person-to-person rare
Incubation period (days)	Average around 30 days, range from 15-50 days	Average around 40 days, range from 15 to 64 days
Clinical presentation	Essentially indistinguishable, typically jaundice, tea-coloured urine and hepatomegaly. Higher bilirubin level, coagulopathy and protracted cholestasis were found to be more common in HEV than HAV infection.	
Clinical course	Occasionally prolonged, relapsing course	Rarely relapsing course
Laboratory diagnosis	Usually with presence of anti-HAV IgM in serum	Anti-HEV IgM in serum or HEV RNA in serum or faeces
Chronicity	No	No
Mortality	0.1-2%	0.5-4%, up to 20% in third trimester of pregnancy

5. Regarding the severity of illness with respect to the genotype, it has been found that genotype 4 infection tends to cause more severe clinical disease than genotype 3 infection. In a Japanese study comparing the clinical features of an acute infection of hepatitis E by genotype 3 and 4, it was shown that genotype 4 had a higher peak alanine aminotransaminase levels and lower prothrombin time.[7] The median duration of hospitalization was also longer for patients suffering from genotype 4 than genotype 3 infection.

6. The alanine aminotransaminase elevation usually rises before manifestation of clinical illness. Peak viraemia and peak shedding of HEV into the faeces occurs during the incubation period and early acute phase of the disease. The period of communicability is unknown but virus excretion in the stool has been demonstrated for up to 14 days after onset of jaundice and then disappears during the recovery phase.[1] The immune response to hepatitis E appears late in the incubation period or during the acute phase of illness. It starts from the brisk rise of anti-HEV IgM and is followed by anti-HEV IgG. Anti-HEV IgM declines rapidly during early convalescence while anti-HEV IgG has been shown to persist for a long period of time (> 14 years).[8]

Susceptibility to Infection

7. Hepatitis E occurs primarily in adults, with the highest rates of symptomatic disease being reported in young to middle-aged adults. Although hepatitis E infection is also frequently seen in children, most of them are asymptomatic and do not have signs of jaundice.[9]

8. The high risk groups for HEV infection include persons who have chronic liver disease, travelers to endemic areas, those residing in areas where extended community outbreaks exist, and persons working with animals such as pigs, cows, sheep and goats from which they may be infected.[1] Women in the third trimester of pregnancy are especially susceptible to fulminant hepatitis.

Routes of Transmission

9. HEV is mainly an enterically transmitted virus that causes waterborne epidemics in developing countries and sporadic cases in developed countries. There are four reported routes of transmission, namely waterborne, zoonotic (foodborne), bloodborne and perinatal. [10] Person-to-person transmission of hepatitis E is rare compared with hepatitis A, which might be related to the low amount of intact HEV particles present in a patient's stool.[1]

10. Waterborne transmission commonly results in both large scale epidemics and sporadic cases. The HEV is transmitted via the faecal-oral route and is easily spread by water contaminated with human faecal matter. In the past, most of the hepatitis E outbreaks occurred after monsoon rains, heavy

flooding, contamination of well water, or massive uptake of untreated sewage into city water treatment plants.[1] Consumption of raw or under-cooked shellfish has also been found to be a common cause of sporadic cases in endemic areas. The probable source of contamination is from human sewage discharge or from infected shellfish harvesters, since shellfish collect the viruses in the course of their filter feeding activity.[11]

11. Humans are the natural hosts for HEV. However, there was evidence suggesting that HEV might be a zoonotic virus. A novel swine virus (swine HEV) that was closely related to, but distinct from, human HEV was isolated in 1997.[12] Further characterization of swine HEV showed that the human HEV genotype 3 and the swine HEV shared more than 97% amino acid identity. [13] In addition, cross-species infection has been experimentally demonstrated between animals, e.g. swine, sheep and rats under laboratory conditions. [14] In Japan, a hepatitis E outbreak investigation identified that inadequately cooked pig liver might be the source of infection because of close genetic identity (either genotype 3 or genotype 4) between the HEV isolates recovered from the patients and those from the pig liver samples.[15] In another outbreak investigation in Japan, identical nucleotide sequence was found in both patients' sera and leftover raw deer meat that they had consumed.[16] Inter-species HEV transmission between wild boar and wild deer has also been shown to occur.[17] The Centre for Food Safety (CFS) has performed the risk assessment study on HEV in fresh pig livers. One hundred pig liver samples were collected from local slaughterhouse during mid-January to May 2009. Among the collected samples, 16 out of 51 (31%) roaster (around four months old) liver samples were found positive for HEV, whilst none of the 49 porker (around six months old) liver samples were found positive. The roaster pigs contributed less than 2% of total admission of live pigs from the Mainland in 2009. Forty-eight cases of human hepatitis E were recorded by CHP with onset time within January to July 2009; HEV isolates from seven of them were found to have same partial ORF2 sequences as those from roaster pigs in the CFS study. Among the seven human cases, three of them had consumed pig offal during incubation period.[37] Furthermore, review of all 190 cases notified to CHP in 2009 to 2010 showed that about 33.2% (n=63) of the cases recalled consumption of pig liver and 7.4% (n=14) recalled consumption of pig offal other than pig liver during incubation period. About 32.1% (n=61) of the cases recalled consumption of shellfish. No common incriminated food or linkage to food premises could be identified among these cases. These results suggested that pigs and other animals might be the natural reservoirs of HEV and that human infection with HEV could be a zoonosis.

12. The possibility of bloodborne transmission of hepatitis E has been discussed, especially in endemic areas.[18,19] A study conducted in the Middle East showed that blood transfusion increased the risk of hepatitis E infection compared with hospital controls. [20] In non-endemic areas, the prevalence of hepatitis E antibody in haemodialysis patients has been reported

to be higher.[21] There is also some direct evidence showing that recipients of blood products develop acute hepatitis after blood transfusion and that HEV nucleotide sequences from the donor blood and the recipient blood are identical.[22,23] In Hong Kong, an asymptomatic blood donor was confirmed to have acute hepatitis E infection,[24] and retrospective analysis of his donated blood showed HEV viraemia by polymerase chain reaction (PCR) and confirmed by sequencing. These findings suggest that blood transfusion may be a risk factor for HEV infection.

13. Perinatal transmission from mother to child is not considered to be an important route of transmission for HEV. However, some evidence shows that such transmission of HEV occurs and carries appreciable perinatal morbidity and mortality.[25] In a study conducted in the United Arab Emirates, all infants born to 26 HEV-RNA positive mothers developed acute clinical infection and were HEV-RNA positive. Hepatitis E in pregnant women has been associated with high rates of pre-term labor and mortality.[26,27]

Laboratory Diagnosis and Management

14. The diagnosis of HEV infection mainly depends on the clinical features and exclusion of other causes of acute hepatitis, especially hepatitis A. Acute hepatitis E infection is usually confirmed by the demonstration of IgM anti-HEV in the serum by ELISA or detection of HEV RNA by PCR in serum or faeces. PCR is useful for detecting HEV during acute phase of infection and has contributed to the identification of new genetic variants of HEV. The sensitivity of PCR testing depends on a proper match between the HEV strain and the PCR primers.[14] For practical purposes, serologic testing serves to confirm the clinical diagnosis, while detection of viral RNA in HEV IgM positive patients could provide supplementary information on the infecting strain, enabling molecular epidemiological studies.

15. Treatment for hepatitis E infection is mainly supportive. Patients should be provided with adequate hydration and electrolyte repletion. Antivirals have not been successfully developed for the treatment and no specific therapy is effective in altering the course of acute hepatitis E infection. Hospitalization is required for patients with poor oral intake, fulminant hepatitis and should be considered for all infected pregnant women.

16. Standard precautions in hospital should be observed to prevent faecal–oral transmission of infection with hand hygiene being emphasized. Gloves should be worn during contact with blood, excretions, secretions and contaminated items, and further hand hygiene should be performed after glove removal. Contact precautions should be practised for those patients with profuse diarrhoea or incontinence, and they should preferably be nursed in a single room. Environmental disinfection should be strictly observed according to hospital policies.

Global Epidemiology

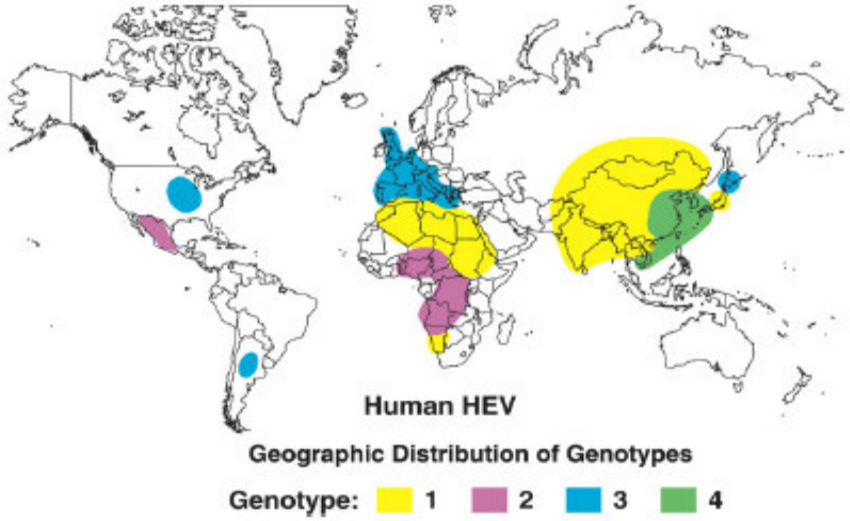
17. Apart from hepatitis A, hepatitis E is another important enteric infection causing large scale outbreaks in many parts of the world. Since the 1950s, epidemics of enterically-transmitted non-A, non-B hepatitis have been frequently documented in the Indian sub-continent. Large epidemics of hepatitis E have been reported in southeast and central Asia, northern and western Africa, and Mexico. In some highly endemic areas, HEV infection also accounts for more than 50% of acute sporadic hepatitis. Infection occurs more frequently in regions with hot climates. The highest prevalence of infection occurs in regions where low standards of sanitation promote the transmission of the virus. One of the largest waterborne hepatitis E outbreaks occurred in Kanpur city, Uttar Pradesh, India in 1991 where over 79,000 clinical cases were reported. The source of this outbreak was traced to faecal contamination of drinking water supplied from the river Ganges.[28]

18. In contrast to epidemics occurring in developing areas, sporadic cases of hepatitis E have been reported in developed countries and they are typically travellers returning from high HEV-endemic areas. However, serological surveys suggest a global distribution of HEV. The seroprevalence of antibody to HEV in non-endemic regions (e.g. the United States) has been much higher than anticipated (1-3%), considering that very few cases of hepatitis E are reported in these countries.[1] The prevalence of anti-HEV has also been demonstrated in 26% of swine veterinarians and 18% in normal blood donors in eight U.S. states.[29] Recent data generated by the use of improved assays for volunteer blood donors in other developed countries has shown the prevalence of anti-HEV antibodies to be 4% in New Zealand, 2.8% in Spain, 3.2% in France, 2.3% in Brazil, 2.0% in the Netherlands, and 2.6-3.9% in Japan.[10] In contrast, the prevalence of anti-HEV IgG is higher among volunteer blood donors in endemic countries: 7.8% in Iran, 12.1% in Albania, 16.9% in Saudi Arabia and 45.2% in Egypt. In China, a study conducted in 8 rural communities in southern China (where families keep pigs near their home) showed an overall anti-HEV seroprevalence of 43%.[30]

Geographic Distribution According to Genotypes

19. The genomes of many HEV strains from Asia, South and North America have been entirely or partially sequenced. The human HEV strains have at least four major groups and their geographic distribution was shown in Figure 1[2].

Figure 1. Geographic distribution of 4 hepatitis E virus genotypes. *(Source: Purcell RH, Emerson SU. Hepatitis E: an emerging awareness of an old disease. J Hepatol. 2008 Mar;48(3):494-503. With permission from Dr RH Purcell)*



- Genotype 1 – Asia (e.g. India, Pakistan, Myanmar, China, Kyrgyzstan) and North Africa
- Genotype 2 – Mexico, Africa
- Genotype 3 – North and South America, Europe and Asia (e.g. Japan)
- Genotype 4 – Asia (e.g. Japan, China, Taiwan, Vietnam)

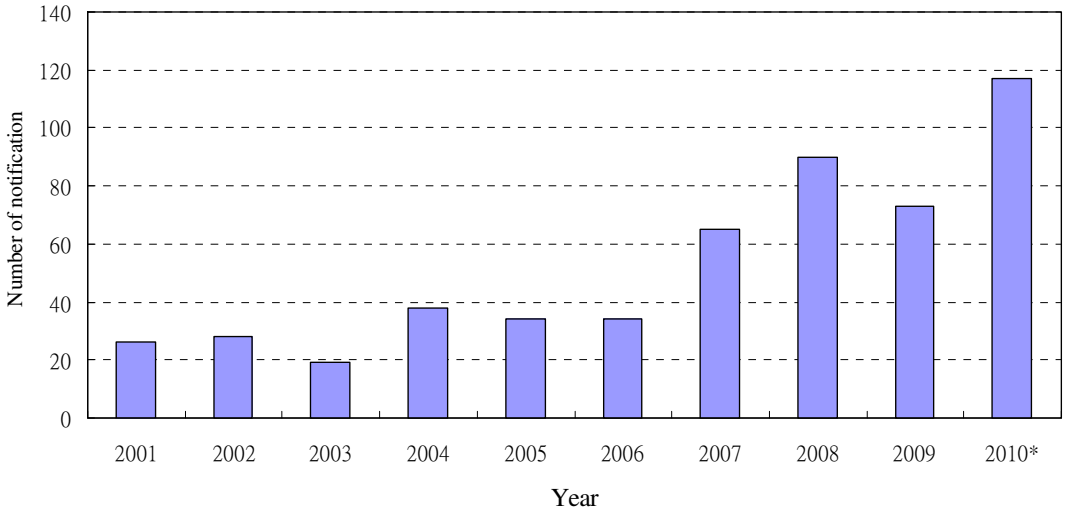
20. Human genotype 1 has been the major cause of water-borne epidemics in Asia and north Africa and a significant cause of sporadic disease, while human genotype 2 has been recovered from epidemics in Mexico and central Africa. Hepatitis E caused by genotypes 3 and 4 more commonly occurs in developed countries and on average affects older people.

Local Situation

21. Viral hepatitis has been a notifiable disease in Hong Kong since 1974. It was classified according to the viral aetiology since 1988 and hepatitis E became a category since 1996. In the last decade, an increasing trend of hepatitis E notification has been observed (Figure 2). The annual notification of hepatitis E infection in the past decade has ranged from 26 to 117 from 2001 to 2010. In 2010, there were 117 cases reported, which exceeded the annual total of the past 9 years in Hong Kong. In fact, hepatitis E became the most common cause of viral hepatitis notified in 2010, accounting for 44.3% of all viral hepatitis cases, followed by viral hepatitis B (27.7%) and viral hepatitis A (24.2%). A seasonal pattern was also observed with the peak occurring in February to April during the late winter/early spring (Figure 3). A small cluster of hepatitis E cases affecting a family involving 2 males (15 & 44 years) and 1 female (42 years) was identified in February and March 2009, they all reported consumption of high risk food items including pig liver and clam during

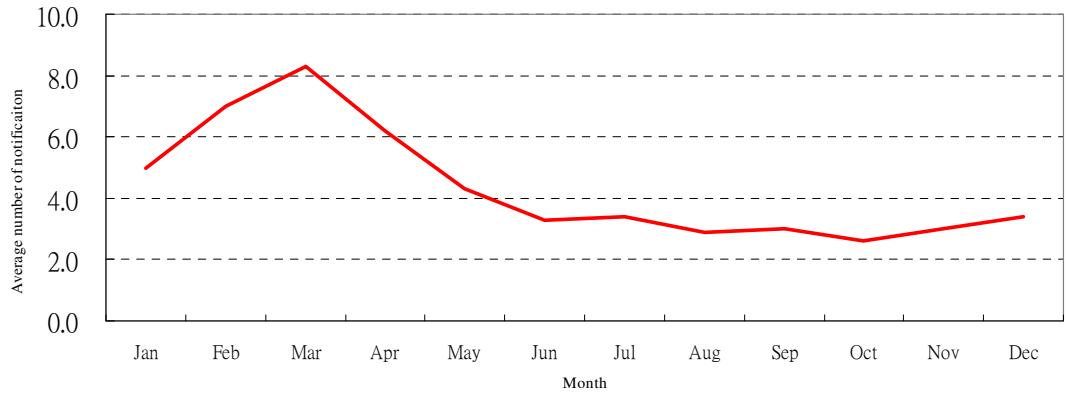
incubation period. The family also had shared multiple hotpot meals at home. Up till now there was no large scale outbreak or common linkage to food premises identified among the cases reported.

Figure 2. Number of notification of hepatitis E (2001 – 2010)



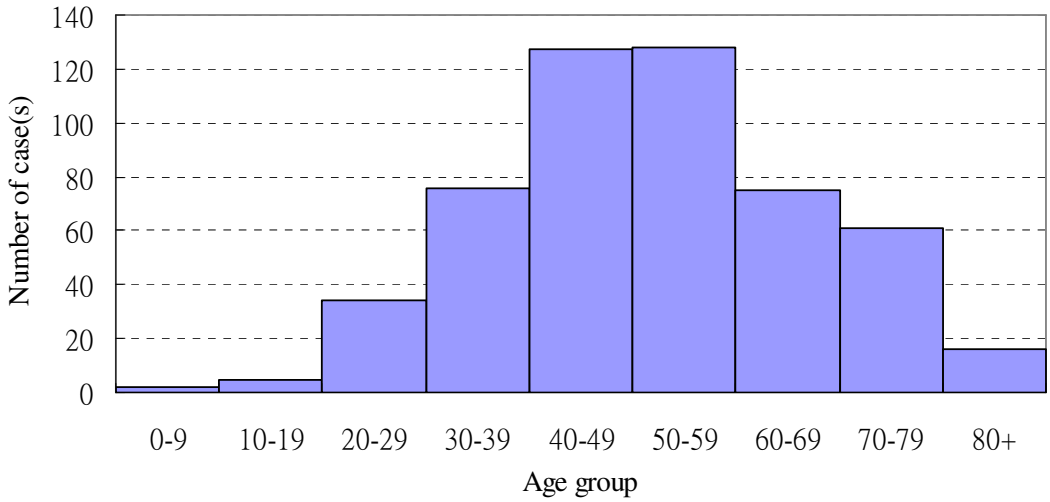
* Provisional figure

Figure 3. Average number of notification of hepatitis E by months (2001 – 2010)



22. Figure 4 shows the age group distribution of the cases reported from 2001 to 2010. During this period, a total of 524 cases were reported, affecting 351 males and 173 females (male to female ratio, 2:1). The majority of the patients were adults with a median age of 50.5 years. Most of the infections were sporadic and 87.8% of the cases were acquired locally. About 78.4% of patients were hospitalized and 12 cases died. Number of fatal cases per year ranged from 0 to 3 in 2001 to 2010. There were two male fatal cases recorded in 2010. The fatal cases (9 males and 3 females) had older ages with a median of 67.5 years. None of them were pregnant women. The case fatality rate was 2.3%, which is comparable with figures from other countries.

Figure 4. Age distribution of hepatitis E virus infection from 2001 to 2010.



23. In an uncontrolled review of the 116 cases notified between January 2007 and April 2008, 41% (n=47) recalled consumption of undercooked shellfish and 22% (n=25) had a history of eating raw fish or shellfish such as sashimi/sushi during the incubation period. Forty-one cases (35%) recalled eating under-cooked pork or pig offal. Further studies are required to establish the source of infection among these cases. None of the subjects had an occupational exposure to livestock or wild animals.

24. In Hong Kong, a community study in 2001 recruited 5017 adult Chinese subjects randomly through telephone interview and 936 attended for blood screening.[31] The overall prevalence of anti-HEV IgG was 18.8%, peaking at 27.7% in the 41-50 year-old group, and then declining thereafter.

Prevention and control for hepatitis E in Hong Kong

25. As most HEV infection is spread by the faecal-oral route, good personal hygiene, high quality public water supplies, proper disposal of sanitary waste and general food safety are the most important means of prevention. The following examines the existing prevention and control measures and discusses potential directions for improvement.

Disease Investigation and Outbreak Detection

26. Viral hepatitis has been a notifiable disease in Hong Kong since 1974 and hepatitis E became a category since 1996. All registered medical practitioners are required to report suspected or confirmed cases to the CHP for investigation and public health control measures. Cases are defined as persons with compatible clinical features and laboratory confirmation. History of exposure to food, travel and other risk factors are elicited to identify the possible source and mode of transmission. Food collaterals, travel collaterals

and household contacts are traced and put under medical surveillance. When a common food source is identified or suspected, the Food and Environmental Hygiene Department (FEHD) will be informed for further investigation of the food source so that control measures can be implemented.

Food and Water Control

27. Waterborne hepatitis E outbreaks and epidemics are well known to occur in many developing countries, although these have not occurred locally. To prevent such large scale outbreaks, it is important to ensure that the water supplies are of a high quality complying with drinking water standards, alongside the proper treatment and disposal of human waste. The Water Supplies Department has implemented Water Safety Plans based on preventive risk management and multi-barrier approach to ensure the safety of drinking water supply from source, through water treatment to consumer taps. All raw water undergoes stringent treatment including coagulation, flocculation, sedimentation, filtration and disinfection before being supplied to consumers. Each year more than 100,000 water samples are taken and tested from the entire supply and distribution system, including intakes, storage reservoirs, treatment works, service reservoirs, connection points, trunk mains and consumer taps, to ensure that the drinking water quality complies with the guideline values recommended by the World Health Organization's Guidelines for Drinking-water Quality. For the period April 2008 to March 2009, the average number of *E. coli* counts was 0 per 100ml for over 26,000 treated water samples taken for microbiological analyses. The Drainage Services Department maintains an effective system for sewage collection, treatment and disposal to ensure public safety and health in Hong Kong.

28. Though the specific role of various food items in hepatitis E infection remained unclear, shellfish and meat have a substantial risk of transmitting the virus. In Hong Kong, the Centre for Food Safety (CFS) of the FEHD is responsible for enforcement of food safety legislation, import control and food surveillance. At the import level, the importers are encouraged to obtain health certificates from respective health authorities of the exporting countries, certifying that the food has originated from an approved source and that it is fit for consumption. There is no food surveillance programme targeting hepatitis E in shellfish currently. Further review on the feasibility and cost-effectiveness of food surveillance for hepatitis E and other food safety measures will be necessary to minimize the chance of foodborne transmission of hepatitis E.

Immunization and Chemoprophylaxis

29. At present, there is no commercially available vaccine or immunoglobulin prophylaxis for the prevention of hepatitis E infection. It is recognized that an efficacious hepatitis E vaccine is feasible because there is

only one HEV serotype. There is one candidate recombinant hepatitis E vaccine that has been shown to be highly immunogenic and efficacious in preventing hepatitis E infection and hepatitis in rhesus monkeys.[32] A phase 2 trial has shown this vaccine to be effective in the prevention of hepatitis E in a high-risk population and to have minimal adverse events.[33] Further studies are required to determine long-term effectiveness, cost-effectiveness and tolerability in pregnant women and young children.

30. Immunoglobulin prepared from donors in non-HEV-endemic countries does not prevent HEV infection. However, experimental studies in primates suggest that passively acquired anti-HEV could modify HEV infection.[34] Immunoglobulin prepared from donors with high titers of anti-HEV or from neutralizing monoclonal antibodies to HEV may be useful for the prevention of hepatitis E during epidemics.[35]

Public health education

31. Hepatitis E is a relatively new infectious disease and awareness on this disease might be limited. The particularly high mortality in pregnant woman should be emphasized so that premature deaths and obstetric complications can be minimized. The Viral Hepatitis Preventive Service of CHP provides viral hepatitis health education through various channels including telephone hotline, internet, printed materials and health talks. A factsheet for hepatitis E is available from the CHP website.

32. It is important to emphasize that HEV infections are spread by the faecal-oral route and good personal and food hygiene could significantly reduce the risks of infection. The public should always wash their hands with soap and water after using the bathroom, changing diapers and before preparing food and eating. They should be advised to cook food adequately before consumption, as HEV survives in an internal temperature of 60^{o}C characteristic of rare-cooked meat.[36] Travellers to countries endemic for hepatitis E should observe strict personal, food and water hygiene, including the avoidance of drinking water and/or ice of unknown purity and the eating of uncooked shellfish, uncooked fruits and vegetables that are not self-peeled or prepared. Food handlers should be adequately trained to reduce the risks of foodborne infection from under-cooked seafood and meat.

Summary and Recommendations

33. Hepatitis E is an emerging infection and is a significant public health concern because of the potential risk of large outbreaks and relative naïve immune status of the Hong Kong population. The disease may cause significant morbidity and is potentially fatal, especially in pregnant women. However, the disease is preventable through stringent public health measures.

To ameliorate the impact of hepatitis E infection in Hong Kong, the following measures are recommended:

1. Disease surveillance and outbreak detection
   - Increase awareness of HEV infection amongst physicians to enhance its diagnosis and reporting, in order to facilitate early epidemiological investigation and outbreak detection.
   - Enhance the testing for hepatitis E in all acute hepatitis cases, especially those that test negative for hepatitis A and B.
   - Strengthen the use of molecular characterization to determine the local prevalence of different genotypes and to identify clustering of cases.
2. Food and water safety
   - Conduct further risk analyses to determine the risks of acquiring hepatitis E from consuming high risk food such as raw or undercooked shellfish and pig offal.
   - Explore the feasibility of implementing a food surveillance programme for hepatitis E.
   - Reinforce the importance of food safety and provide training for food handlers to reduce the risk of HEV and other enteric infections.
3. Public health education
   - Raise the awareness of general public about the risks of HEV and other enteric infections through various channels and advise the importance of good personal and food hygiene.
   - Advise public to cook food, especially seafood (e.g. shellfish), pork and pig offal thoroughly before consumption.
   - Advise travelers to adopt appropriate preventive measures when traveling to endemic areas.
4. Local study
   - Conduct regular review of serological data on hepatitis E to monitor the prevalence of infection and changes in its epidemiology.
   - Conduct studies to better understand the risk factors of HEV infection in the local Hong Kong population.

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