衞生防護中心
Centre for Health Protection

Scientific Committee on Enteric Infections and Foodborne Diseases

Epidemiology and Prevention of Hepatitis E

Preamble

Hepatitis E is a liver disease caused by the hepatitis E virus (HEV). HEV is a positive-sense single-stranded RNA virus of the *Orthohepevirus* genus under the *Hepeviridae* family (1). HEV comprises four species, namely *Orthohepevirus* A-D (also known as HEV-A to HEV-D), which circulate in different hosts (Table 1).

Table 1. Summary of some known hosts or sources of *orthohepeviruses* for humans (2).

Species	Animal Host or Reservoir
Orthohepevirus A (HEV-A)	Human, swine, wild boar, deer, rabbit, camel
Orthohepevirus B (HEV-B)	Chicken
Orthohepevirus C (HEV-C)	Rat, voles, ferret, brown bear
Orthohepevirus D (HEV-D)	Bats

2. While HEV-A is the species usually causing human infection, cases of human infection with HEV-C (also known as rat HEV) have been reported.

3. The World Health Organization (WHO) estimated that there were about 19 million cases of hepatitis E infections worldwide in 2021. This paper reviews the latest global and local epidemiology of hepatitis E (HEV-A infections only) and examines the public health measures to prevent and control the disease.

The pathogen and the disease

4. There are a total of 8 HEV-A genotypes (genotypes 1 to 8), but only four genotypes (genotypes 1 to 4) have been commonly associated with human infections (3). While HEV-A genotypes 1 and 2 exclusively infect humans, genotypes 3 and 4 can infect a wide spectrum of hosts including humans, pigs, etc. (4). A case of human infection with genotype 7 has been documented in a liver transplant patient from the Middle East who had regularly consumed camel meat and milk (5).

Routes of Transmission

5. Different HEV-A genotypes have distinct hosts, leading to differences in modes of transmission. HEV genotypes 1 and 2 are mainly transmitted by faecal-oral route via consumption of contaminated water. Genotypes 3 and 4, on the other hand, are considered zoonotic and are transmitted through direct contact with pigs or consumption of raw or undercooked meat (6).

Waterborne transmission

6. Waterborne transmission, via water contaminated with human faecal matter containing HEV, commonly results in large scale epidemics and sporadic cases (7). There is considerable epidemiological evidence of waterborne HEV transmission, such as the temporal relationship between the time of contamination of drinking water and onset of disease in epidemics (8, 9). The detection of HEV strains closely related to human infections in untreated sewage and water supplies further supports waterborne transmission of HEV (10-13). Although there has been no report of infection via contact with surface waters, it is theoretically possible if raw sewage water containing HEV is being discharged to surface waters (14).

Foodborne transmission

7. Consumption of raw or undercooked contaminated bivalve shellfish has been recognised as a potential source of HEV for human infection. The probable source of contamination of shellfish is from human sewage discharge or farm run-offs, since shellfish accumulates and concentrates pathogens in the course of their filter feeding activity (15). Studies conducted in Eastern China

and Japan have found 17.5% and 6.3% of the shellfish samples tested positive for HEV-A, respectively (16, 17). A retrospective study of an HEV outbreak on a cruise ship has found that consumption of shellfish while on board was the possible source of the outbreak (18).

8. Among the major hepatitis viruses (including hepatitis A, B, C and D), HEV is the only one with known animal reservoirs, making zoonotic transmission an important factor in human infection with HEV-A, particularly zoonotic foodborne transmission (14). Swine (i.e. pigs) is known to be one of the major reservoirs of HEV-A, with evidence showing that liver is the main target organ of HEV-A replication in pigs (19). Investigation of a hepatitis E outbreak in Japan suggested that inadequately cooked pig liver could be the source of infection, due to the close genetic identity between the HEV isolates recovered from the patients and those from pig liver samples (20). A study conducted in France in 2011 found that 68 out of 394 (17.3%) food samples of products containing raw pork liver tested positive for HEV RNA (21). A case-control study conducted in Southern France discovered significant genetic links between the HEV RNA sequences in pig liver sausages purchased from grocery stores and those recovered from autochthonous hepatitis E patients who ate pig liver sausages (22). A more recent study conducted in France in 2018 found 2.8% of slaughterhouse pig livers tested positive for HEV-A (23). All these results suggested the zoonotic risk of HEV-A infection through consumption of infected pork, pig offal and related products.

9. In Hong Kong, the Centre for Food Safety (CFS) of the Food and Environmental Hygiene Department (FEHD) performed a risk assessment study on HEV in fresh pig livers in 2010. Among the 100 pig liver samples collected from local slaughterhouse between January and May 2009, 16 out of 51 (31%) roaster (pigs around four months old) liver samples tested positive for HEV, whilst none of the 49 porker (pigs around six months old) liver samples tested positive (24).

10. According to another local study conducted from 2014 to 2016, HEV-A was detected in pig livers purchased from local markets with a prevalence of 1.5% (25). The study found that the HEVs detected in local human cases and food products from retail markets were genetically similar. This study also showed that HEV-A was also detected in locally purchased pig intestines

and oysters, but at lower prevalences (0.4% and 0.2% respectively). As such, foodborne transmission via raw or undercooked contaminated food products is considered to be a major route of HEV-A transmission in Hong Kong.

11. Apart from pigs, there are other animal reservoirs of HEV-A. An outbreak of acute hepatitis E infection in Japan has been linked to consumption of raw deer meat, as identical virus sequences were found between the HEV isolates recovered from the patients and the leftover deer meat (26). There were also reports of HEV in cattle, dairy cows and cow's milk in Chinese Mainland (27-29). Currently, the oral infectious dose of HEV-A for humans is still unknown (15).

Other routes of transmission

12. The possibility of transfusion-associated transmission of HEV has been a global concern. Transfusion recipients have developed acute hepatitis following receipt of infected blood products, with HEV nucleotide sequences from donor blood and recipient's blood being identical (30, 31). A retrospective study performed in the United Kingdom found that 0.04% of blood donations contained HEV RNA, and 42% of the recipients of viraemic donations had evidence of HEV infection (32). Prevalence studies conducted in Chinese Mainland and Japan have also found a significant proportion of donors to be HEV infected (33, 34). These findings suggest that blood transfusion could be a risk factor for HEV infection, yet the need for HEV screening of all blood donations remains controversial (35). The United Kingdom, Japan and the Netherlands are some of the countries known to perform universal donor screening for HEV (36).

13. Vertical transmission of HEV can lead to significant foetal loss, perinatal morbidity and mortality (37). In a study conducted in India (38), out of 26 pregnant women with HEV infection before delivery, 15 completed the pregnancy with normal deliveries and four delivered premature babies. Among the 19 babies delivered, 15 had evidence of HEV infection at birth, with six subsequently died from liver failure and another one died from premature birth (38).

14. Person-to-person transmission of hepatitis E is rare compared to hepatitis A, but cannot be excluded (9, 39).

Clinical Presentation and Course of the Disease

15. The incubation period usually ranges from 2 to 10 weeks, with a mean of 5 to 6 weeks. The clinical features of acute hepatitis E resemble those of other types of acute viral hepatitis. Patients initially present with non-specific symptoms such as fever, vomiting and loss of appetite, followed by abdominal pain, jaundice, tea-coloured urine, pale stools and enlarged liver. The symptoms usually last for 1 to 6 weeks. HEV infections are often asymptomatic, but the proportion of asymptomatic infections is currently unknown (40).

16. Hepatitis E is commonly considered an acute and self-limiting illness, but it can also be severe and result in fulminant hepatitis. Pregnant women are at increased risk of acute liver failure, and the case fatality rate can be up to 30% among pregnant women infected in their third trimester, especially with genotypes 1 and 2 (35). In general, hepatitis E infection does not progress to chronicity. Nonetheless, chronic hepatitis E infection has been reported in immunocompromised individuals, such as organ transplant recipients and HIV-positive patients (41- 43).

17. Extrahepatic manifestations have been reported in both acute and chronic hepatitis E infections, including but not limited to myocarditis, acute pancreatitis and polyarthritis (40). However, the most commonly reported complications are neurological, such as Guillain-Barre syndrome, neuralgic amyotrophy and encephalitis/ myelitis (44).

18. Peak viraemia occurs during the incubation period and early acute phase of the illness, with detectable HEV in blood and faeces before onset of the disease (45). Similar to other forms of acute viral hepatitis, patients with HEV infections have elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, bilirubin and gamma-glutamyltransferase (46, 47).

19. Regarding the severity of illness with respect to genotypes, there has been some evidence showing that genotypes 3 and 4 are less pathogenic in humans when compared to genotypes 1 and 2 (48). According to a Japanese study comparing the clinical features of acute hepatitis E by genotypes 3 and 4, genotype 4 had a higher peak alanine aminotransaminase levels and longer median duration of hospitalisation (49).

Susceptibility to Infection

20. Hepatitis E infections occur primarily in adults but different genotypes have slightly different affected populations. For HEV genotypes 1 and 2, the highest rates of symptomatic disease are reported in young to middle-aged adults (aged 15 to 40 years), with men being more likely to be infected than women (50, 51). For HEV genotypes 3 and 4, older men (median age 63 years) are affected, with men being three times more likely to be infected compared to women (50). Although hepatitis E infection is also seen in children, most of them are either asymptomatic or suffer from mild illness without jaundice (51). The gender difference in infection is also not seen in children (45).

21. The high risk groups for HEV infection include adult men, persons who have pre-existing liver disease, travellers to endemic areas, and persons working with animals such as pigs, cows, sheep and goats from which they may be infected (50, 52). Pregnant women, particularly those in the third trimester of pregnancy are especially susceptible to fulminant hepatitis and high mortality rates. Pregnant women are also more likely to experience adverse outcomes such as abortion, premature delivery or neonatal death if infected with HEV (40).

Laboratory Diagnosis and Treatment

22. The diagnosis of acute HEV infection mainly depends on clinical features and exclusion of other causes of acute hepatitis, especially hepatitis A. Acute hepatitis E infection is usually confirmed by demonstration of anti-HEV IgM in serum by ELISA or detection of HEV RNA by PCR in serum or stool. HEV RNA is detectable in blood and stool after onset of symptoms and lasts for up to four weeks and six weeks respectively (40). Nevertheless, absence of detectable HEV RNA does not necessarily indicate the lack of infection, due to numerous factors such as minimal viral RNA quantity in collected samples, narrow viraemic window (40). On the other hand, anti-HEV IgM level usually peaks at clinical presentation and remains high for about eight weeks before it starts to decline rapidly. Anti-HEV IgG level starts increasing after onset of symptoms, reaches a peak in about four weeks, and remains at a high level for over a year (53). For immunocompromised individuals, HEV RNA should always be tested if HEV infection is suspected, because seroconversion could be delayed in these individuals (54). Therefore, the optimal diagnosis of acute

HEV infection should be achieved by a combination of molecular and serological testing (53).

23. Treatment for acute hepatitis E infection is mainly supportive, with most patients recovering spontaneously. There is no effective antiviral or specific therapy which can alter the course of acute hepatitis E infection. Ribavirin has been used for off-label treatment of HEV infection (55). Hospitalisation is required for patients with fulminant hepatitis and should be considered for symptomatic pregnant women.

Global Epidemiology

24. The WHO estimated that there were over 19 million cases of hepatitis E infections worldwide in 2021 (51). It is also a leading cause of acute viral hepatitis in some areas, including Chinese Mainland (56, 57). A meta-analysis published in 2020 estimated that the global HEV viral RNA-positive rate in general population was 0.20% (58). After stratifying the data among continents excluding Antarctica, the highest anti-HEV IgG seropositive rate was found in Africa, followed by Asia, Europe, North America, South America and Oceania.

25. The geographic distribution of HEV globally varies depending on the distinct genotypes. Genotypes 1 and 2 are prevalent in developing countries, such as those in Africa and Asia (40). Genotypes 3 and 4, on the other hand, are prevalent in developed countries. Such distribution is due to the different modes of transmission among different genotypes. Genotypes 1 and 2 are typically transmitted via the faecal-oral route, often resulting in outbreaks in areas with poor sanitation through contamination of drinking water. Genotypes 3 and 4 are transmitted through consumption of undercooked meat, consumption of contaminated crops or direct contact with animals such as pigs, causing sporadic and autochthonous cases in developed countries (50).

<u>HEV genotypes 1 and 2</u>

26. HEV genotype 1 is present in South Asia (e.g. India, parts of China, Bangladesh) and most countries in sub-Saharan Africa. In 1955, a large outbreak of hepatitis E caused by HEV genotype 1 was recorded in Delhi, India. Since then, large outbreaks have been commonly reported in India, Pakistan,

Nepal, Bangladesh and other countries in South Asia (59). These outbreaks were caused by waterborne transmission of HEV genotype 1. Countries in Africa including Egypt and the Central African Republic have also reported outbreaks of HEV genotype 1, mostly linked to contaminated water and humanitarian crises (59). It is believed that improved sanitation and water treatment has eliminated waterborne outbreaks of HEV genotype 1 in the United States and Europe (59).

27. The first outbreaks linked to HEV genotype 2 were reported in 1980s in Mexico. Subsequently, outbreaks have been recorded in Namibia, Chad, Sudan, Nigeria and the Central African Republic (23, 60-63).

HEV genotypes 3 and 4

28. In contrast to epidemics occurring in developing areas, hepatitis E infections in developed countries were considered rare and largely confined to travellers returning from HEV hyperendemic areas (64). However, sporadic cases of hepatitis E without recent travel history have been becoming more common in developed countries in the past two decades, leading to recognition that autochthonous HEV infections caused by genotypes 3 and 4 are a clinical concern in developed countries (45).

29. Genotype 3 is now present in Europe, the United States, Japan, New Zealand and Australia, while genotype 4 is mainly found in Chinese Mainland and Japan (59). According to an assessment study funded by the European Centre for Disease Prevention and Control, hepatitis E, predominantly HEV genotype 3, was the major cause of acute viral hepatitis in France, Germany, England and Wales, and the Netherlands during 2014 and 2015, overtaking hepatitis A (65).

Situation in Chinese Mainland

30. In the twentieth century, the majority of hepatitis E cases in Chinese Mainland were attributed to HEV genotype 1, linked to waterborne outbreaks. However, the most common genotype of HEV human infection has been replaced by genotype 4 in the past two decades, both in Northern and Southern China (66, 67). The shift from genotype 1 to genotype 4 is likely driven by zoonotic foodborne transmission of genotype 4, suggesting that hepatitis E in

Chinese Mainland is shifting from hyperendemicity to low endemicity (67).

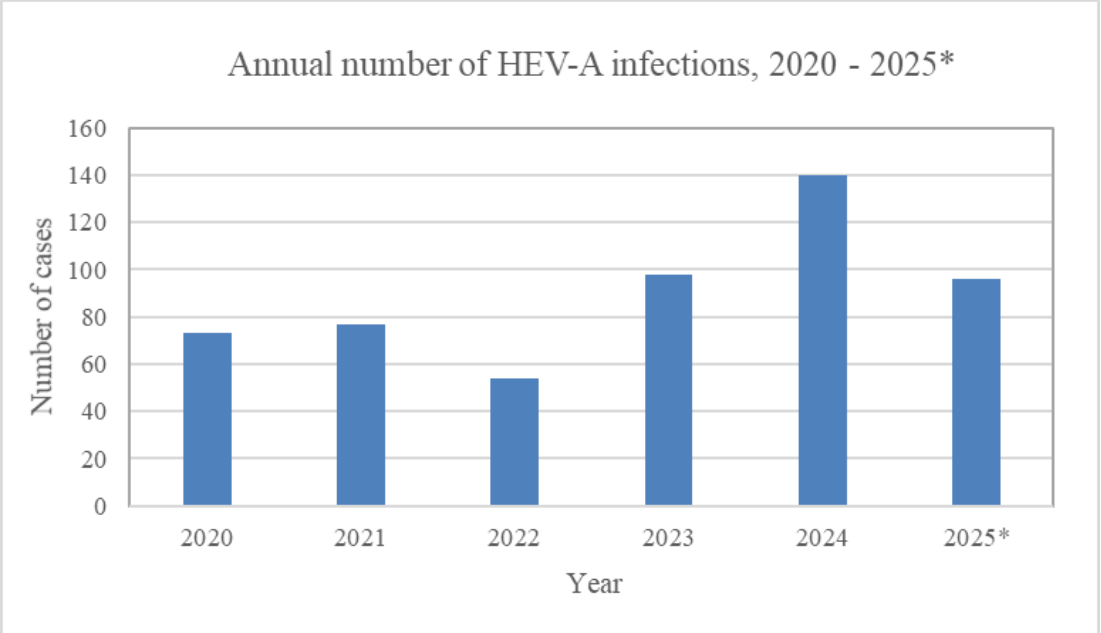
31. According to a systematic review and meta-analysis including 152 studies published between 1997 and 2022, the pooled seroprevalence of anti-HEV IgG in China was 23.17% (68).

Local Situation

32. Viral hepatitis, including acute hepatitis caused by HEV, is a notifiable disease under the Prevention and Control of Disease Ordinance (Cap 599). A confirmed case of acute hepatitis E infection is defined by a clinically compatible case with positive anti-HEV IgM test results or detectable HEV RNA.

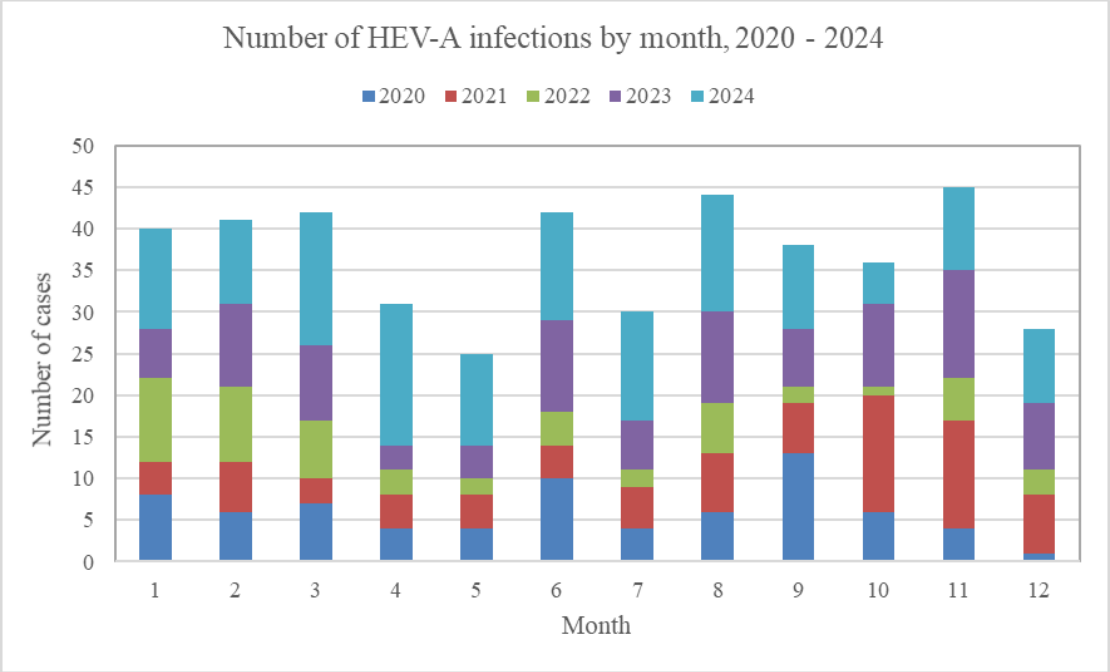
33. In the past five years (2020 to 2024), the Centre for Health Protection (CHP) of the Department of Health recorded a total of 442 confirmed cases of acute hepatitis E infection caused by HEV-A, with annual number of cases ranging from 54 to 140 (Figure 1). In 2025 (as of 31 October), 96 cases have been reported so far. Hepatitis E has become the most common cause of viral hepatitis notified since 2019. In 2024, HEV accounted for 63.2% of all viral hepatitis cases, followed by viral hepatitis A (23.3%), viral hepatitis C (8.5%) and viral hepatitis B (4.9%).

Figure 1. Annual number of HEV-A infection, 2020 – 2025 (*data as of 31 October, 2025).



34. The 442 involved 266 males and 176 females (male-to-female ratio 1:0.66), with ages ranging from 20 to 102 years (median: 62 years). Most cases (405, 91.6%) were locally acquired infections, while 12 cases (2.7%) were imported infections. The places of infection of the imported cases included Chinese Mainland (six cases), Pakistan (two cases), Germany (one case), India (one case), Japan (one case), and Thailand (one case). The places of infection for the remaining 25 cases (5.7%) could not be determined either because the patients had stayed both in and outside Hong Kong during the incubation period, or due to loss to follow-up. Cases were reported throughout the year with no obvious seasonal pattern (Figure 2).

Figure 2. Number of HEV-A infections by month (2020 - 2024)



35. The majority of cases (369 cases, 83.5%) required hospitalisation, with a median length of stay of eight days. At least 26 patients (5.9%) developed liver failure. A total of four fatal cases were recorded (case fatality rate of 0.9%). For the four fatal cases, their ages ranged from 71 to 78 years (median: 77 years), and all were known to have underlying illnesses. There was no pregnant woman among all cases recorded between 2020 and 2024.

36. Over 70% of the cases (331 cases) had underlying chronic illnesses, including 10 immunocompromised patients, such as organ transplant recipients

and HIV carriers. At least 120 cases (27.1% of total cases) had some degree of pre-existing liver disease, such as chronic hepatitis B carrier, fatty liver, etc.

37. Regarding risk factors for infection, 384 (86.9%) and 186 (42.1%) patients reported consumption of pork and pig liver during the incubation period, respectively. Among those who consumed pig liver, most had consumed it with hotpot, congee, or noodles, with 20 cases (10.8%) claiming that the pig liver eaten was rare or undercooked. Besides, 190 (43.0%) patients reported consumption of shellfish during the incubation period. The most common shellfish consumed was clams (104, 54.7%), followed by oysters (98, 51.6%) and razor clams (54, 28.4%). Among those who had consumed shellfish, 37 (19.5%) reported consuming it raw or undercooked.

Seroprevalence

38. According to the estimation of the Population Health Survey (PHS) 2020-22, 5.5% of the participants in the general population aged between 15 and 84 tested positive for anti-HEV IgG (69). Analysis by age groups have found that the proportion of people infected with HEV increased with age, from 1.9% for those aged 15 – 24 to 7.7% for those aged 65 – 84.

Prevention and control for hepatitis E in Hong Kong

39. The prevention and control measures for hepatitis E infections in Hong Kong include disease surveillance, epidemiological investigation and public education. The latest information on hepatitis E vaccine will also be discussed.

Disease Surveillance and Epidemiological Investigation

40. Viral hepatitis has been a notifiable disease in Hong Kong since 1974 and hepatitis E became a distinct 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 high risk food, travel history 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 food source related to food premises is identified or suspected, the FEHD will be informed for further investigation of the food source so that control measures can be implemented.

Public Health Education

41. Since foodborne transmission is considered to be the major route of transmission of HEV-A in Hong Kong, together with well-established faecal-oral transmission of HEV-A, safe food preparation and good personal hygiene are the most important means of prevention of hepatitis E.

42. As promulgated by the WHO, the CHP and the CFS promote "Five Keys to Food Safety" to prevent foodborne diseases. As shellfish and meat have a substantial risk of transmitting HEV, it is important to ensure complete inactivation of the virus during food preparation. In general, the stability of the virus decreases with increasing temperature. Members of the public are advised to cook food adequately before consumption, as HEV has been shown to be moderately resistant to heat inactivation up to 60^{o}C, which is the typical internal temperature of rare-cooked meat (70). Complete inactivation was achieved at 71^{o}C for 15 minutes in most studies (14). Food handlers should also be adequately trained to reduce the risk of foodborne infection from handling uncooked seafood and meat.

43. Travellers to countries endemic for hepatitis E should observe strict personal, food and water hygiene, including avoidance of drinking water and/or ice of unknown purity and the eating of uncooked shellfish, uncooked/ undercooked meat, raw fruits and vegetables that are not self-peeled or prepared (40).

44. It is important to emphasise that HEV infections can be spread by the faecal-oral route and good personal hygiene could significantly reduce the risk 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.

45. The CHP and the CFS have prepared a variety of health education materials such as fact sheets on hepatitis E, pamphlets and posters on hand hygiene, food and water safety, and ways to prevent foodborne diseases, to raise awareness among the general public. Relevant information is disseminated

through various online and offline channels including the websites, press releases and the media.

Vaccination

46. A recombinant hepatitis E vaccine based on HEV-A, Hecolin (HEV 239), has been developed and licensed in Chinese Mainland in 2011 (71). The vaccine has been found to provide long-lasting and cross-genotype protection while being safe (72). This is currently the only hepatitis E vaccine, and it is not available elsewhere apart from Chinese Mainland and Pakistan (73). In a position paper published in 2015, the WHO did not recommend routine use of the vaccine due to lack of data (74). In 2022, in response to a hepatitis E outbreak in Bentiu, South Sudan, the first mass hepatitis E vaccination campaign was implemented (75). More than 24 000 people, including pregnant women, were vaccinated in the three-round campaign (51).

47. A Phase IV trial in Bangladesh examined the safety of Hecolin vaccine in women of childbearing age. It found that women vaccinated shortly before or during pregnancy had an increased risk of spontaneous abortion compared with the control group (76). However, re-analysis of data from the mass vaccination campaign in South Sudan and a randomised controlled trial conducted in 2013 found no evidence of increased risk of miscarriage in vaccinated women (77-79). In response to the contradictory results, the Hepatitis E Vaccine Safety Working Group was formed in January 2024 and the outcomes were presented at the Strategic Advisory Group of Experts on Immunization (SAGE) meeting in March 2024. The WHO Global Advisory Committee on Vaccine Safety (GACVS) meeting in May 2024 concurred with the conclusions and recommendations of the Working Group, that the risk of spontaneous abortion associated with Hecolin should be further investigated (80). However, given the high risk of severe disease in pregnant women, the benefits of vaccinating women of childbearing age outweigh the potential risk in fragile, conflict-affected and vulnerable settings (80).

48. A second recombinant hepatitis E vaccine, ZyVac-HEV, developed by Zydus Lifescience Ltd. is currently in a phase II clinical trial (81).

Summary and Recommendations

49. Hepatitis E is a significant public health concern because of the increasing incidence globally, and its zoonotic risk from the wide host range of genotypes 3 to 8. The disease may cause significant morbidity and is potentially fatal, especially in immunocompromised individuals and pregnant women. Surveillance systems and public health measures are in place for the prevention and control of hepatitis E infection in Hong Kong.

50. Public health education remains a crucial component of the prevention of hepatitis E, by raising awareness among the general public about the risks of HEV through various channels and emphasising the importance of good personal and food hygiene. It is of utmost importance to advise the public to cook food, especially seafood (e.g. bivalve shellfish), pork and pig offal thoroughly before consumption. Travellers should be advised to adopt appropriate preventive measures when traveling to endemic areas.

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November 2025

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