衞生防護中心
Centre for Health Protection

Scientific Committee on Vector-borne Diseases

Prevention of Yellow Fever in Hong Kong

Purpose

Yellow fever is an arthropod-borne viral haemorrhagic fever. It is endemic in the tropical Africa and South America where the WHO estimates an annual incidence of 200,000 cases with 30,000 deaths.(1) This paper reviews the global and local epidemiology of yellow fever, examines the potential risks of yellow fever in Hong Kong and discusses the preventive strategies.

The virus

2. Yellow fever is caused by the yellow fever virus, an arthropod-borne virus from Flavivirus genus of the family Flaviviridae. It is a single-stranded, RNA virus with a ribonucleoprotein core and a lipoprotein envelope which make up a viral particle of 35 to 45 nm in size. The virus has seven genotypes within a single serotype. Five genotypes are found in Africa and two in South America. Each of the five genotypes in Africa circulates in a distinct geographical region, whilst the two in South America do not have a distinct geographical distribution.(2) Thus the East and Central African genotype is found in Central African Republic and central Sudan; the East African genotype is found in Kenya, southern Sudan, and Uganda; the West Africa genotype I is found from eastern Ivory Coast and Burkina Faso to Cameroon; the West Africa genotype II is found in western Ivory Coast and Mali to Senegal, and the Angola genotype is only found in Angola. However, there is little difference in virulence observed among different genotypes. The virus can be inactivated with lipid solvents (ether, chloroform), heat (56℃ for 30 minutes) and ultraviolet light.(1)

The disease

3. The clinical features of yellow fever vary from a non-specific, self-limiting illness to a fatal haemorrhagic fever.(3-5) Sub-clinical infection can occur. Symptomatic patients usually present 3 to 6 days after the bite of an infective mosquito and the disease may evolve in three phases.

4. In phase one, the period of infection, the patient may have non-specific symptoms with sudden onset of fever, chills, malaise, headache, lower backache, generalized myalgia, nausea and vomiting. The patient may have a relative bradycardia with fever (Faget's sign). The symptoms may last for one to seven days.

5. The second phase, i.e. the period of remission, may last for one to two days during which fever and all other symptoms disappear. Some patients recover at this stage.

6. The third phase, i.e. the period of intoxication, may occur in about 15 to 25% of symptomatic cases. Reappearance of fever and the onset of jaundice characterize this phase. Vomiting, epigastric pain, and other features such as renal failure with albuminuria and oliguria, and haemorrhagic phenomena such as petechiae, ecchymoses, epistaxis, gum bleeding, haematuria, coffee-grounds haematemesis, melaena or metrorhagia, may occur. Of those who develop hepatorenal disease 20 to 50% die. The overall case fatality rate is 5% in endemic regions but may reach 20-40% in individual outbreaks.(3)

7. Currently, there is no specific anti-viral agent available for treating yellow fever. Hence, treatment is mainly supportive. Once infected, those who survive the disease will develop life long immunity.(4,6)

Diagnosis

8. Definitive diagnosis of yellow fever (4, 7, 8) relies on
(a) isolation of virus by viral culture; or
(b) detection of viral antigen in serum or blood during the initial phase; or
(c) detection of viral genome in serum or liver tissue by PCR or hybridization; or
(d) serology.

9. Viral antigen may be detected in serum or blood using enzyme-linked immunosorbent assay (ELISA). Polymerase chain reaction (PCR) can be used to detect the viral genome in serum up to the first month after onset of illness.(1) Detection of specific IgM antibodies by ELISA or immunofluorescence test in a single serum taken in the late acute or early convalescent phase, about 5 to 7 days after onset, provide a presumptive diagnosis.

10. A four-fold rise of antibody titre in paired sera is confirmatory. Cross-reaction between yellow fever and other flaviviruses may complicate the interpretation of serological results.

11. Liver biopsy may reveal a typical midzonal necrosis with eosinophilic degeneration of hepatocytes (Councilman bodies) in liver cells and viral antigens in the tissue may be detected by immunohistochemistry.(3,7)

Ecology of Yellow fever virus

12. There are three epidemiological transmission cycles of yellow fever occurring in three different ecologies.(2,3) In the jungle (sylvatic) cycle, non-human primates, such as monkeys or chimpanzees, are primarily infected. Humans are the primary hosts in the urban cycle. The intermediate (savannah) cycle refers to yellow fever occurring in both humans and non-human primates. Transmission of yellow fever virus between primate hosts relies on the existence of mosquito vectors. *Aedes aegypti*, which feed on human hosts, is the urban cycle vector whereas other sylvatic *Aedes*, *Haemagogus* and *Sabethine* species are responsible for transmission of yellow fever in jungle and intermediate cycles. All three cycles produce the same clinical disease in humans. There is a difference in the outcome of infection between the non-human primates of Africa and South America. In South America, primates often succumb to infection and die whereas in Africa, the infected primates typically have no signs of infection.(2)

Mosquito Vectors

13. *Aedes* spp. in Africa, and *Haemagogus* and *Sabethine* spp. in South America are the major vectors.(2,3,6) Susceptible mosquito species acquire a life-long infection after feeding on an infected host during the viraemic phase. *Aedes aegypti*, the urban cycle vector, becomes infective to a susceptible host 8 to 12 days after the virus has completed an extrinsic cycle inside the mosquito. Vertical transmission of the virus to its progeny allows the virus to survive through the dry and cold seasons making mosquitoes the true reservoir.(4,6)

Host

14. Primates appear to be the only host involved in the transmission cycle of yellow fever virus in nature. Nearly all monkey species in the wild nature and humans are susceptible hosts. Experimentally, other vertebrates, such as marsupials, may be infected and develop a sufficient level of viraemia to infect mosquitoes. In human, viraemia is present from shortly before to 4 days after onset so that the person may serve as a source of infection for mosquitoes. Once infected, life long immunity develops if the person or non-human primates survive the disease.(2,4,6)

Transmission cycles

15. Transmission cycles of yellow fever are the result of interaction between the available hosts and mosquito species and are found in different geographical regions as summarized below (2,4,6):

Transmission type	**The cycle (host – vector – host)**	**Region of occurrence**	**Mosquito species involved**
Jungle (or sylvatic) cycle	Monkey – mosquito – monkey (human as an incidental host)	Rainforest in Africa and South Americas	Africa: *Aedes africanus* South Americas: *Haemagogus janthinomys* *Haemagogus leucocelaenus* *Sabethine Cholropterus*
Intermediate (or savannah) cycle	Monkey / human – mosquito – monkey / human	Moist savannahs in Africa only	*Aedes africanus* *Aedes furcifer* *Aedes luteocephalus* *Aedes metallicus* *Aedes neoafricanus* *Aedes opok* *Aedes simpsoni* complex (probably *Aedes bromeliae)* *Aedes taylori* *Aedes vittatus* Other species
Urban cycle	Human – mosquito – human	Urban areas in Africa and South America; dry savannahs in Africa	*Aedes aegypti*

(a) Jungle cycle (or sylvatic cycle): Yellow fever is enzootic in the tropical areas of Africa and South America and is maintained by the jungle cycle. This transmission cycle involves non-human primates as the amplifying host and tree holes breeding mosquitoes as the vector in the forest canopy. *Aedes africanus* in Africa, and *Haemagogus janthinomys*, *Haemagogus leucocelaenus* and *Sabethine Cholropterus* in South America are the principal jungle vectors. Jungle yellow fever in human beings may result from biting by infected mosquitoes when the person enters the jungle cycle accidentally, e.g. during occupational and recreational activities.

(b) Urban cycle: Urban yellow fever occurs in the urban centres and dry savannas in Africa. Urban cycle involves transmission of yellow fever virus between humans by the principal urban vector, *Aedes aegypti*, which is a domestic type mosquito. Once the urban cycle is established, epidemics of yellow fever occur.

(c) Intermediate cycle: An intermediate or savannah cycle is only found in Africa. It occurs in the moist savannah areas in Africa where some human activity exists. This area is recognized as the zone of emergence since it may reflect the possible mechanism of evolution of yellow fever from the jungle cycle to become an important human disease. Vectors involved in this cycle are sylvatic *Aedes* include *Aedes africanus*, *Aedes furcifer*, *Aedes luteocephalus*, *Aedes taylori*, *Aedes metallicus*, *Aedes neoafricanus, Aedes opok, Aedes vittatus* and *Aedes simpsoni* complex. Besides monkeys, these wild mosquitoes may feed on humans so that transmission of yellow fever between monkey and human is established when people intrude into an ongoing jungle cycle and become infected. Cyclic epizootics among primates and epidemics in human population occur in these areas during the rainy season when vector populations reach a very high level.

Global epidemiology

16. WHO estimates that 200,000 cases of yellow fever occur worldwide yearly resulting in 30,000 deaths. Yellow fever is endemic in the tropical Africa and South America. Yellow fever has never been reported in Asia.

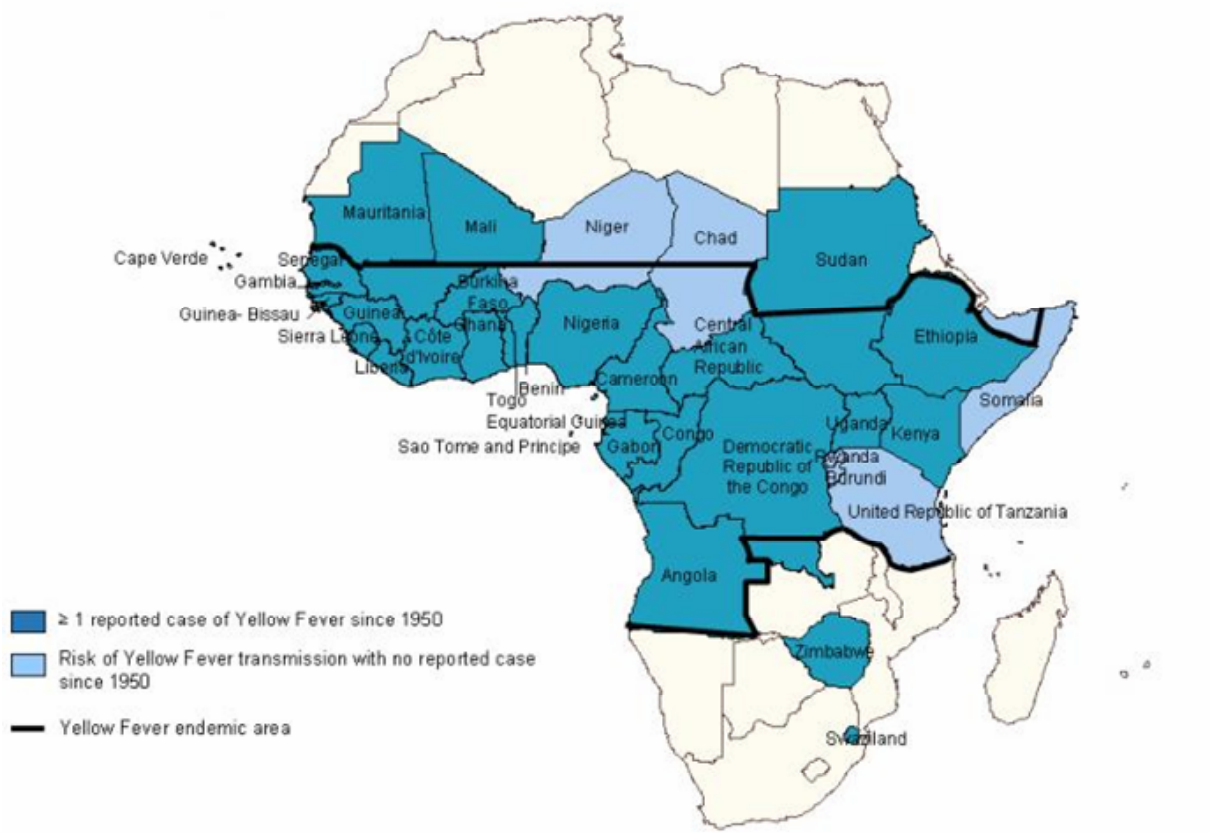
Situation in Africa

17. Yellow fever virus is native in some tropical areas of Africa. It is estimated that 90% of yellow fever cases occurring annually are from Africa.(1) In the past, the disease was very active, especially in the Western region, until the implementation of mass immunization of yellow fever vaccine in Francophone West Africa in 1940. However, epidemics of yellow fever reappeared after mass immunization was suspended in these countries in 1961. The disease reached its highest activity in the period 1986 to 1991. At this time, Nigeria was the country worse-affected with at least 1 million cases.(6)

18. All the outbreaks in Africa occurred in the vicinity of the emergence zone in the moist savannah or in the dry savannah, along the genuine “yellow fever belt” stretching from Senegal to Ethiopia and Kenya and ranging from 15°N to 15°S of the equator (figure 1).(1,9) At present, 32 countries, with a total population of 610 million, are at risk in Africa. In Africa, a total of 2,570 yellow fever cases were reported from 18 countries in the period 2000 to 2004. Thirteen of these countries are in the West African region.

In 2005, yellow fever epidemics were particularly numerous and a total of 2,058 cases with 106 deaths were reported in 16 countries.(10) The major epidemics occurred in Guinea, Mali, and Sudan and accounted for 40% of the cases reported. Since 2006, WHO has reported 2 outbreaks occurring in Cote d'Ivoire and Togo.

Figure 1: Yellow fever epidemiology in Africa from 1950 to 2004 (9)



19. WHO also warned against an increased risk of epidemics of urban yellow fever in Africa with increase in vector density related to increasing rainfall, migrations of non-immunized people from non-endemic to endemic regions, urbanization but poor water supply and non-immunized population. Since 2000, 2 urban outbreaks occurred in Adidjan, Cote d'Ivoire in 2001 and in Touba, Senegal in 2002.(10-12)

Situation in Americas

20. Yellow fever was introduced into Americas in the 15th centuries.(2,6) At that time, epidemics of yellow fever affected major cities and were associated with intensive commercial activities which extended from as far south as Chile to as far north as Canada. However, yellow fever has never been reported in North America after the last outbreak in New Orleans in 1905. In South America, the last urban cycle occurred in 1942 in Brazil (Rio de Janeiro). Eradication programs targeting *Aedes aegypti* using DDT after World War II has virtually eliminated the urban vector for yellow fever in the

Americas.(13) Since then, yellow fever virus has become enzootic in the Amazon basins and jungle yellow fever associated with recreational and occupational activities continues to be reported in tropical South America.(4,6,10)

21. Currently, yellow fever is endemic in 10 South and Central American countries and in several Caribbean islands. Bolivia, Brazil, Colombia, Ecuador, Peru and Venezuela are considered at greatest risk (figure 2).(9) In the period 2000 to 2004, a total of 629 cases were reported from 6 countries in South America. Brazil, Colombia and Peru had the highest disease activity. The number of cases and deaths in South America remains relatively stable. Thus 117 cases and 52 deaths were reported from 5 countries in 2005. This is comparable to 2004. (10) The risk of reemergence of yellow fever in urban centres has increased as *Aedes aegypti* has re-infested all countries of South America. This is partly related to waned efforts in mosquito control.(2,6,13,14)

Figure 2: Yellow fever epidemiology in America from 1950 to 2004(9)

Situation in Europe

22. Yellow fever caused epidemics in Europe during the 17th to 19th centuries. The transmission was initiated by ship-borne infections and hence ports of the major cities were commonly affected. However, the disease was

never endemic in Europe. Also, the urban vector, *Aedes aegypti*, disappeared from southern Europe and North Africa shortly after World War II and this may have been associated with mosquito control efforts.(13)

Situation in Asia

23. Indigenous yellow fever has never been reported in Asia although the urban vector, *Aedes aegypti*, and non-primate hosts are widely distributed in many Asian and Pacific countries.(2,6,13,14) Apart from an imported yellow fever case reported in Hong Kong in 1945, there was no imported case documented in other Asian areas.

24. WHO estimates that the risk of an unvaccinated person contracting yellow fever and dying of the disease when entering into an area of epidemic activity for a two-week trip is 1:267 and 1:1333 respectively.(1) From 1996, there were 6 fatal cases of yellow fever affecting unvaccinated travellers from the United States and Europe who succumbed after returning from yellow fever endemic countries to their homes.(2)

Prevention and Control of Yellow Fever

25. In endemic and at-risk countries, WHO recommends strategies for yellow fever prevention and control to include routine infant and child immunization, mass preventive vaccination campaigns to prevent epidemics, outbreak detection and rapid response, vaccination for travellers to at risk countries, disease surveillance and mosquito control in urban centres.(3,10) The International Health Regulations provide the legal framework for international cooperation on the prevention of international spread of infectious diseases across borders on the global level.

Yellow fever vaccination in endemic countries

26. Yellow fever vaccine was developed in the 1930s. It is a live attenuated vaccine produced in chicken embryo tissue culture. It contains an attenuated variant strain, 17D yellow fever virus, and is the only commercially available vaccine.(1,6)

27. The yellow fever vaccine is given as a single subcutaneous or intramuscular injection. It can be given simultaneously with other live or inactivated vaccines including measles, oral polio, diphtheria-tetanus-pertussis, hepatitis B, hepatitis A, oral cholera, and oral or parenteral typhoid. However, if live vaccines are not given simultaneously, they should be given at least one month apart.

28. Yellow fever vaccine is safe and effective. The protective level of neutralizing antibodies develops in 90% and 99% of vaccinees within 10 and 30 days respectively. Protection appears to last at least 30 -35 years. A small

proportion of vaccinees may experience mild side effects whilst serious vaccine-associated neurotropic disease and vaccine-associated viscerotropic disease are extremely rare. The vaccine should only be administered to persons with no contraindications. (Annex 1)

29. In countries at risk for yellow fever, routine childhood immunization with yellow fever vaccine to children aged 9 months or above is among the strategies for prevention and control of the disease. In 2006, 32 out of 43 at risk WHO Member States have introduced yellow fever vaccine in the routine immunization programme.(15)

30. In order to protect susceptible older age groups, and to boost the population immunization coverage, the WHO has also recommended mass catch-up preventive immunization campaigns. It is a planned vaccination programme for at-risk populations for implementation in high risk areas in countries with resource constraints.(1)

31. During yellow fever epidemics, WHO recommends outbreak response immunization to high-risk groups to control the extent of outbreak and prevent further spread of the disease. This will be implemented as part of the outbreak control measures in parallel with laboratory investigation of suspected cases, epidemiological and entomological investigation, as well as vector control.(1,3,10)

Surveillance and laboratory capacity in endemic areas

32. WHO recommends case-based surveillance in endemic or at-risk areas. A more sensitive case definition is adopted to detect suspected yellow fever cases while confirmation relies on laboratories that are capable of providing specific laboratory tests with good quality control. In 2004, such a laboratory network was established comprising 22 national laboratories in Africa.(12)

33. In endemic African countries, active surveillance by annual serologic surveys of young children, surveys of yellow fever antibodies in monkeys and entomological surveys of the mosquito vectors have been used as the sources of evidence of circulation of the virus. (6) In South America, post-mortem histopathological reviews of liver specimens collected from patients who were suspected to have died of yellow fever have been used for surveillance purposes. (3)

Mosquito control

34. In general, mosquito control is an important preventive and control measure of vector-borne diseases. By controlling the domestic vector, *Aedes aegypti*, in the urban centres, the risk of urban yellow fever epidemics can be greatly reduced. Mosquito control also serves as a buy-time measure

during an epidemic so that more time is gained for the population to build up immunity after receiving vaccination.(1,3,10)

Yellow fever vaccination as a strategy to reduce international spread

35. Yellow fever has always been considered a priority disease for international control and was made notifiable to WHO in 1948. Together with cholera and plague it was among the three quarantinable diseases specified in the International Health Regulations (1969). In 2005, WHO adopted the International Health Regulations (IHR) (2005) for enforcement in June 2007 and yellow fever remains the only disease for which proof of vaccination may be required for travellers to enter a country.(16)

36. An international certificate of vaccination against yellow fever may be required for any traveller leaving an area with a risk of yellow fever transmission. Countries with or without yellow fever cases where the mosquito vector and potential non-human primates hosts of yellow fever are present can establish such mandatory requirements for travellers entering into their countries, including air transits, according to the IHR. If yellow fever vaccination is contraindicated for medical reasons, a medical certificate is required for exemption.

37. In addition, the WHO also requires the specific yellow fever vaccine used to have been WHO approved in order for the international certificate of vaccination to be valid. Yellow fever vaccination becomes valid from the tenth day onwards and the validity lasts for 10 years. A booster dose is required every ten years to obtain a valid certificate of vaccination.

38. Yellow fever is a quarantinable disease under IHR. In a country receptive to yellow fever, e.g. in the presence of yellow fever vector, the local health authority may require a traveller who cannot produce a valid certificate of vaccination against yellow fever to be quarantined until the certificate becomes valid or a period of six days from last possible exposure to infection has elapsed.

39. Yellow fever remains as one of the diseases constituting a pubic health emergency of international concern in the IHR (2005). According to the Regulations the local health administration is required to notify the WHO about any case of yellow fever within 24 hours of assessment.

Yellow Fever Prevention in Hong Kong

40. Yellow fever is neither endemic in Hong Kong nor in any other Asian country. Nonetheless, people from Hong Kong may acquire the infection during travel to endemic countries if appropriate preventive measures are not undertaken. The Hong Kong Tourism Board registers about 182,000 tourists entering Hong Kong from Africa or South America annually. Such

tourists constituted 1.2% of the total number of visitors to Hong Kong in the first seven months of 2007 (17), and pose a theoretical risk of importing, and thus introducing, yellow fever virus into Hong Kong. We now examine defences against the introduction of yellow fever into Hong Kong.

Disease Surveillance

41. In Hong Kong, yellow fever is a statutorily notifiable disease. The Director of Health must be informed of any suspected case of yellow fever whence investigation and control measures will be implemented. There have been no cases of yellow fever in Hong Kong in the past 60 years. The last case of imported yellow fever was recorded in 1945 and there is no information available regarding the clinical course of this case.

42. Laboratory capabilities for diagnosing yellow fever are available in Hong Kong. The Public Health Laboratory Services Branch of the CHP provides support for virology testing for suspected cases in both public and private sectors. PCR for genome detection, virus culture and serology are available to confirm the diagnosis

Surveillance in non-human primate hosts (18)

43. In Hong Kong, the species of wild monkeys include rhesus macaque (*Macaca mulatta*) (about 68%), longtailed macaque, (*Macaca fasicularis*) (about 2%) and their hybrid (about 30%). The total population was estimated to be about 1,600 in 2007. The macaque population in Hong Kong is an isolated population in that there is no natural communication or contacts between other macaque populations in nearby areas of southern China. Although the rhesus macaques are susceptible to yellow fever infection, there has never been a reported outbreak of yellow fever in Asian macaque populations. Staff of the AFCD keep records of dead monkeys found during routine patrols in Country Parks and other areas where monkeys are frequently seen. About 20 monkeys are found dead due to traffic accidents each year. However the sudden death of a large number of monkeys or an unusual mortality has not been detected in past years. Veterinary staff of the AFCD are responsible for taking care of all animals kept in parks and the zoo under the management of the Leisure and Cultural Services Department (LCSD). All persons wanting to import animals into Hong Kong have to provide an animal health certificate in order to obtain a special permit for importation.

Vector surveillance and control

44. The Food and Environmental Hygiene Department (FEHD) regularly conducts specific surveys for mosquito vectors of malaria, dengue fever and Japanese encephalitis covering the mosquito species *Anopheles minimus*, *Anopheles jeyporiensis*, *Aedes albopictus*, *Aedes aegypti* and *Culex tritaeniorhynchus etc*. *Aedes aegypti* was the only yellow fever vector present

in Hong Kong. However ongoing vector surveillance by the FEHD has failed to find this urban vector in Hong Kong since the mid-1950s. In the absence of a mosquito vector, Hong Kong is regarded as a non-receptive area for yellow fever according to WHO.(19,20)

45. On the other hand, *Aedes albopictus*, is widely distributed in Hong Kong. Whilst having been demonstrated experimentally to be a possible vector of yellow fever, it is not as competent and important as *Aedes aegypti*. It is not regarded as a vector capable of causing epidemic disease in nature.(4,21,22) Nonetheless, Hong Kong has already in place an aggressive mosquito control programme targeting *Aedes albopictus*.

Public health education

46. Increasing awareness and enhancing knowledge on yellow fever amongst the public, especially amongst travellers, is an important aspect of disease prevention. Fact sheets on yellow fever are available at the CHP website. In addition, health education materials on various mosquito-borne diseases are disseminated through the Travel Health Centres, the websites of Travel Health Service and the Centre for Health Protection, and via announcements of public interest through the media. The Food and Environmental Health Department also produce materials on mosquito control measures including leaflets and dissemination of electronic materials on their website.

Prevention measures for Travellers

47. An increase in travel to yellow fever endemic countries will increase both the risk of infection in travellers and the spread of the disease to non-endemic areas. According to IHR, a vaccination centre for yellow fever must be designated by the local health administration. In Hong Kong the two Travel Health Centres of the Department of Health are the yellow fever vaccination centres.

48. All Hong Kong travellers visiting countries in yellow fever endemic areas are recommended to undergo yellow fever vaccination after a thorough assessment of the risk of infection and any contraindications to vaccination. In general, recommendations are in accordance with the WHO. The list of countries at risk of yellow fever transmission, the requirements for entry and recommendations for yellow fever vaccination can be accessed on the WHO website at http://www.who.int/ith/countries/en/index.html.(28)

Conclusion

49. There is a potential of yellow fever infection in travellers visiting or returning from endemic areas. Medical practitioners need to be aware of the disease in patients with a relevant travel history. While the risk for local

transmission is low, on-going surveillance on the disease, mosquito vectors, and non-human primates; effective vector control, and prompt disease investigation and control remains the essential preventive strategies. When travelling to yellow fever endemic areas, Hong Kong travellers are reminded to take mosquito bite preventative measures as well as to undergo yellow fever vaccination. Potential travellers should consult the Travel Health Centres of the Department of Health if they are visiting countries where entry requirements specify yellow fever vaccination.

Centre for Health Protection
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Annex 1: Side effects and contraindication for yellow fever vaccination

Potential side effects of 17 D yellow fever vaccination (1,6,11,23-25)

About 2 - 5% of the vaccinees may have mild systemic reactions such as headache, myalgia, malaise and weakness for 5 – 10 days after vaccination. The rate of severe hypersensitivity reactions, in particular anaphylactic reactions, is very low. Two other types of rare serious adverse reaction to the 17D vaccine are vaccine-associated neurotropic disease and vaccine-associated viscerotropic disease.

Since 1945, 26 cases of proven or probable post-vaccinal encephalitis related to 17D vaccine have been reported, of whom 16 were infants aged under 7 months. Due to the high incidence of vaccine-associated neurotropic disease among infants, the vaccine is contraindicated in infants under six months of age and not recommended for those aged 6-8 months. The risk of vaccine-associated neurotropic disease is less than 0.125 per million doses distributed.

Since 1996, there have been reports of small number of cases of serious viscerotropic infection similar to yellow fever disease following the yellow fever vaccination. Most of these reactions occurred in the elderly. Besides age, history of thymectomy or conditions associated with thymomas may also be a risk factor for this serious reaction. The risk of yellow fever vaccine-associated viserotropic disease appears to be limited to the first immunization against yellow fever. The crude estimated risk of developing this serious reaction ranged from 0.09 (in Brazil) to 2.5 (in the United States) per 1 million doses distributed. The risk among elderly above 60 years of age estimated in the United States is 20 – 25 per 1 million doses distributed.

Contraindications (4,24,26,27)

The contraindications for yellow fever vaccination include:

(a) Having a febrile illness.
(b) Person known to have hypersensitivity reactions to neomycin, polymyxin and egg.
(c) Pregnant women.
(d) Infants under six months old.
(e) On immunosuppressive treatment or having radiotherapy.
(f) Suffering from immunosuppressive diseases such as lymphoma, thymoma, leukaemia, Hodgkin' s disease and hypogammaglobulinaemia.
(g) Safety is uncertain in both symptomatic or asymptomatic HIV positive individuals.