Commentary

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Yellow fever in China is still an imported disease

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Summary **Yellow fever is a vector-borne disease endemic to tropical regions of Africa and South America. A recent outbreak in Angola caused hundreds of deaths. Six cases of yellow fever imported from Angola were reported recently in China. This raised the question of whether it will spread in China and how it can be prevented. This article discusses the possibility of yellow fever transmission in China and the strategies to counter it.**

Keywords: Yellow fever, China, vector, traveler, vaccine

1. Introduction

A 32-year-old Chinese man had a fever and chills while in Luanda, the capital of Angola, on March 8, 2016. He sought medical treatment after returning to China two days later. His serum sample was positive for yellow fever virus RNA according to nucleic acid amplification test. The National Health and Family Planning Commission of China then reported the first case of yellow fever in Asia on March 13, 2016 (*1*). Within two weeks, three more cases were confirmed in Beijing, one was confirmed in Shanghai, and another case was confirmed in Fujian Province (*2-5*). All six cases were imported from Angola. This raised the question of whether yellow fever will spread in China and how it can be prevented.

Yellow fever is caused by the yellow fever virus, an RNA virus of the genus *Flavivirus*. Members of the genus *Flavivirus* also include the West Nile virus, dengue virus, Zika virus, and several other viruses which may cause encephalitis. The vector for virus transmission is the mosquito. There are three epidemiologically different infectious cycles in which the virus is transmitted from mosquitoes to humans or other primates (*6*). Different genera of mosquitoes serve as vectors during different infectious cycles. In the "urban cycle," *Aedes aegypti* is the only vector. The mosquito can also transmit other diseases, including Zika fever, dengue fever, and chikungunya fever. The urban cycle is responsible for the major outbreaks of yellow fever in Africa. In the sylvatic "jungle cycle", monkeys act as the host and *Aedes africanus* and other *Aedes spp*. act as the vector. In Africa, there is also an intermediate transmission cycle that occurs in rural areas typically at the edges of forests. Both humans and non-human primates act as the host and *Aedes spp*. act as the vector.

Most patients infected with the yellow fever virus experience mild flu-like symptoms, including a fever, muscle pain with prominent backaches, headaches, shivers, loss of appetite, and nausea or vomiting. These symptoms disappear after 3 to 4 days. Only around 15% of cases progress to the toxic stage, and up to 50% of patients with an untreated severe infection will die (*7*).

Yellow fever is endemic to tropical regions of Africa and South America, which have a combined population of over 900 million people; 90% of these people are in Africa. A recent analysis of the country-by-country geographic risk of yellow fever classified 27 of 32 countries in Africa as having a risk for yellow fever transmission and five countries as having a "low potential" for exposure to yellow fever (*8*). An estimated 130,000 cases of yellow fever with a fever and jaundice or hemorrhage occurred in Africa in 2013 and an estimated 78,000 people died from the disease (*9*). In the current yellow fever outbreak in Angola, at least 450 people were infected and 178 died (*10*).

Few cases have been reported in areas where the disease is not endemic. From 1970 to 2013, a total of 10 cases of yellow fever were reported in unvaccinated travelers from the United States and Europe who

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traveled to West Africa (5 cases) or South America (5 cases). Eight (80%) of the 10 travelers died (*11*). An important aspect is the susceptibility of many areas where the disease is not endemic, particularly in Southeast Asia, to the introduction and spread of yellow fever since the *A. aegypti* density in this area is relative high (*12*).

2. Yellow fever has not spread in China

Yellow fever is a tropical disease that mainly occurs in Africa and South America. With growing migration and an increasing density of *A. aegypti* in Asia, there is an increased risk of yellow fever outbreaks in Asia (*13*). However, no case of yellow fever has been previously reported in Asia. Many hypotheses have been postulated to explain why the disease has never appeared in Asia (*14*). The most reasonable explanation is the different distribution and varied capacity of the vectors in Asia and Africa.

A. aegypti primarily survives in the tropics and sub-tropics, with concentrations in northern Brazil and Southeast Asia, but there are relatively few areas suitable for its survival in Europe and temperate North America (*12*). In China, previous studies indicated that *A. aegypti* was only found south of latitude 22° North, a region including coastal areas of Taiwan, Hainan, Guangdong, Guangxi, and some offshore islands. Following the development of border trade, tourism, and global warming, *A. aegypti* has expanded its range to north of latitude 25° (*15*). The current cases were identified in Beijing, Shanghai, and Fujian, none of which are areas where *A. aegypti* is distributed. Temperature is the most important predictor of the global distribution of *A. aegypti* (*12*). A minimum mean temperature of 8°C in January and a minimum annual mean temperature of 16°C are threshold values for the establishment of *A. aegypti* in China (*15*). Temperatures in March in the aforementioned areas were not suitable for *A. aegypti*. Thus, the possibility of yellow fever transmission in China is extremely low.

However, this does not exclude the possibility of autochthonous transmission due to rapidly increasing migration in Southern China, where the *A. aegypti* density is relatively high especially in summer. The recent spread of another virus transmitted in a human-to-mosquito-to-human cycle – the dengue virus – in Guangzhou, China illustrates the threat (*16-18*). Although the outbreaks of dengue fever that occurred in China were mainly due to imported cases from Southeast Asia, the dengue virus was transmitted locally, resulting in around fifty thousand cases of dengue fever and six deaths in 2014 (*19,20*). Fortunately, there is still enough time to take action to prevent the spread of yellow fever in China. The recommended strategies to control yellow fever will now be described.

3. Border Screening

The old strategy of border control that included border entry/exit screening, quarantine, and isolation is the most powerful component of the public health response to imported infectious diseases. Border entry screening can be undertaken through self-reports, reporting of sick passengers to health authorities by airline/transit agencies, visual inspection of travelers, and/or screening of travelers for a fever through the use of infrared thermal imaging scanners (*21*). In the six cases of yellow fever, all six patients had symptoms when they left Angola. The family of one traveler reported his medical status to health authorities in advance, so he was identified and isolated when he entered China, but only two of the other five travelers were detected at the airport. The Government has recognized the importance of border screening and it has enhanced quarantine since the first case of yellow fever (*22*). Travelers from Angola must now provide proof of yellow fever vaccination. Travelers without that proof will be quarantined when they enter China.

However, experience from the 2003 SARS epidemic has shown that screening and quarantining entering travelers at international borders does not substantially delay the introduction of a virus, except in some island countries (*23*). Border screening is indiscriminant and costly. In 2003, 619 individuals with a fever who entered China through the port of Shenzhen were tested for typical mosquito-borne pathogens including the dengue virus, Japanese encephalitis virus, Chikungunya virus, yellow fever virus, West Nile virus, and malaria. Pathogens were detected in only 9% of the travelers (*24*).

Communication has now been suggested as a key component of border control since it has a small positive influence on health care-seeking behavior among incoming travelers (*23,25,26)*. Communication can take multiple forms, including informational videos, posters, signs, in-flight announcements, flyers, and health alert notices, and those forms should also include the Internet or short text messages to mobile phones in the modern era (*21,23*). Thus, information about the yellow fever epidemic in Angola, symptoms of the disease, procedures for self-reporting if one has symptoms while entering the country, and advice on seeking care if one develops symptoms after entering the country should be provided. In conjunction, clinicians should be trained to recognize yellow fever since this awareness can be highly effective in facilitating the rapid identification and isolation of incoming travelers who are possibly infected. Individuals with a fever of jaundice should also be asked about their travel history. Procedures for primary care doctors should including reporting and referral of individuals who may be infected.

In addition to travelers, luggage and cargo from Angola may carry infected mosquitoes that may then

bite unvaccinated people. Thus, measures should also be implemented to eliminate mosquitoes in vehicles and containers from affected areas.

4. Vector Control

Currently, the best way to prevent the spread of yellow fever in China is to prevent the six patients from coming into contact with vectors. However, this approach will not work if asymptomatic cases were overlooked at the border. Experience with Dengue control in southern China showed the importance of vector management. The incidence of dengue fever decreased gradually along with surveillance and rapid detection of *Aedes* vectors in 2014 (*27*). Like dengue fever, yellow fever and other vector-borne diseases need to be prevented in China through integrated vector management (IVM). Supervised efforts at IVM by the National Health and Family Planning Commission and the rapid detection of the dengue vector *Aedes* by the Chinese CDC have been shown to be effective in controlling the vector (*27*). Research has repeatedly suggested that vector control requires interventions with intersectorial partnerships, the involvement of local communities, and IVM (*28*). Embedding social participation in decision-making and environmental management to improve vector control was feasible and significantly reduced vector densities (29).

Integrated approaches that tackle all life stages of the mosquito are recommended. Although fogging to kill adult mosquitoes provides the most visible evidence that a government is taking action, it is not that effective. All mosquitoes require water to complete 3 of the 4 stages of their life cycle. Mosquitoes need an area with stagnant or slow moving water to lay their eggs. Thus, eliminating places where mosquitoes can breed is the most effective intervention for mosquito control.

The Government should conduct surveys to collect data on the abundance, distribution, and types of places where mosquitoes can breed. Health program planners should improve people's knowledge of yellow fever prevention and control, inform the public that mosquitoes are vectors for transmission of yellow fever, and educate the public to instill hygiene in daily life to eliminate breeding grounds. In a successful approach to control of dengue fever in Uruguay, the public collected containers that could hold water where mosquitoes could breed and the Government then disposed of those containers (*30*). Large cisterns need to be covered, modified so that they no longer hold water, or treated with long-lasting larvicide.

The public should also take personal protective measures to prevent mosquito bites, such as avoiding outdoor activities during twilight hours (dawn and dusk), and preventive actions (such as using repellent, using bed nets, and wearing long-sleeved shirts and socks).

5. Vaccination

Vaccination is the most important measure to prevent yellow fever. The vaccine is effective, with more than 600 million doses administered worldwide; the vaccine provides effective immunity against yellow fever within 10 days for more than 90% of people vaccinated and within 30 days for 99% of people vaccinated (*7*). Historically, there has been debate over the duration of protection after vaccination. Currently, a single dose of yellow fever vaccine is deemed to be sufficient to confer life-long protection against yellow fever and a booster every 10 years is not necessary (*31*). Under International Health Regulations, the validity of proof of yellow fever vaccination for travel will changed from 10 years to the duration of one's life for people vaccinated in June 2016. Until then, revaccination after 10 years will still be required, and some countries may continue to request that travelers provide proof of vaccination or a booster within the last 10 years (*32*).

The vaccine is also safe and mild adverse events only occur in 10-20% of recipients (*33*). People who should not be vaccinated include infants younger than 9 months, pregnant women, people with severe allergies to egg protein, people with severe immunodeficiency due to symptomatic HIV/AIDS or other causes, or people with a thymus disorder (*7*).

The Chinese public does not need to be vaccinated against yellow fever. However, travelers who will go to an area where the disease is endemic should be vaccinated 10 days before travelling. The risk of acquiring yellow fever for travelers visiting an area where the disease is endemic is difficult to predict. For a 2-week stay, the estimated risk of contracting yellow fever is 50 per 100,000 for an unvaccinated traveler visiting an area in West Africa where the disease is endemic and 5 per 100,000 for an unvaccinated traveler visiting such an area in South America (*11*). The yellow fever vaccine effectively protects travelers from been infected. There has been only 1 documented case of yellow fever in a vaccinated traveler (*11*). However, the patient in the sixth imported case that was reported in Fujian Province was vaccinated in Angola 4 days before the onset of symptoms (*5*). Generally, neutralizing antibodies are produced within 10 days. Thus, the likelihood is that the patient was infected before the vaccine became effective.

Patients in all six cases had not been vaccinated against yellow fever before going to Angola. The reason for a failure to be vaccinated may be because travelers are unaware of the need to be vaccinated, fear of an adverse reaction, the individual is misidentified as someone for whom the vaccine is contraindicated, *etc*. Thus, greater efforts should be made to inform travelers about yellow fever and where they can be vaccinated and to ensure that they have been vaccinated at least 10 days before travelling to an area where the disease is endemic.

6. Conclusion

Yellow fever is still an imported infectious diseases in China. If no action is taken, it may spread in Southern China. The main strategies to locally control yellow fever transmission are to perform border screening, to control vectors of the disease, and to vaccinate travelers going to areas where the disease is endemic. All of these actions require cooperation from the public, so public education is key.

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