衞生防護中心
Centre for Health Protection

Scientific Committee on Vector-borne Diseases

Review of Hantavirus Infection in Hong Kong

Purpose

This paper reviews the global and local epidemiology of hantavirus infection and examine the prevention and control measures in Hong Kong.

The Pathogen and the Reservoir

2. Hantaviruses belong to the genus *Hantavirus*, family Bunyaviridae[1]. They can cause haemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS) in human[1-4].

3. Haemorrhagic fever with renal syndrome has been described prior to World War II in Manchuria along the Amur River[2], in Russia and Sweden in 1930s[3]. Between 1950 and 1953, large human outbreaks have been reported when 3000 US soldiers were stricken with the disease during the Korean War [1-3] and the fatality ranged from 6-8% to over 33% in some small outbreaks[1]. However, the causative virus has not been isolated until 1978 from a field rodent (*Apodemus agrarius*) near the Hantaan river[3,5] and was subsequently termed Hantaan virus[6]. HFRS was later found to be caused by other viruses as well, including Seoul, Puumala and Dobrava virus, affecting more than 200,000 people per year in Europe and Asia[6] . They are also grouped under the genus *Hantavirus*, family Bunyaviridae. Hantaviruses that cause HFRS are termed Old World hantaviruses (Table 1).

4. In 1993, a new disease appeared in the southwestern US, namely Four Corners region (New Mexico, Arizona, Colorado and Utah)[3]. The disease was later called "hantavirus pulmonary syndrome (HPS)". This disease was found to be caused by a genetically distinct hantavirus, and it was termed Sin Nombre virus[6]. Its reservoir was the deer mouse (*Peromyscus maniculatus*). Since then, several new hantaviruses causing human HPS were reported in U.S. Hantaviruses that can cause HPS are called New World hantaviruses[1,6].

5. Each of the viruses have a different rodent as its main reservoir, and they each have different clinical and pathological effects on man (Table 1)[1-3,6]. Rodents after infection can remain asymptomatic[1]. Studies have shown that rats inoculated within 24 hours of birth died about 30 days later; and those that survived continued to maintain the virus in persistent form for up to 25 weeks postinoculation and the virus could be isolated from almost all organs[1]. Another study has found the viremia in rodents can last 7-10 days, and the virus can persist in tissue for at least 100 days without producing clinical symptoms[1].

6. Besides rodent, a study has also detected specific antibodies against various serotypes of hantavirus in other animals such as cats, dogs, pigs, cattle and deers[6]. However, further studies are still underway to investigate the possibility of human infection from non-rodent species[6].

Source of Infection and Mode of Transmission

7. Hantavirus infection is a zoonotic disease[2]. It can occur in various ecological environments, including cultivated fields, forests, homes and gardens. Human get the infection either by entering the habitats of rodents or when rodents invade habitats of human. Male adults working in forests or cultivated fields are particularly prone to infection, whereas infection in urban areas does not show any pattern by age and sex[1]. Besides, indoor exposure in closed, poorly ventilated homes, vehicles and outbuildings with visible rodent infestation are also important for hantavirus infection[2].

8. Virus can be found in rodent excreta such as urine, feces and saliva in infected asymptomatic rodents with maximal virus concentration in the lungs[2]. Human gets infection through contact with rodents and their excreta primarily via aerosol route[1,2], though rodent bites may also result in infection[1]. Contamination of food with the excreta of rodents is suspected to be the cause of epidemics in cities[1]. Although person-to-person transmission has been documented in Argentina and Chile, it was considered to be a rare route of transmission and has only been documented with Andes virus, under the genus *Hantavirus*[1].

Table 1 : Members of the genus *Hantavirus*, family Bunyaviridae

Source: Modified from Schmaljohn, C., B. Hjelle. Hantaviruses: A global disease problem. Emerging Infectious Diseases. Vol 3 (2) : 95-104, 1997. [Table 1]

Species	Disease	Principal Reservoir	Distribution of Virus
Hantaan(HTN)	HFRS[a]	*Apodemus agrarius* (striped field mouse)	China, Russia, Korea
Dobrava-Belgrade (DOB)	HFRS	*Apodemus flavicollis* (yellow-neck mouse)	Balkans
Seoul (SEO)	HFRS	*Rattus norvegicus* (Norway rat)	Worldwide
Puumala(PUU)	HFRS	*Clethrionomys glareolus* (bank vole)	Europe, Russia, Scandinavia
Thailand (THAI)	nd[b]	*Bandicota indica (bandicoot rat)*	Thailand
Prospect Hill (PH)	nd	*Microtus pennsylvanicus* (meadow vole)	U.S., Canada
Khabarovsk (KHB)	nd	*Microtus fortis* (reed vole)	Russia
Thottapalayam (TPM)	nd	*Suncus murinus* (musk shrew)	India
Tula (TUL)	nd	Microtus arvalis (European common vole)	Europe
Sin Nombre (SN)	HPS[c]	*Peromyscus maniculatus* (deer mouse)	U.S., Canada
New York (NY)	HPS	*Peromyscus leucopus* (white-footed mouse)	U.S.
Black Creek Canal (BCC)	HPS	*Sigmodon hispidus* (cotton rat)	U.S.
El Moro Canyon (ELMC)[d]	nd	*Reithrodontomys megalotis* (Western harvest mouse)	U.S., Mexico
Bayou (BAY)[d]	HPS	*Oryzomys palustris* (rice rat)	U.S.
Topografov (TOP)	nd	*Lemmus sibiricus* (Siberian lemming)	Siberia
Andes (AND)[d]	HPS	*Oligoryzomys longicaudatus*[f] (long-tailed pygmy rice cat)	Argentina
Laguna Negra (LN)	HPS	*Calomys laucha* (vesper mouse)	Paraguay
Isla Vista (ISLA)[d]	nd	*Microtus californicus* (California vole)	U.S.
Bloodland Lake (BLL)[d]	nd	*Microtus ochrogaster* (prairie vole)	U.S.
Muleshoe (MUL)[d]	nd	*Sigmodon hipidus* (cotton rat)	U.S.
Rio Segundo (RIOS)[d]	nd	*Reithrodontomys mexicanus* (Mexican harvest mouse)	Costa Rica
Rio Mamore (RIOM)[d]	nd	*Oligoryzomys microtis* (small-eared pygmy rice rat)	Bolivia

[a] HFRS, hemorrhagic fever with renal syndrome
[b] nd, none documented
[c] HPS, hantavirus pulmonary syndrome
[d] Not yet isolated in cell culture
[e] Viruses for which incomplete characterization is available, but for which there is clear evidence indicating that they are unique.
[f] Suspected host, but not confirmed.

Clinical presentation

9. The incubation period of hantavirus infection is around two to three weeks[1]. Old World hantaviruses can cause HFRS, and the New World hantaviruses can cause HPS. Infection with different viruses can give rise to different clinical characteristics, with different levels of severity (Table 2).

Haemorrhagic fever with renal syndrome (HFRS)

10. The disease course of HFRS can be divided into five phases (Table 3) which frequently overlap[1,3,7]. Its fatality rate ranges from 1 to 15%, depending on the virus causing the disease. The most severe forms of HFRS are caused by Hantaan virus and Dobrava-Belgrade virus. Infection caused by Seoul virus is moderate and that caused by Puumala virus is usually milder with less pronounced symptomatology and lower case fatality of less than 1% (Table 2).

Table 2. Distinguishing clinical characteristics for HFRS and HPS

(Modified from Pan American Health Organization. Zoonoses and communicable diseases common to man and animals. Vol II. Third edition. 2003. p. 99-109. Table 3)

Disease		**HFRS**		**HPS**	
Pathogens		**- Hantaan - Seoul - Dobrava-Belgrade**	**- Puumala**	**- New York - Sin Nombre**	**- Andes - Bayou - Black Creek Canal**
Distinguishing Characteristics*	**Haemorrhage**	+++	+	+	+
	Azotemia / Proteinuria	+++ / ++++	+/++++	+	++/+++
	Pulmonary capillary leak	+ / ++	-/+	++++	+++/++++
	Myositis	+ / +++	+	-	++/++++
	Conjunctival injection	++ / ++++	+	-/+	-/++
	Eye pain / myopia	++ / ++++	++/++++	-	-
Severity		moderate to severe	mild	prototype	renal variant
Death rate		1 % – 15%	< 1%	> 40%	>40%

* Minimum / maximum occurrence of the characteristics : - rarely reported;
+ infrequent or mild manifestation;
++,+++,++++ more frequent and severe manifestation

Table 3. Five phases of HFRS and its clinical features

Phase	Duration	Key clinical features
1. Febrile phase :	3 - 7 days	• fever of 40°C or higher; • chills, generalized discomfort, myalgia, extensive edema of the peritoneum due to increased permeability of the capillaries, leading to severe abdominal and lumbar pain. • flushing of the face, neck, and thorax; • congestion of the conjunctiva, palate, and pharynx; • petechiae can appear on different parts of the body with pronounced proteinuria
2. Hypotensive phase :	• comes on abruptly; • may last from a few hours up to 2 days	• shock soon occurs with one-third of the deaths caused by irreversible shock; • capillary haemorrhage is common
3. Oliguric phase :	• follows the hypotensive phase; • lasts for 3 to 7 days	• blood urea and creatinine levels elevated; many become hypertensive; • nausea, vomiting and haemorrhage common; • around 50% die in this phase
4. Diuretic phase :	• over a few hours to days	• recovery begins with the onset of diuresis.
5. Convalescent phase :	• usually 2 to 3 months	• can last up to months before recovery is complete

Hantavirus Pulmonary Syndrome (HPS)

11. It is usually the most severe type of disease caused by hantaviruses and particularly affects the lungs. Its course can be divided into three phases: prodromal febrile phase, cardiorespiratory phase and the convalescent phase[8]. The prodromal febrile phase usually lasts for 3-6 days. Symptoms include chills, myalgia, headache and abdominal pain. During cardiorespiratory phase, usually lasting for 7-10 days, there is coughing and rapid development of respiratory insufficiency[1,8]. HPS has a high case-fatality rate of more than 40%[1]. Death results from bilateral pulmonary (noncardiogenic) edema caused by the increased permeability of alveolar capillaries[1]. In some cases there is marked hypotension[1]. Renal haemorrhagic manifestations are rarely reported except in some severe cases[2]. For survivors, recovery from acute illness is rapid, but full convalescence may require weeks to months. Restoration of normal lung function generally occurs, but pulmonary function abnormalities may persist in some individuals[2]. Recently, it became clearer that the heart is also heavily affected, leading to intractable cardiovascular shock and death. In view of that, the disease name "hantavirus cardiopulmonary syndrome" is preferred by some authors[4].

Laboratory Diagnosis

12. Presence of proteinuria, leukocytosis, hemoconcentration, thrombocytopenia and elevated blood urea support the diagnosis of hantavirus infection[1,2]. The diagnosis can be confirmed by serology tests[1,2,9]. They include detection of hantavirus-specific IgM antibodies, or a four-fold or greater rise in

hantavirus-specific antibody titres between acute and convalescent sera; detection of hantavirus-specific RNA sequence by PCR in an appropriate clinical specimen or detection of hantavirus antigen by immunohistochemistry.

Clinical Management

13. There is no specific treatment for both HFRS and HPS and their treatments are mainly supportive. Sedation, analgesics, and the maintenance of fluid balance are indicated during the febrile phase. Blood pressure control is crucial during the hypotensive phase. In the oliguric phase, fluids should be tightly controlled and hypocalcemia should be corrected. Haemodialysis may be required in severe cases. In the diuretic phase, the fluid and electrolyte balances should be monitored and treated if necessary[1].

14. For HPS, early pulmonary ventilation is recommended, along with careful monitoring of fluid and electrolyte balance and arterial pressure[1].

Global Epidemiology

15. Nowadays, Hantaviruses are widely distributed throughout the world (Table 1)[1]. In Asia, China showed a decreasing trend in the recent years. The number of cases of human hantavirus infection dropped from around 26,000 in 2004 to around 8,745 in 2009[10]. The number of death has also dropped from 213 to 104 in the same period[10]. The infection in China is mainly caused by Hantaan virus (HTNV) carried by *Apodemus agrarius* and Seoul virus (SEOV) carried by *Rattus norvegicus*[11]. The former thrives in rural areas, while the latter is an anthropophilic urban species[11]. In Japan, outbreaks of HFRS were reported between 1960 and 1972 with 100 people infected and two died[1]. It was also reported to have sporadic cases in rural areas between 1978 and 1980[12]. In Korea, several hundred to several thousand cases were reported each year[1]. There is no report of human cases of hantavirus infection in Australia[13]

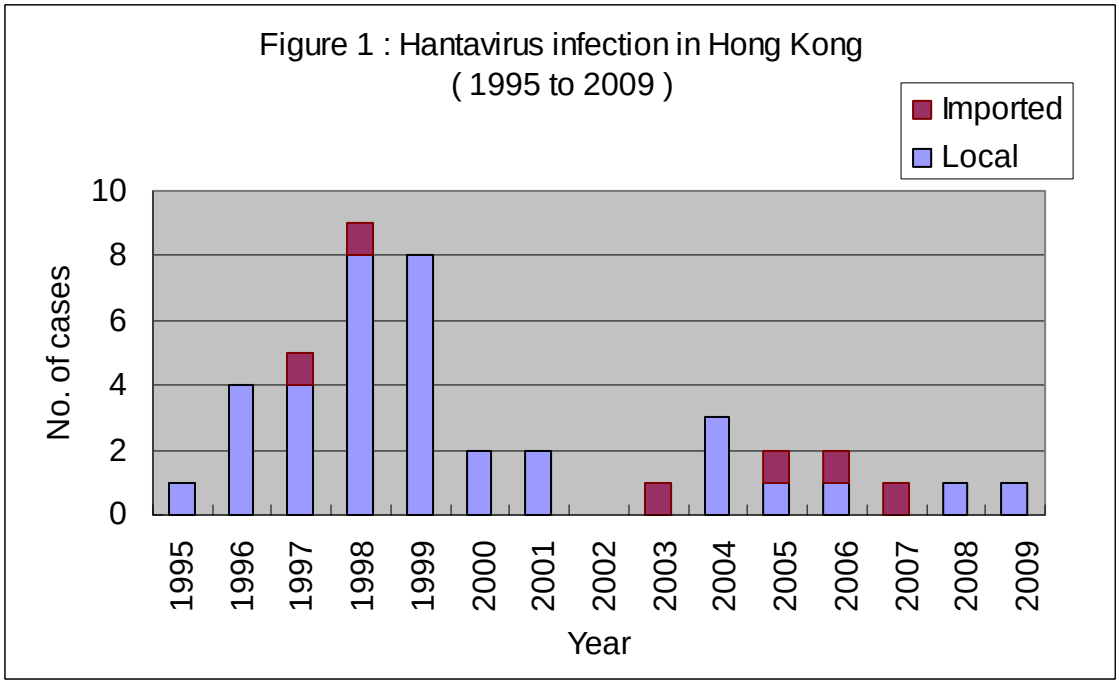
16. Hantavirus infection are widely distributed in Europe[14]. It was reported that 30,000 cases of hantavirus infection were confirmed between 1990 and 2006 among 19 European Union countries, and Finland accounted for 69.6% of all reported cases in Europe. Russia reported 89,162 cases from 1996 to 2006.

17. From 1993, since the emergence of the first HPS case in US, a total of 465 cases of hantavirus pulmonary syndrome have been reported up to March 2007 and 35 % of all reported cases have resulted in death[15]. In Canada, cases were first reported in 1994, and about 50 cases have been reported since then[16]. For Central and South America, including Panama, Argentina, Bolivia,

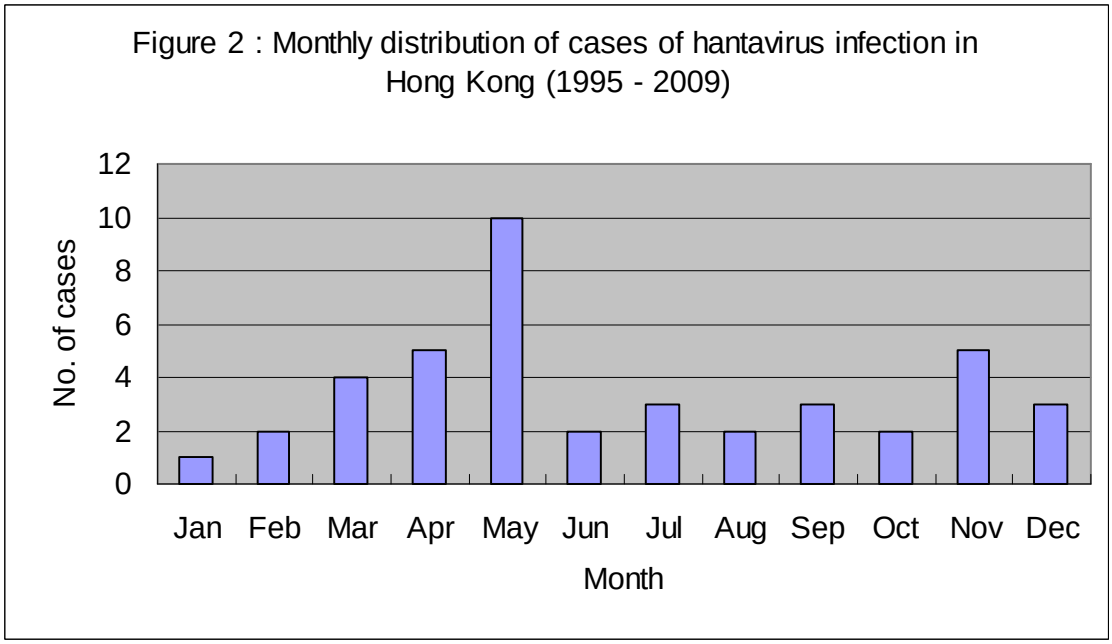
Brazil, Chile, Paraguay and Urugua, a total of 1910 cases and 384 deaths were reported from 1993 to 2004 April[17]. There is little information about hantavirus infections in Africa.

Hantavirus infection in Hong Kong

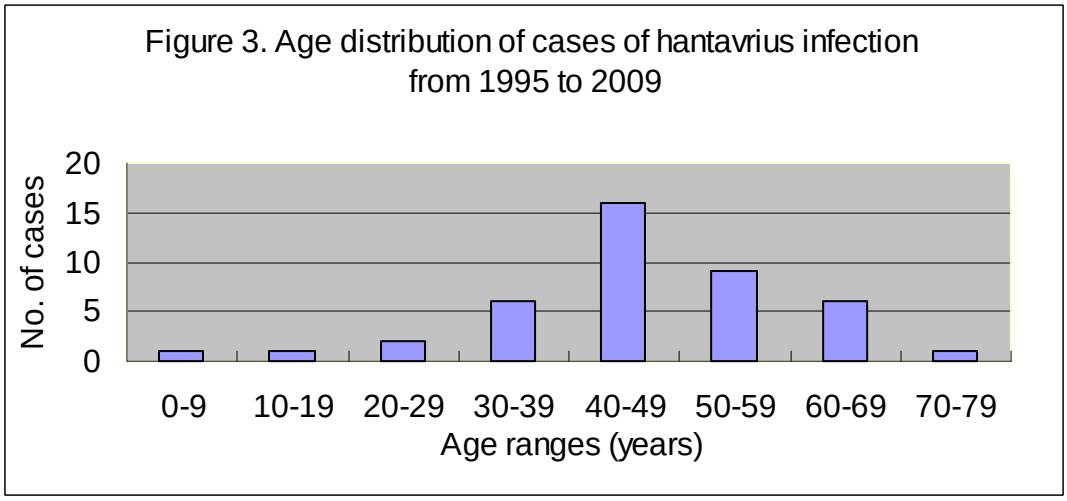
18. In Hong Kong, hantavirus infection has been made notifiable since 14 July 2008. A total of 42 sporadic cases of hantavirus infection were reported to the Department of Health from 1995 to 2009. The number of cases reported per year ranges from 0 to 9. Majority (86%) were local cases while six cases (14%) were suspected to have contracted the infection from outside Hong Kong, including five from Mainland and one from Macao (Figure 1).



19. Cases were reported throughout the whole year with more cases occurred in May (Figure 2). This pattern is different from that of Mainland China, in which more cases were found in winter months[10].



20. Out of the 42 cases, 35 (83%) were males and seven (17%) were female. Their age ranged from 6 to 76 years, with a median of 45 years. Majority (73%) of them were middle aged within the age group of 40 to 69 (Figure. 3). No particular high risk occupation could be identified. Sixteen (38%) of them were labour workers of various different sectors. Students, housewives and the unemployed constituted eleven cases (26%). Other cases involved various different job natures.



21. All the cases were classified as HFRS. They all presented with fever or non-specific generalized symptoms like sore throat, headache, malaise, or myalgia. Thirty three cases (79%) had gastrointestinal symptoms of nausea, vomiting, abdominal pain or diarrhoea. Seven cases (17%) complained of respiratory symptoms, six of them complained of cough and one suffered from respiratory failure (Table 4). Eleven cases (26%) had signs of bleeding tendency in form of petechiae bruising, haematuria or gastrointestinal bleeding.

Their clinical presentations are compatible with that of HFRS.

22. Thirty five patients (83%) had low platelet counts and 13 (31%) showed deranged clotting profile. Forty (95%) showed some degree of deranged renal function. All the cases were diagnosed by serology tests with a four-fold or greater rise in hantavirus-specific antibody titres between acute and convalescent sera or a positive IgM result[9]. All the cases were treated in hospitals and one of them died. The fatal case is a local case involving a 54 years old man who died of disseminated intravascular coagulation.

23. Among all the cases, 30 of them recalled a history of rodent exposure. Six patients (14%) recalled history of contact with rodent or their excreta during the incubation period, twenty one (50%) recalled seeing rodents at their residence, workplaces or their vicinity, two (5%) had visited places with rodent infestation and one (2%) recalled being bitten by rodent.

24. For local cases, sources of infection have been 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, workplaces as well as other possible sites of contraction have been carried out.

25. Investigation results showed that signs of rodent infestation have been found in patient's home (4 cases), workplace (14 cases) and in the vicinity of their residence (22 cases) such as flower bed, rubbish collection points, markets and rear lanes. Rodent control measures were stepped up at these places. Epidemiological investigation did not identify linkage between the cases.

Table 4. Summary of Hantavirus cases occurred from 1995 to 2009

Cases		42	
Age range		6-76	
Median age		45	
Clinical features	Flu-like symptoms	42	100%
	Fever	41	98%
	Chills and rigors	20	48%
	Malaise	18	43%
	Headache	11	26%
	Sore throat	6	14%
	Myalgia	8	19%
	Gastrointestinal symptoms	33	79%
	Nausea/vomiting	25	60%
	Abdominal pain	14	33%
	Diarrhoea	13	31%
	Respiratory symptoms	7	17%
	Cough	6	14%
	Respiratory failure	1	2%
	Bleeding tendency	11	26%
	Haematuria	7	17%
	Gastrointestinal bleeding	2	5%
	Petechiae / bruises	2	5%
Laboratory findings	Deranged renal function	40	95%
	Thrombocytopenia	35	83%
	Deranged liver function	25	60%
	Deranged clotting profile	13	31%
	Proteinuria	12	29%
	Leucocytosis	11	26%
Hospitalized		42	100%
Fatality		1	2%

Rodents in Hong Kong

26. According to the PCAS of FEHD, the three common species of commensal rodent in Hong Kong are *Rattus norvegicus*, *Rattus rattus and Mus musculus*[18,19]. *Rattus norvegicus*, also known as Norway rat, is commonly found in mainland[11]. It often nests in burrows, and inhabit underground sewers. *Rattus rattus*, also known as roof rat, in contrast to Norway rat, like to inhabit in overhanging structures such as attics, false ceilings, roof spaces, and crossbeams of the buildings. *Mus musculus*, is usually found indoors particularly around food storage.

Situation of rodent infestation in Hong Kong

27. Rodent infestation is not uncommon in Hong Kong. To facilitate the planning of rodent prevention and control strategies, the PCAS has been regularly performing routine, territory-wide Rodent Infestation Survey (RIS) to monitor the rodent infestation situation since 2000[19]. It helps to determine rodent trouble sports so that prompt action could be taken to prevent proliferation of the rodent population[18].

28. Rodent Infestation Survey is a scientific and objective method to determine the degree of rodent infestation in areas of interest. It is conducted twice a year in 19 districts by using census baiting. About fifty bait stations of at least 50 metres apart were set in each study area. The Rodent Infestation Rate (RIR) is then calculated by the percentage of bait consumed by rodent[18].

RIR = (No. of bait consumed by rodent / Total no. of bait set retrieved) x 100%

29. Information from PCAS has showed that the RIR has been improving from 16.0% in 2000 to 6.1% in 2009[20] (Table 5).

Table 5. Rodent Infestation Rate in Hong Kong from 2000 to 2009

Year	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Rodent Infestation Rate	16.0%	8.8%	9.0%	5.6%	4.1%	4.4%	2.9%	4.8%	6.3%	6.1%

Seroprevalence in rodents for hantavirus infection

30. From 1983 to 1986, a study was conducted to investigate the prevalence of Hantavirus infection among urban rats in Hong Kong[21]. In this study, 781 serum samples (748 were Rattus norvegicus) were tested for immuno-fluorescent antibody to Hantaan and Hantaan-related virus. One hundred and fifty four (19.7%) were positive. The seropositive rodents were widely distributed in Hong Kong Island and Kowloon Peninsula (Rodents from New Territories were not captured in this study). The positive rates ranged from 11% to 32% in different areas. Nine strains of Hantavirus were isolated from lung tissues of seropostive rats and results showed that the prevailing strains appeared to be antigenically close to Seoul virus[21].

Current Preventive and Control measures in Hong Kong

31. To prevent and control hantavirus infections, a coordinated approach encompassing environmental hygiene, personal protection, disease surveillance, source investigation, rodent monitoring and infestation control and health education have been adopted.

A. Preventive measures

32. Rodent prevention is most important in the prevention of the disease. The most effective way to control rodent infestation is by eliminating food, harbourage and passages for the rodents. Food should be properly stored and refuges should be properly handled. Blockage and elimination of rodent passages can be achieved by installation of gratings, wire mesh or metal plates[19]. Precautions should be taken when cleaning rodent-infested areas. Spraying disinfectants such as diluted bleach before cleaning is encouraged. Plastic or rubber gloves should be used when handling dead rodents. Keeping the area found with rodent excreta well ventilated could avoid accumulation of infective aerosol droplets. Those occupational high risk groups frequently exposed to rodents should use protective face masks and gloves when handling rodents and rodent traps and should disinfect the gloves before removing them[1,2] .

33. Community education is regularly done by the FEHD and CHP. Every year, FEHD will hold a territory-wide interdepartmental anti-rodent Campaign to enhance the public alert on rodent prevention, and to enlist support from the community in controlling rodents. A spectrum of publicity instruments were used for public education including display of banners and posters, distribution of leaflets, talks, exhibitions, broadcasting of TV announcement of public interest and organizing health education activities at public markets [22,23]. Health information related to prevention of hantavirus infection is also available in the Centre for Health Protection website[24]. Health education to patients and their families will be provided by the Centre for Health Protection upon receiving report of hantavirus infection.

34. The Port Health Office of the Department of Health conducts inspections at airports, seaports, and ground crossing to monitor the hygiene and sanitation condition and coordinates efforts of the respective managements in the efforts of rodent infestation prevention and control.

35. Inactivated vaccines have already been developed in Korea and China and are being used in these countries[4]. Reduction in the number of HFRS cases have been recorded[5,28]. A study showed that Hantavax, which is an inactivated vaccine developed in Korea and grown in suckling mice brain, was able to produce a seroconversion rate of 97% 1 month after inoculation of second dose. No obvious side effects were reported. However, after 1 year the

antibody titres dropped significantly to 37.5%[28]. Another inactivated vaccine produced in China also showed a promising seroconversion rate of higher than 85% with low side-effect rate after two doses[4]. Nevertheless the vaccines require further improvement in its long-lasting neutralizing immune response[5,28]. Up till now, WHO does not make any recommendation on the use of hantavirus vaccine in human.[4,25-27] In addition, there is still no hantavirus vaccine approved for use by U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMEA).

B. Other control measures

Disease surveillance

36. Hantavirus infection has become a statutory notifiable disease in Hong Kong since 2008. Doctors should report the diseases to Centre for Health Protection of the Department of Health. To facilitate clinicians to make the diagnosis, laboratory testing for hantavirus is available free of charge from the Public Health Laboratory Services Branch of the Centre for Health Protection, Department of Health.

Source investigation

37. After receiving report of human infection, the Centre for Health Protection (CHP) of Department of Health will carry out investigation to collect epidemiological information about places they have visited and condition of their contacts. PCAS will also conduct prompt investigation for rodent activity around the patients' homes and their vicinity, workplaces and markets they have visited to investigate the source of infection. Control measures will be carried out to prevent the spread of disease in the community. Health education is also used as a tool to alert the parties concerned on the prevention and control of rodent and the disease.

Rodent surveillance and control of infestation

38. The PCAS has been conducting routine, territory-wide Rodent Infestation Survey since 2000 to monitor the rodent problem in different areas. The FEHD has performed a wide range of direct disinfestations by using chronic anti-coagulants as rodenticide. Besides that, cage trap, snap trap or break back trap are also used to trap rodents for supplementing environmental improvement measures[18,19].

Conclusion

39. Hantavirus infection is a disease that is found worldwide and can be fatal. The reported incidence of hantavirus infection in Hong Kong is less than one per million population. Rodents of *Rattus spp.*, which are the main reservoirs of hantavirus, can be commonly found in our locality. The current prudent control and prevention measures should be continued for prevention and control of the disease in Hong Kong.

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