衞生防護中心
Centre for Health Protection

Scientific Committee on Vector-borne Diseases

Update on epidemiology, prevention and control of yellow fever

Purpose

Yellow fever is an acute viral haemorrhagic disease transmitted by infected mosquitoes. The virus is endemic in tropical areas of Africa and Central and South Americas.[1] In view of the recent outbreaks of yellow fever in some African countries and Brazil, this paper reviews the latest global epidemiology of yellow fever and examines the preventive measures in Hong Kong.

Background

I. The virus

2. The yellow fever virus is a single-stranded RNA virus and belongs to the genus *Flavivirus* and family *Flaviviridae*.[2,3] The virus has one serotype and seven distinct genotypes with two in South America and five in Africa.[2]

II. Transmission

3. Mosquitoes acquire the virus by feeding on infected primates (human or non-human) and then transmit the virus to other primates (human or non-human). Yellow fever virus has three transmission cycles: jungle (sylvatic), intermediate (savannah), and urban.[4]

(a) The jungle (sylvatic) cycle involves transmission of the virus between non-human primates (e.g. monkeys) and mosquito species found in the forest canopy. The virus is transmitted by mosquitoes from monkeys to humans when humans are visiting or working in the jungle.

(b) In Africa, an intermediate (savannah) cycle exists that involves transmission of virus from mosquitoes to humans living or working in jungle border areas. In this cycle, the virus can be transmitted from monkey to human or from human to human via mosquitoes.

(c) The urban cycle involves transmission of the virus between humans and urban mosquitoes, primarily *Aedes aegypti*. The virus is usually brought to the urban setting by a viremic human who was infected in the jungle or savannah.

III. Mosquito vectors

4. Yellow fever is transmitted by mosquitoes belonging to the *Aedes*, *Haemagogus* and *Sabethes* species.[4] The mosquito species which are major vectors in each transmission cycle are shown in Table 1.

Table 1. Mosquito species which are major vectors in different transmission cycles[4]

Transmission cycle	Major vectors
Jungle cycle	Africa: *Aedes africanus* South America: *Haemagogus* species *Sabethes* species
Intermediate cycle	*Aedes* species
Urban cycle	*Aedes aegypti*

IV. Clinical features

5. The incubation period ranges from three to six days. Many people who contract the virus do not experience symptoms. In those who develop symptoms, the most common symptoms are fever, muscle pain with prominent backache, headache, loss of appetite, and nausea or vomiting.[1] While symptoms disappear after 3 to 4 days in most cases, a small percentage of patients enter a second, more toxic phase within 24 hours of recovering from initial symptoms.[1] High fever returns and several body systems are affected, usually the liver and the kidneys. In this phase people are likely to develop jaundice, dark urine and abdominal pain with vomiting. Bleeding can occur from the mouth, nose, eyes or stomach. Half of the patients who enter the toxic phase die within 7 - 10 days.[1] Those who recover from yellow fever generally have lasting immunity against subsequent infection. [5]

V. Diagnosis

6. For laboratory diagnosis of cases with epidemiological and clinical indication, the choice of testing is dependent on the timing of presentation of the patient to the healthcare setting. Detection of viral RNA could provide definitive diagnosis. Virus isolation is slow, less sensitive and requires laboratory safety considerations. Antibody testing is prone to cross-reaction with other *flaviviruses*. Liaison with the microbiology laboratory is necessary for determination of the optimal testing strategy in suspected patients and for result interpretation.

VI. Treatment

7. There is currently no specific anti-viral drug for yellow fever and treatment is symptomatic. Rest, fluids, and use of pain relievers and medication to reduce fever may relieve symptoms of aching and fever.[5] Specific care to treat dehydration, liver and kidney failure, and fever improves outcomes.[1] Good and early supportive treatment in hospitals improves survival rates, hence yellow fever patients should be hospitalised for supportive care and close observation whenever possible.[1,5]

Global Epidemiology

8. Yellow fever is endemic in tropical and subtropical areas in Africa and South America (Figures 1 and 2)[6]. According to the World Health Organization (WHO), 47 countries in Africa (34) and Central and South America (13) were endemic for yellow fever.[1,6,7] WHO estimates from the early 1990s indicated that 200 000 cases of yellow fever, with 30 000 deaths, were expected globally each year, with 90% occurring in Africa.[8] A recent modelling study based on African data sources estimates that the burden during 2013 is 84 000-170 000 severe cases and 29 000-60 000 deaths. The recent situation of yellow fever in several countries with major outbreaks is described below.

Figure 1 Yellow fever risk classification in Africa, 2016[6]

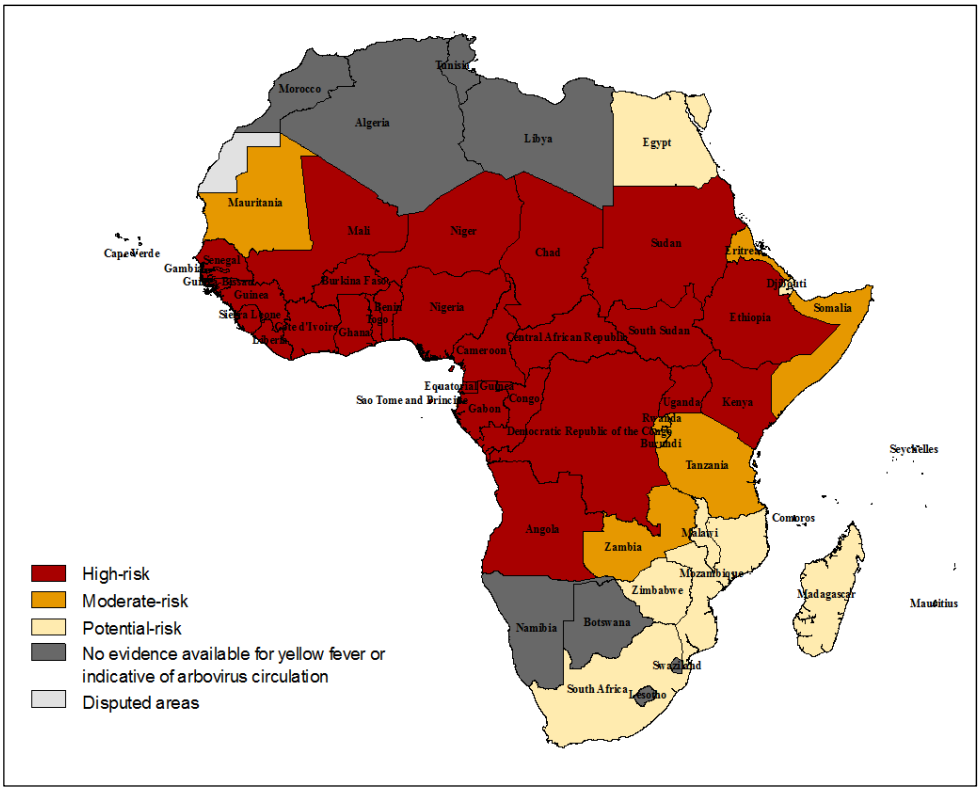
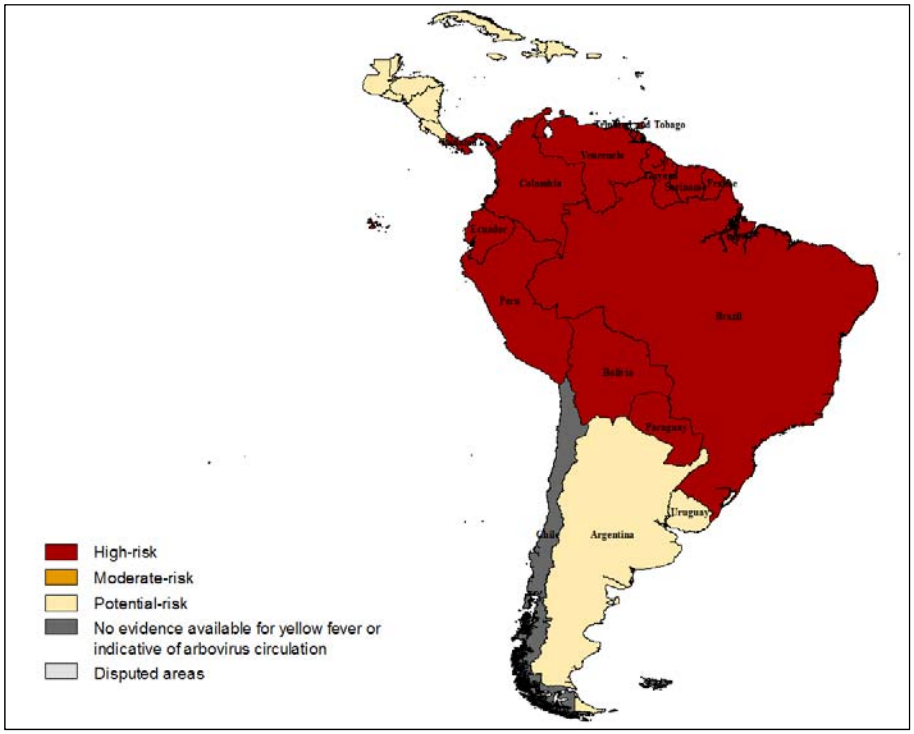


Figure 2 Yellow fever risk in South America, 2016[6]



I. Angola

9. Yellow fever is endemic in Angola[7] and the largest yellow fever outbreaks were reported from late 2015 to December 2016.[9] The Angolan outbreak was unusual not just for it size but because it was a largely urban outbreak, centred on the capital Luanda. The outbreaks started in a crowded urban environment from Luanda and spread quickly to the rest of the country and beyond borders. Cases of yellow fever in Angola had been exported to countries including Democratic Republic of Congo (DRC), Kenya and Mainland China.

10. The yellow fever outbreak was detected in Angola in December 2015 and a rapid increase in the number of cases was observed since mid-January 2016.[10] From early December 2015 to late July 2016, a total of 3 818 cases were reported. Among these, 3 294 cases had laboratory tests and 879 were confirmed. Laboratory confirmed cases were reported from 16 out of 18 provinces and from 80 out of 126 reporting districts. Luanda province reported the majority of the confirmed cases 487 (55.5%), followed by Huambo, 127 (14.5%) and Benguela, 116 (13.2%). Local transmission had been documented in 45 districts in 12 provinces. The majority of the confirmed cases were in males aged 15-19 years (215 cases, 20.8%), followed by 20-24 years (173 cases, 16.7%).[10]

11. In view of the unprecedented outbreaks, the national task force under the National Director of Public Health had strengthened surveillance (with a focus on case investigations and laboratory confirmation), vaccination, vector control, case management and social mobilisation to control the outbreaks. Emergency vaccination campaigns included mop up and preventative campaigns in hard-to-reach areas to ensure vaccine protection for as many people in all areas of risk as possible.[11] As of mid-June 2016, Angola had received 11 635 800 vaccines and almost half of the country (10 641 209 people) had been vaccinated.[12] This response exhausted the global stockpile of yellow fever vaccines several times.[11]

12. The last case in Angola was detected on 23 June 2016. In late December 2016 Angola declared the end of the yellow fever outbreak.[11] Angola reported a total of 4 306 cases and 376 deaths, of which 884 cases and 121 deaths were laboratory confirmed (case fatality rate among confirmed cases: 13.7%).[11]

II. Democratic Republic of the Congo

13. DRC is located in a geographical area known to be yellow fever endemic and autochthonous cases are regularly reported. On 22 March 2016, the National International Health Regulations (IHR) Focal Point of the DRC notified WHO of cases of yellow fever in connection with the outbreak occurring in Angola.[13]

14. In response to the outbreaks, the Ministry of Health of DRC implemented reactive vaccination, surveillance and laboratory, vector control, social mobilisation, and case management.[14] In May 2016, national authorities set up a mobile laboratory in DRC to accelerate case confirmation. As most of the Capital's districts (71%) had insufficient yellow fever vaccination coverage (<80%) between 2012-2014[15], the International Coordinating Group (ICG) on Vaccine Provision approved the vaccine request for DRC and released 2.2 million doses of vaccines and operational fund for the vaccination campaign.[14] In addition, WHO also supported the Ministry of Health in DRC to vaccinate 10.7 million people in the city of Kinshasa using a dose-sparing strategy (using one fifth of a regular dose of the yellow fever vaccine) as a short-term measure that would provide immunity against yellow fever for at least 12 months and likely longer.[11]

15. The last case in DRC was detected on 12 July 2016. In mid-February 2017 DRC declared the end of the yellow fever outbreak.[11] A total of 2 987 cases of yellow fever were reported from all 26 provinces of DRC during the outbreak, of which 81 cases had been laboratory confirmed, with 16 deaths (case fatality rate among confirmed cases: 20%).[11] Most of the confirmed cases acquired the infection in Angola.[16]

III. Brazil

16. In Brazil, 21 of the 27 states and the Federal District were considered to have areas at risk for yellow fever transmission.[17] The previous yellow fever outbreak in the state of Minas Gerais was recorded in 2002–2003, when 63 confirmed cases, including 23 deaths (case fatality rate: 37%), were detected.[18]

17. In December 2016, cases of yellow fever were reported in Minas

Gerais again and the outbreak extended to areas located in proximity of Minas Gerais. As of mid-April 2017, a total of 2 422 cases (including 623 confirmed, 1 128 discarded, and 671 suspected cases under investigation) were reported.[19] These included 326 deaths (209 confirmed, 53 discarded, and 64 cases under investigation). The case fatality rate among confirmed cases was 34%.[19] The cases were reported in 359 municipalities, while the confirmed cases were distributed among 108 municipalities in 5 states (Espírito Santo, Minas Gerais, Pará, Rio de Janeiro and São Paulo). The majority of the confirmed fatal cases were in Minas Gerais (151 cases), followed by Espírito Santo (48 cases).[19]

18. The government of Brazil, with support from PAHO and WHO, carried out vaccination campaigns for yellow fever in several states, while strengthening surveillance and case management throughout the country since January 2017.[20] As of late March 2017, 3.5 million doses of vaccine from the emergency stockpile were deployed to the country through the ICG on Vaccine Provision for yellow fever.[20] The ICG oversees a continuously replenished emergency stockpile of 6 million doses of yellow fever vaccine. Vaccine distribution plans are being updated as the situation evolves.[20]

19. Given the limitations on the availability of vaccines and with the aim of promoting the rational use, the Pan American Health Organization (PAHO) and WHO reiterated their recommendations to national authorities[19]:

(a) Conduct an assessment of vaccination coverage against yellow fever in areas at risk at the municipal level to guarantee at least 95% coverage among the resident population of these areas;

(b) Countries that are not currently experiencing outbreaks should not conduct immunisation campaign. Priority should be given to the use of vaccines in susceptible populations and to avoid revaccination;

(c) Ensure vaccination of all travellers to endemic areas at least 10 days before traveling;

(d) Depending on vaccine availabilities, Member States should have a small stock that allows them to respond to outbreaks;

(e) Postpone routine vaccination in children in non-endemic areas until sufficient vaccines are available. Once there is availability, catch-up campaigns should be conducted to complete vaccination schedules.

IV. Situation in Asia

20. Although the vector, *Aedes* spp. mosquitoes, are present in Asia, no autochthonous yellow fever cases are reported so far.[21]

21. Angola has large numbers of expatriate workers, including Mainland China. Mainland China, which had never had a yellow fever outbreak before, reported 11 imported cases who had returned from Angola in March and April 2016.[9] The 11 affected persons included eight males and three females, aged from 18 to 53 years. The majority of them were from the province of Fujian (7 cases), two were from Jiangsu, and one each was from Sichuan and Zhejiang respectively. At least five of them did not receive vaccination against yellow fever before going to Angola.[22] One case did receive yellow fever vaccine in Angola, but then developed symptoms within 4 days of receiving the vaccine so is likely to have acquired the infection before protection from the vaccination could develop.[22]

22. Regarding the imported yellow fever cases reported in China, WHO made the assessment that the risk of establishment of a local cycle of transmission in Mainland China was low due to the climatic condition at the time of importation of the cases, which was unfavourable for the competent vector *Aedes aegypti* mosquito.[23] However, imported cases of yellow fever in Mainland China highlighted the risk of international spread of yellow fever through non-immunised travellers and underlined the need to reinforce the implementation of vaccination requirements, in accordance with the IHR (2005).[23] WHO also urged Members States to strengthen the control of immunisation status of travellers to all potentially endemic areas.[23]

Response of WHO

23. In view of outbreaks of yellow fever outbreaks in Angola and DRC and international concerns, two meetings of Emergency Committee (EC) regarding yellow fever were convened by the Director-General under the IHR (2005) in May and August 2016. After discussion, it was the view of the Committee that yellow fever outbreaks in Angola and DRC was a serious public health event which warranted intensified national action and enhanced international support.[24,25]

24. WHO and its partners in the ICG for Vaccine Provision activated an emergency stockpile which was supported by the Global Alliance for Vaccine and Immunization (GAVI) to control the outbreaks in Angola and DRC. More than 41 000 volunteers and 8000 vaccination teams with more than 56 Non-governmental organisations (NGO) partners were involved in the mass immunisation campaigns. The vaccines used came from a global stockpile co-managed by Médecins Sans Frontières (MSF), International Federation of the Red Cross and Red Crescent Societies (IFRC), United Nations Children's Fund (UNICEF) and WHO.[11] More than 30 million people were vaccinated in Angola and DRC in emergency vaccination campaigns.[11]

I. WHO yellow fever strategic response plan[26]

25. In response to the yellow fever outbreak in Angola in 2016, WHO has developed the "Yellow Fever Strategic Response Plan". This document provided an overview of the recent outbreaks in Africa and outlined the response strategy for the rapid containment of outbreaks and prevention of international spread.

26. The objectives of the WHO yellow fever strategic response framework included (1) Surveillance and risk assessment; (2) Vaccination; (3) Case management; (4) Social mobilisation and risk communication; and (5) Vector Control.

27. The recommended yellow fever response interventions by country context were summarised in Annex 1.[26]

28. According to the WHO strategic response framework, countries and areas (e.g. Hong Kong) at risk of importation through international travel and trade and at risk of an outbreak due to infestation of *Aedes* spp. mosquitoes were recommended the following:

A. Surveillance and risk assessment

(i) Effective yellow fever surveillance is critical to ensure that new cases and newly affected areas are identified quickly and that all data are transmitted to decision makers in a timely manner.

(ii) Ad-hoc surveillance should be strengthened and entry screening of yellow fever vaccination status at entry points for travellers coming from affected countries may be implemented.

B. Vaccination

(i) Vaccination is the most important measure for preventing yellow fever. It provides effective immunity within 10 days for more than 90% of people vaccinated and within 30 days for 99% of people vaccinated. A single dose confers sustained immunity and life-long protection.

(ii) Travellers planning to visit yellow fever endemic and epidemic countries or returning from affected countries should be vaccinated at least ten days before travelling to the affected country or at least ten days prior to return to a non-affected country.

C. Case management

(i) All countries should be ready to detect cases of yellow fever and to transfer patients with suspected yellow fever (either from country entry point or from health facility of first admission) to pre-identified infectious disease health units competent to manage yellow fever cases.

(ii) There is no specific cure for yellow fever. Case management is based on supportive case and provision of insecticide-impregnated mosquito nets, including for daytime use, to prevent transmission to other patients via infected mosquitoes at the site of treatment.

(iii) Paracetamol can be used to relieve symptoms include fever and pain. However, non-steroidal anti-inflammatory agents (e.g. salicylates) should not be used to reduce the risk of bleeding in severely cases.

D. Social mobilisation and risk communication

(i) Health authorities should assess the pertinence of developing contingency plans and ensure that information is made available at the entry points.

(ii) Travellers to affected countries should be made aware of the compulsory requirement for vaccination at least ten days prior to departure.

(iii) Travellers returning from affected countries should be informed of how to recognise signs and symptoms, the importance of case notification and how to seek treatment in case of suspected infection.

E. Vector control

(i) Well-implemented vector control can effectively reduce the transmission of vector-borne diseases. For countries with *Aedes* but no yellow fever human transmission, the vector control must be taken before human cases of yellow fever occur.

II. Fractional dose of yellow fever vaccine as a dose-sparing option for outbreak response[27]

29. Owing to the potential shortages in yellow fever vaccine due to the outbreak in Angola and DRC, WHO Strategic Advisory Group of Experts (SAGE) on Immunization reviewed existing evidence and demonstrated that using a fifth of a standard vaccine dose (0.1ml instead of 0.5ml) would still provide protection against the disease for at least 12 months and possibly much longer. SAGE found that the available evidence was sufficient to determine that fractional dosing of yellow fever vaccine could be a safe and effective option for mass vaccination campaigns to control urban outbreaks in situations of acute vaccine shortage.

30. Fractional dosing was under consideration as a short-term measure, in the context of a potential vaccine shortage for use in emergencies. This approach is not proposed for routine immunisation, as there is not yet enough data available to show that lower doses would confer the life-long protection provided by a vaccination with one full dose. A yellow fever vaccine given at a fractional dose would not qualify for a yellow fever certificate under the IHR requirements. Travellers will need to obtain the full dose of the vaccine to be eligible for the yellow fever certificate.

Prevention of yellow fever in Hong Kong

I. Disease Surveillance

31. In Hong Kong, yellow fever is a notifiable infectious disease. The Centre for Health Protection (CHP) of the Department of Health (DH) must be notified of any case of yellow fever whence investigation and control measures

will be implemented. The last case of imported yellow fever was recorded in 1945 and there had been no case of yellow fever in Hong Kong in the past 70 years.

32. Laboratory capabilities for diagnosing yellow fever are available in Hong Kong. The Public Health Laboratory Services Branch of the CHP could be contacted for advice and virology testing service for suspected cases.

II. Vector surveillance and control

33. In Hong Kong, the urban vector *Aedes aegypti* is not found. The prevailing species *Aedes albopictus* had been demonstrated experimentally to be a possible vector of yellow fever, but it is not as competent and important as *Aedes aegypti*. It is not regarded as a vector capable of causing epidemic disease in nature[28,29] but was suggested to be a possible bridge of the gap between the jungle and urban cycles.[30] Nonetheless, as *Aedes albopictus* is the vector for transmitting chikungunya fever, dengue fever and Zika virus infection, Hong Kong has already in place an aggressive mosquito control programme targeting *Aedes albopictus*.

34. Since 2000, the Food and Environmental Hygiene Department (FEHD) has been using Oviposition Trap (Ovitrap) to detect the presence of adult *Aedes* mosquitoes in selected areas. Starting from October 2015, there are a total of 52 locations selected for the vector surveillance. The Ovitrap Index for *Aedes albopictus* can be classified into 4 levels. Specific preventive and control measures will be initiated accordingly.[31]

III. Public Health Education

35. In view of the outbreak of yellow fever in Angola in 2016, an article was published on Communicable Diseases Watch, and letters were sent to doctors and hospitals in March 2016 to raise the awareness among doctors and the public. CHP has produced various health education materials, such as pamphlets, posters and infographics, for distribution in the community. Health information related to vector-borne diseases, including yellow fever, is available at the CHP website. Besides, disease information and preventive measures, including proper use of insect repellents, have been delivered through various channels such as CHP Facebook Fanpage, CHP YouTube Channel, television

and radio stations, 24-hour health education hotline (2833 0111), newspapers and media interviews. The health advice and education materials are updated according to the latest situation. Latest yellow fever outbreak information as well as current advice for international travellers are also published on DH's travel health service webpage (http://www.travelhealth.gov.hk/eindex.html) and updated regularly.

IV. Preventive measures for Travellers

36. Under IHR (2005), each State must designate at least one yellow fever vaccination centre, but, if it so wishes, no longer has to restrict the issuance of yellow fever vaccination certificates to such an officially-designated centre. The yellow fever vaccine used must be approved by WHO. The WHO no longer maintains a list of vaccinating centres designated for the administration of yellow fever vaccine and for the issue of International Certificates of Vaccination or Revaccination against yellow fever.[32]

37. In Hong Kong, yellow fever vaccination is only available in the two Travel Health Centres of DH. WHO recommends immunisation against yellow fever for all travellers aged 9 months and above, travelling to and from at-risk areas, unless they are contraindicated for vaccination.[33]

38. It is the only disease specified in the IHR (2005) for which countries may require proof of vaccination from travellers as a condition of entry under certain circumstances. A list of countries with risk of yellow fever transmission and countries requiring yellow fever vaccination can be found on WHO website at http://www.who.int/ith/2017-ith-annex1.pdf?ua=1.

39. For those who are contraindicated for vaccination, they should obtain a letter of exemption from the medical practitioner and seek advice from the relevant embassy before travel. Travellers departing from Hong Kong to visit countries in yellow fever endemic areas are recommended to arrange a travel health consultation with doctors at Travel Health Centres at least six weeks before departure for a thorough assessment and for yellow fever vaccination, if indicated.

40. The vaccination comprises a single subcutaneous injection administered from the age of 9 months onwards. The vaccine provides lifelong

protection. When travellers are vaccinated against yellow fever, they will be given an International Certificate of Vaccination or Prophylaxis. The certificate is valid only 10 days after the vaccine is given and the first dose of vaccine takes 10 days to provide good protection. Following the amendment to the IHR (2005) on 11 July 2016, the certificate of vaccination against yellow fever is valid for the life of the person vaccinated, instead of 10 years. This lifetime validity applies automatically to all existing and new certificates, beginning 10 days after the date of vaccination.[34]

41. The most common systemic side effects after full dose yellow fever vaccine included headache, asthenia, myalgia, malaise, fever, rash and chills. Serious adverse events such as yellow fever vaccine-associated viscerotropic disease, neurological diseases, and severe hypersensitive reactions were uncommon. The incidence of acute viscerotropic disease after yellow fever vaccination ranged from 0 to 0.21 cases per 100 000 vaccine doses in regions where yellow fever is endemic, and from 0.09 to 0.4 cases per 100 000 doses in populations not exposed to the virus. Neurological (or neurotropic) disease was estimated to occur about 0.8 cases per 100 000 vaccine doses administered. [9]

42. Nevertheless, a suspected case of yellow fever vaccine-associated viscerotropic disease was recorded in 2014 in Hong Kong. The patient was a 65-year-old man who had received the primary dose of yellow fever vaccine in Hong Kong before his trip to South America. He developed fever, loss of appetite, headache and mild myalgia five days after vaccination. He also had difficulty to concentrate, experienced restless and malaise. Tea-coloured urine was also noticed. He became mildly confused ten days after vaccination and was admitted to hospital for investigation. Laboratory test revealed that both blood and cerebrospinal fluid (CSF) samples were tested positive for yellow fever virus of vaccine strain. The patient was eventually discharged after 14 days of hospitalisation.[35] DH consulted the Yellow Fever Initiative of WHO for their expert views on this case. After reviewing the clinical presentation and laboratory findings, it was concluded that this case was not compatible with adverse events following yellow fever immunisation.

43. There are four manufacturers which have been prequalified by WHO to produce yellow fever vaccine (Annex 2). In the United Kingdom, Stamaril, with Sanofi Pasteur as the marketing authorization holder, is the only licensed yellow fever vaccine. Besides, Sanofi Pasteur also manufactures yellow fever vaccine named YF-VAX and is the only yellow fever vaccine approved in the United States (US) and Canada. In Hong Kong, there is only one registered yellow fever vaccine, namely Stamaril Pasteur (Yellow Fever) Vaccine, which has been registered since 1996. DH is maintaining a steady

supply of yellow fever vaccines for immunisation of travellers.

44. Shortage of yellow fever vaccines increased the challenge of prevention and control of yellow fever. Due to the recent manufacturing problems of YF-VAX by Sanofi Pasteur, the Centers for Disease Control and Prevention (CDC) of the US announced in April 2017 that shortage of yellow fever vaccines was expected to lead to a complete depletion of the vaccine available for the immunisation of US travellers by mid-2017. In this connection, Sanofi Pasteur submitted an application of Stamaril which is another yellow fever vaccine manufactured by Sanofi Pasteur France and is not licensed in the United States.[36]

Conclusions

45. Yellow fever is a serious disease. Due to the large volume of international travel, there is risk of importation of yellow fever into Hong Kong. Although the risk for local transmission is low, ongoing surveillance, mosquito control and prompt disease investigation and control are essential to prevent the disease. Travellers should be reminded to consult Travel Health Centres if they are going to visit countries with yellow fever transmission.

46. It is also important to keep abreast of the latest development of vaccine strategy (e.g. dose-sparing strategy) and to consider assessment of the local applicability.

Centre for Health Protection

Department of Health

June 2017

References

1. World Health Organization. Yellow fever Fact sheet. 2016; http://www.who.int/mediacentre/factsheets/fs100/en/. Accessed 21 Apr 2017.
2. John Hopkins Medicine. Yellow fever virus. 2016; https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540672/all/Yellow_fever_virus. Accessed 25 April 2017.
3. Heymann DL. *Control of Communicable Disaeses Manual*. 19ed. Washington DC: American Public Health Association; 2008.
4. Centers for Disaese Control and Prevention. Transmission of Yellow Fever Virus. 2015; https://www.cdc.gov/yellowfever/transmission/index.html. Accessed 25 April 2017.
5. Centers for Disaese Control and Prevention. Yellow fever - symptoms and treatment. 2015; https://www.cdc.gov/yellowfever/symptoms/index.html. Accessed 26 April 2017.
6. World Health Organization. Eliminate Yellow fever Epidemics (EYE): a global strategy, 2017-2026. *Wkly Epidemiol Rec.* 2017;92(16):193-204.
7. Jentes ES, Poumerol G, Gershman MD, et al. The revised global yellow fever risk map and recommendations for vaccination, 2010: consensus of the Informal WHO Working Group on Geographic Risk for Yellow Fever. *Lancet Infect Dis.* 2011;11(8):622-632.
8. World Health Organization. Vaccines and vaccination against yellow fever. WHO position paper -- June 2013. *Wkly Epidemiol Rec.* 2013;88(27):269-283.
9. World Health Organization. Epidemic focus on yellow fever: a rapid "need to know" spotlight. http://www.who.int/csr/disease/epidemic-focus/yellow-fever/en/. Accessed 21 Apr 2017.
10. World Health Organization. Yellow fever situation report - Angola (29 July 2016). http://www.who.int/emergencies/yellow-fever/situation-reports/29-july-2016/en/. Accessed 21 Apr 2017.
11. World Health Organization Regional Office for Africa. The yellow fever outbreak in Angola and Democratic Republic of the Congo ends (14 February 2017). http://www.afro.who.int/en/media-centre/pressreleases/item/9377-the-yellow-fever-outbreak-in-angola-and-democratic-republic-of-the-congo-ends.html. Accessed 24 APr 2017.
12. World Health Organization. Disease outbreak news: Yellow fever – Angola (14 June 2016). http://www.who.int/csr/don/14-june-2016-yellow-fever-angola/en/. Accessed 21 Apr 2017.
13. World Health Organization. Yellow Fever – Democratic Republic of the Congo (11 April 2016). 2016; http://www.who.int/csr/don/11-april-2016-yellow-fever-drc/en/. Accessed 10/5/2017, 2017.
14. World Health Organization. Disease outbreak news: Yellow fever – Democratic Republic of the Congo (2 June 2016). http://www.who.int/csr/don/02-june-2016-yellow-fever-drc/en/. Accessed 24 Apr 2017.
15. World Health Organization. Disease outbreak news: Yellow fever – Democratic Republic of the Congo (2 May 2016). http://www.who.int/csr/don/02-may-2016-yellow-fever-drc/en/. Accessed 27 Apr 2017.
16. World Health Organization. Yellow fever situation report (28 October 2016). http://www.who.int/emergencies/yellow-fever/situation-reports/28-october-2016/en/. Accessed 24 Apr 2017.
17. Pan American Health Organization WHO. Brazil Works to Control Yellow

Fever Outbreak, with PAHO/WHO support 2017; http://www2.paho.org/hq/index.php?option=com_content&view=article&id=13098%3Abrazil-control-yellow-fever-outbreak-paho-support&catid=740%3Apress-releases&Itemid=1926&lang=en. Accessed 2 May 2017.
18. World Health Organization. Disease outbreak news: Yellow fever – Brazil (13 January 2017). http://www.who.int/csr/don/13-january-2017-yellow-fever-brazil/en/. Accessed 24 Apr 2017.
19. Pan American Health Organization. Yellow Fever – Epidemiological Update (17 April 2017). http://www2.paho.org/hq/index.php?option=com_docman&task=doc_download&Itemid=270&gid=39286&lang=en. Accessed 24 APr 2017.
20. World Health Organization. WHO dispatched 3.5 million doses of yellow fever vaccine for outbreak response in Brazil. 2017; http://www.who.int/csr/disease/yellowfev/vaccination-in-Brazil/en/. Accessed 2 May 2017.
21. World Health Organization. Epidemic focus-Yellow fever. 2017; http://www.who.int/csr/disease/epidemic-focus/yellow-fever/en/. Accessed 9 May 2017, 2017.
22. World Health Organization. Disease outbreak news: Yellow Fever – China (6 April 2016). http://www.who.int/csr/don/6-april-2016-yellow-fever-china/en/. Accessed 24 Apr 2017.
23. World Health Organization. Disease outbreak news: Yellow Fever – China (22 April 2016). http://www.who.int/csr/don/22-april-2016-yellow-fever-china/en/. Accessed 24 Apr 2017.
24. World Health Organization. Meeting of the Emergency Committee under the International Health Regulations (2005) concerning Yellow Fever 2016; http://www.who.int/mediacentre/news/statements/2016/ec-yellow-fever/en/. Accessed 2 May 2017, 2017.
25. World Health Organization. Second meeting of the Emergency Committee under the International Health Regulations (2005) concerning yellow fever 2016; http://www.who.int/mediacentre/news/statements/2016/yellow-fever-second-ec/en/. Accessed 2 May 2017, 2017.
26. World Health Organization. Yellow Fever Strategic Response Plan. 2016; http://apps.who.int/iris/bitstream/10665/246103/1/WHO-YF-ENB-16.2-eng.pdf. Accessed 2 May 2017, 2017.
27. World Health Organization. Lower doses of yellow fever vaccine could be used in emergencies. 2016; http://www.who.int/mediacentre/news/statements/2016/yellow-fever-vaccine/en/. Accessed 4 May 2017.
28. Gubler DJ. Aedes albopictus in Africa. *Lancet Infect Dis.* 2003;3(12):751-752.
29. Monath TP. Yellow fever: an update. *Lancet Infect Dis.* 2001;1(1):11-20.
30. Monath TP. Aedes albopictus, an exotic mosquito vector in the United States. *Annals of internal medicine.* 1986;105(3):449-451.
31. Food and Environmental Hygiene Department. Pest Control - Dengue fveer. 2017; http://www.fehd.gov.hk/english/safefood/dengue_fever/index.html. Accessed 27 April 2017.
32. World Health Organization. Frequently asked questions about the International Health Regulations (2005). 2009; http://www.who.int/ihr/about/FAQ2009.pdf. Accessed 19 May 2017.
33. World Health Organization. Countries with risk of yellow fever transmission and countries requiring yellow fever vaccination. 2017; http://www.who.int/ith/2017-

ith-annex1.pdf?ua=1. Accessed 19 May 2017.
34. World Health Organization. New yellow fever vaccination requirements for travellers. http://www.who.int/ith/updates/20160727/en/. Accessed 25 April 2017.
35. Leung WS, Chan MC, Chik SH, Tsang TY. First case of yellow fever vaccine-associated viscerotropic disease (YEL-AVD) in Hong Kong. *J Travel Med.* 2016;23(4).
36. Gershman MD AK, Ritchey J. Addressing a Yellow Fever Vaccine Shortage — United States, 2016–2017. *MMWR Morb Mortal Wkly Rep.* 2017;ePub: 28 April 2017.
37. World Health Organization. Prequalified Yellow Fever Vaccine (Institut Pasteur de Dakar). 2017; https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=66. Accessed 8 May 2017, 2017.
38. World Health Organization. Prequalified Yellow Fever Vaccine (Bio-Manguinhos/Fiocruz). 2017; https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=19. Accessed 8 May 2017, 2017.
39. World Health Organization. Prequalified Yellow Fever Vaccine (Sanofi Pasteur SA). 2017; https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=112. Accessed 8 May 2017, 2017.
40. World Health Organization. Prequalified Yellow Fever Vaccine (Chumakov Institute). 2017; https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=175. Accessed 8 May 2017, 2017.

Annex 1 Recommended yellow fever response interventions (by country context) by WHO[26]

	Current yellow fever outbreak	**Endemic or adjacent to outbreak**	**At risk of importation and *Aedes spp* present**
Surveillance and risk assessment			
Assess the risk of the spread or start of an outbreak	✓	✓	✓
Prepare for the importation of (more) cases from another area or country	✓	✓	✓
Ensure prompt and open information sharing in country and with the WHO and members states at risk through the IHR focal person.	✓	✓	✓
Strengthen case detection and reporting, including laboratory diagnostic capabilities	✓	✓	✓
Monitor the course of the epidemic and the outcome of interventions	✓		
Vaccination			
Undertake reactive mass vaccination in areas where it is still likely to have an impact on the course of the outbreak, primarily in urban settings	✓		
Consider halting yellow fever vaccination provided through the expanded program of immunisation, in order to prioritize the use of available vaccine for mass vaccination	✓	✓	
Case management			
Prevent excess mortality among suspected and confirmed cases	✓	✓	✓
Social mobilisation and risk communication			
Community engagement and social mobilisation	✓	✓	
Risk communication	✓	✓	✓
Vector control			
Intensify vector surveillance and control	✓	✓	

Annex 2 Characteristics of Yellow fever vaccines prequalified by WHO[37-40]

Manufacturer	Country	Commercial Name	Type	Pharmaceutical Form	No. of Doses	Route of Administration	Shelf Life	Storage	WHO recommendations on Handling of opened multi-dose vials
Sanofi Pasteur SA	France	STAMARIL	Live attenuated	Lyophilised active component to be reconstituted with excipient diluent before use	10	Intramuscular or Subcutaneous	36 months	2-8°C and protected from light	Opened vials should be discarded after 1-6 hours after opening (Note: See the manufacturer's product insert for specific details) or at the end of the immunisation session, whichever comes first
Bio-Manguinhos/ Fiocruz	Brazil	Yellow Fever	Live attenuated	Lyophilised active component to be reconstituted with excipient diluent before use	5, 10, 50	Intramuscular or Subcutaneous	36 months	2-8 °C and protected from light	Opened vials should be discarded after 1-6 hours after opening (Note: See the manufacturer's product insert for specific details) or at the end of the immunisation session, whichever comes first
Chumakov Institute	Russian Federation	-	Live attenuated	Lyophilised active component to be reconstituted with excipient diluent before use	2, 5, 10	Intramuscular or Subcutaneous	24 months	2-8°C and protected from light	Opened vials should be discarded after 1-6 hours after opening (Note: See the manufacturer's product insert for specific details) or at the end of the immunisation session, whichever comes first
Institut Pasteur de Dakar	Senegal	Stabilized Yellow Fever Vaccine	Live attenuated	Lyophilised active component to be reconstituted with excipient diluent before use	5, 10, 20	Intramuscular or Subcutaneous	36 months	2-8°C and protected from light	Opened vials should be discarded after 1-6 hours after opening (Note: See the manufacturer's product insert for specific details) or at the end of the immunisation session, whichever comes first