衞生防護中心
Centre for Health Protection

# Scientific Committee on Vector-borne Diseases

## Epidemiology, Prevention and Control of Human Infection of Rat Hepatitis E Virus in Hong Kong

### Purpose

This paper reviews the latest epidemiology of human infection of rat hepatitis E virus, and examines the preventive and control strategies in Hong Kong.

### Background

2. Hepatitis E is an inflammatory liver disease caused by Hepatitis E virus (HEV). It is estimated by the World Health Organisation (WHO) that there are 20 million HEV infections in the world every year (1). The disease is found worldwide but most commonly in Asia.

3. Hepatitis E virus is under the *Orthohepevirus* genus of the *Hepeviridae* family, which can be further divided into four species (Table 1). The usual HEV causing human infection belongs to *Orthohepevirus A* (HEV-A). The three other species are *Orthohepevirus B* that circulates in birds, *Orthohepevirus C* (HEV-C) in rats and ferrets, and *Orthohepevirus D* in bats (2).

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

Table 1. Summary of some known hosts or sources of orthohepeviruses for human (3).

Rat Hepatitis E virus

4. HEV-C was first discovered in 2010 from faecal and liver specimens from rats (4, 5), and a few genotypes of HEV-C have been identified so far[1] (6, 7).

5. HEV-C1 or *Rocahepevirus ratti*, a genotype commonly known as rat hepatitis E virus, has been detected in multiple wild rat species across at least three continents (Asia, America and Europe) since its discovery (3). There were studies showing that HEV-C1 also has the potential to infect other mammals, including Asian mush shrew, Syrian brown bear and other non-rat rodents (3).

6. HEV-C1 only shares 50% to 60% nucleotide identity with HEV-A such that it was previously not considered to have the ability to infect human (8, 9). However, studies conducted among forestry workers in Germany and febrile inpatients in Vietnam have demonstrated the zoonotic potential of HEV-C1, that possible subclinical HEV-C1 infection was found in some study subjects (10, 11). In December 2018, the Department of Microbiology of the University of Hong Kong (HKU) published the first report of human case of HEV-C1 infection in a liver transplant recipient (12).

Clinical features

7. Most hepatitis E infections are asymptomatic or self-limiting.

[1] In addition to HEV-C1, HEV-C2 was reported in Western polecats from Netherlands in 2012, and two novel genotypes (preliminarily named HEV-C3 and HEV-C4) were discovered in Chevrier's field mouse and Pere David's Vole in China.

However, HEV infection in high-risk individuals such as elderly with major underlying illnesses (especially transplant patients), pregnant women, people with chronic liver diseases and glucose-6-phosphate dehydrogenase ("G6PD") deficiency may develop severe illness (13, 14). The case fatality rate in the general population ranges from 0.1% to 4%, but it could go up to 10% to 40% for pregnant women with severe HEV infection (15-18). Hepatitis E infection can also become persistent in immunocompromised individuals (19).

8. As for rat hepatitis E infection, while there is currently insufficient literature on its clinical features, some suggested that it is clinically indistinguishable from general HEV infections (20). The common symptoms include fever, abdominal pain, anorexia and jaundice (21). Current evidence supports that HEV-C1 is capable of causing both acute and persistent hepatitis, as well as subclinical infection in human (3). A local study on eight patients with HEV-C1 infection suggested that it is generally milder than HEV-A hepatitis, with most patients showing mild liver dysfunction with lower alanine transaminase (ALT) and bilirubin levels (6).

Mode of transmission

9. HEV-A is mainly transmitted through the faecal-oral route, for example, following faecal contamination of drinking water. Foodborne transmission of HEV-A is also possible given the virus has been detected in pig livers (22, 23).

10. As for HEV-C1, there is no scientific information to determine the exact mode of transmission to human at the moment (6). Possible routes of transmission include ingestion of food/ water and exposure to environment/ objects contaminated by rodents or their excreta, and direct contact with rodents or their excreta. Studies have found high homology between the viral sequences found in some of the human cases and those identified in rodents captured from the same areas, suggesting direct or indirect contact with rodents is likely the route of infection; though none of the cases reported direct contact with rodents (6, 20). Besides, the possibility of an intermediate animal host between rodents and human cannot be excluded, such as pigs and ruminants (6, 24). The risk of HEV-C1 being transmitted through blood transfusion and/ or organ

transplantation is also undetermined (3).

Diagnosis

11. Diagnosis of hepatitis E depends on the clinical feature and the exclusion of other causes of acute hepatitis, especially hepatitis A virus. In general, presence of anti-HEV-A IgM or detectable HEV-A RNA is sufficient to confirm HEV-A infection. For rat hepatitis E infection, serological method relying on antibodies against HEV-A has the risk of being false negative due to the antigenic divergence between HEV-A and HEV-C1 (25). Currently, rat hepatitis E infection can only be confirmed by the detection of HEV-C1 RNA in blood by reverse transcriptase-PCR (RT-PCR) technique.

Treatment

12. As the disease is usually self-limiting in immunocompetent persons, mainstay of treatment is supportive care. Hospitalization is required for patients with poor oral intake or fulminant hepatitis, and should be considered for infected pregnant women. Medications that can adversely affect liver function should be avoided, such as paracetamol. Immunosuppressive therapies should be reduced if possible.

13. Ribavirin therapy has shown to be an effective treatment for HEV-C1 infections, even in immunocompromised patients, with viremia cleared in most patients within three months of therapy (21).

Vaccine

14. A recombinant hepatitis E vaccine based on HEV-A, Hecolin, has been developed and licensed in China in 2011 (26). This is currently the only hepatitis E vaccine, and it is not available elsewhere apart from China and Pakistan (27). The WHO does not recommend routine use of the vaccine due to the significant lack of data (28). As of 2022, the vaccine had been used in China for individuals travelling abroad to high risk areas and was used in a HEV outbreak response campaign at South Sudan in March 2022 (1, 29).

15. There is little evidence on the effectiveness of Hecolin against rat hepatitis E infection in human. A study on rats suggested that HEV-A vaccination is not protective against HEV-C1 (25).

## Global Situation

16. The circulation of HEV-C1 in rats has been described worldwide (3, 20), but there was no report of human infection before 2018. Since the first case of human HEV-C1 infection reported in Hong Kong in 2018, three other countries have reported cases of human rat hepatitis E infection. In 2019, Canada reported a severe case of acute hepatitis caused by HEV-C1, who had likely contracted the infection in Africa (30). The HEV-C1 strain found in this patient was genetically distant from the first reported case in Hong Kong. Spain also reported three cases of HEV-C1 infection in 2022, with two of them showed self-resolved acute hepatitis (20); the remaining case involved an immunosuppressed individual who presented with severe acute hepatitis and passed away nine days after hospitalisation. In 2023, a French research team reported another case of chronic infection caused by HEV-C1 in a renal transplant recipient (31). Though retrospective screening studies of archived human blood samples for HEV-C1 RNA have been conducted in France and Germany, no case was found (32, 33). The true global prevalence of human HEV-C1 infection remains uncertain.

## Local situation

HEV-C1 infection in human

17. Viral hepatitis (including hepatitis E) is a statutorily notifiable disease in Hong Kong. Medical practitioners are required to report suspected or confirmed cases of hepatitis E to the Centre for Health Protection (CHP) of the Department of Health (DH) for investigation and follow-up actions. For the past 10 years, the annual number of hepatitis E cases ranged from 44 to 96 (median 82) (Figure 1). There has been no apparent upsurge of overall hepatitis E infection observed since the first report of human rat hepatitis E infection in 2018.

18. As of July 31, 2023, a total of 19 cases of human infection of rat HEV have been recorded by the CHP since 2018 (Figure 1). The 19 cases involved 15 male and four female patients aged between 17 and 89 years (median 67 years).

19. All cases had underlying illnesses, and 14 of them (73.7%) with immunocompromised conditions. Nearly half of the patients (47.4%) were asymptomatic, while the remaining patients presented with typical viral hepatitis symptoms such as anorexia (26.3%), malaise (26.3%), fever (15.8%) and jaundice (10.5%). Eleven cases (57.9%) required hospitalisation, and three patients passed away due to unrelated causes.

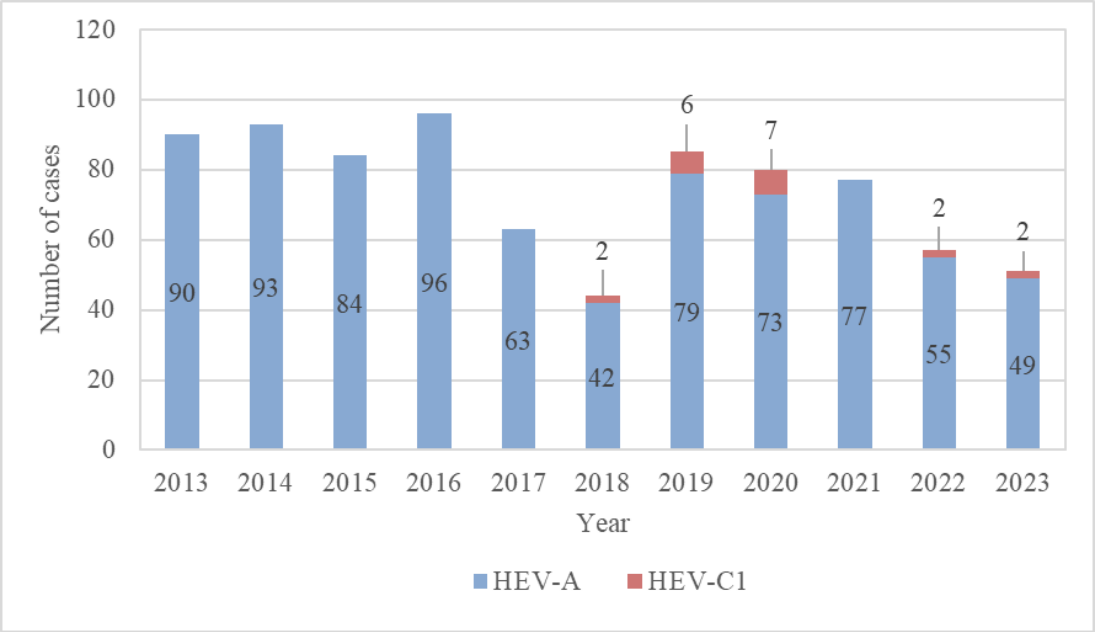


Figure 1. Number of hepatitis E (HEV-A) and rat hepatitis E (HEV-C) cases since 2013 (as of July 31, 2023).

20. According to the CHP's epidemiological investigation, the 19 patients resided in eight different districts in Hong Kong, including Wong Tai Sin (five cases), Kowloon City (four cases), Kwai Tsing (two cases), Southern (two cases), Tuen Mun (two cases), Tai Po (two cases), Kwun Tong (one case) and Yuen Long (one case).

21. Majority (84.2%) had no travel history during the incubation period; one patient had travelled to Taiwan and Korea and the other one to Shenzhen regularly, and there was one patient with unknown travel history due to loss to

follow-up.

22. None of the patients reported to have consumed raw pork or pork offal, but three patients (15.8%) reported contacting raw pork at wet market or during cooking process. All patients did not recall having direct contact with rodents or their excreta, but three (15.8%) reported having seen rodents or suspected rodent excreta in the vicinity of their residence, workplace or restaurant visited.

23. Investigations by the CHP revealed that they were all sporadic cases with no epidemiological linkage, and no symptomatic home contacts were identified.

24. Sources of infection were investigated by the Pest Control Advisory Section (PCAS) of the Food & Environmental Hygiene Department (FEHD). Investigation for rodent activity and corresponding control measures around the patients' home or vicinity, workplace as well as other possible sites of contraction had been carried out. Investigation results from the most recent case in May 2023 showed signs of rodent infestation such as rodent droppings in the patient's residence and workplace.

<u>HEV-C1 infection in rats</u>

25. It was first reported in 2018 when researchers retrospectively detected HEV-C1 RNA in an archived sample of a street rat collected in 2012 (12). In a later study, 186 rats were captured from 12 districts between January 1, 2017 and June 30, 2019, of which seven were tested positive for HEV-C1 RNA. One HEV-C1 isolate from a rat captured in 2019 was closely related to the strain that infected seven human HEV-C1 cases in Hong Kong (6).

26. On the other hand, FEHD has on-going collaboration with the HKU's team to screen for HEV-C1 in rat samples captured in Hong Kong. In 2022, out of the 175 rats screened, 15 (8.6%) were tested positive for HEV-C1 RNA. Follow-up rodent control operations had been conducted in the surrounding areas where HEV-C1 positive rodents were captured.

## Prevention and Control Measures

Enhanced public health surveillance

27. Since November 2018, the DH has enhanced the surveillance of HEV by conducting further testing on HEV-C1 in the samples collected from HEV patients, in addition to regular testing on HEV-A (34).

Epidemiological investigation and control

28. The CHP conducts epidemiological investigation for all notified viral hepatitis E cases including rat hepatitis E. Cases of rat hepatitis E infection are defined as persons with compatible clinical features and the detection of HEV-C1 RNA in blood by RT-PCR.

29. The rat hepatitis E patient as well as the attending physician will be interviewed for relevant clinical and epidemiological information. History of exposure to food, travel, contact with rodents and other risk factors are elicited to identify possible source(s) and mode of transmission.

30. Health education on personal, environmental and food hygiene, with emphasis on cooking food thoroughly before consumption, would be provided to rat hepatitis E patients and their close contacts. If the patient is a food handler, FEHD would be informed to suspend the patient from food handling work for two weeks after onset of symptoms.

31. For all cases of human infection with HEV-C1, the CHP would also inform the PCAS of the FEHD to carry out rodent survey and control measures as deemed necessary.

Rodent control

32. Rodent control is important in the prevention and control rodent-borne diseases. The Government has all along attached great importance to anti-

rodent work. Within the Government, the interdepartmental Pest Control Steering Committee (PCSC) sets the overall directions for pest control efforts. It also coordinates and oversees the implementation of measures by the relevant bureaux and/or departments (B/Ds), which carry out targeted rodent prevention and control work in the venues under their purview. A Cross-sectoral Territory-wide Anti-rodent Action has been launched by the end of 2022 under the steer of the PCSC with a view to engage relevant B/Ds and stakeholders such as property management, private pest control sector, construction contractors, etc. to strengthen rodent prevention and control work.

33. As the leading department, the FEHD has also been conducting rodent control work in public places, providing technical support to relevant B/Ds, as well as conducting the Rodent Infestation Survey (RIS) regularly since 2000 to monitor rodent infestation in Hong Kong. The Rodent Infestation Rate generated by the survey can help gauging the general situation of rodent infestation in individual survey locations and form the basis for devising anti-rodent measures (35). The results of RIS also serve as reference for assessing the overall efficacy of rodent prevention and disinfestation work. To improve the accuracy and representativeness of the surveillance, FEHD is working with HKU for enumerating a new index by taking into consideration various factors such as rodent complaints and data collected from the thermal camera monitoring system.

Personal and environmental hygiene

34. To prevent rat HEV infection, members of the public are urged to maintain good personal, food and environmental hygiene. High-risk individuals, such as elderly persons with a major underlying illness (especially those who have undergone organ transplantation), pregnant women, patients with chronic liver disease and patients with G6PD deficiency, may develop a serious illness if infected with rat HEV, so they should exercise extra caution.

35. As rodents can transmit multiple diseases to humans directly and indirectly, members of the public should actively participate in rodent prevention and control work. The most effective way is to eliminate the three survival conditions of rodents, namely food, harbourage and passages (36), i.e.

to eliminate food sources and hiding places of rodents, as well as blockage of their dispersal routes. It is also important to avoid direct contact with rodents, and wear gloves and face mask if handling of dead rodents is necessary.

Public health education

36. Risk communication of rodent-borne diseases is regularly conducted by the CHP and FEHD through various channels including press releases, health education materials, social media, announcements in the public interest, etc. Health information related to prevention of rat hepatitis E infection is available on the CHP website (37). The CHP has published feature articles on rat hepatitis E in its on-line publication "Communicable Diseases Watch" to provide healthcare professionals and members of the public with up-to-date news and knowledge.

## Discussion and way forward

37. Rat hepatitis E virus is an emerging cause of acute and chronic hepatitis in human, not limited to immunocompromised individuals. The global burden of HEV-C1 infection is under-recognised due to blind spots of the current diagnostic tests (21). In Hong Kong, the surveillance for human infection of rat hepatitis E has been enhanced since late 2018, with sporadic cases being detected throughout the years.

38. Over 70% of the rat hepatitis E cases recorded in Hong Kong involved immunocompromised individuals. However, as most HEV-C1 infections in human are asymptomatic, the disproportionate burden in immunocompromised patients could be a result of more frequent blood taking and closer follow-up of this population, that infections are more likely to be detected and investigated (38). The CHP will keep in view the latest development in human rat hepatitis E surveillance, including the development of serological tests to facilitate a wider scope of HEV-C1 seroprevalence studies, in order to assess the true burden of rat hepatitis E infection in Hong Kong.

39. Asymptomatic or subclinical HEV-C1 infection without deranged liver function constitutes a potential threat to transfusion safety, as the current

screening platform of blood products cannot detect HEV-C1 infection (6, 39, 40). Potential modes of transmission, including organ and blood transfusion, should be further researched in order to assess the risk of transmission of the disease.

40. Although the exact route of HEV-C1 transmission is still elusive, it is likely that humans are infected through direct contact with rats or indirectly through environmental surfaces contaminated by rat droppings (6). Therefore, rodent control and environmental hygiene remain the top priorities in the prevention and control of human infection of rat HEV. It is also important to continue with the surveillance of HEV-C1 infection in commensal rats to identify high-risk areas, particularly as the Rodent Infestation Rate alone does not accurately reflect the risk of HEV-C1 infection (6).

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