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Review

Yellow fever cases in Asia: primed for an epidemic

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SUMMARY

There is currently an emerging outbreak of yellow fever in Angola. Cases in infected travellers have been reported in a number of other African countries, as well as in China, representing the first ever documented cases of yellow fever in Asia. There is a large Chinese workforce in Angola, many of whom may be unvaccinated, increasing the risk of ongoing importation of yellow fever into Asia via busy commercial airline routes. Large parts of the region are hyperendemic for the related *Flavivirus* dengue and are widely infested by *Aedes aegypti*, the primary mosquito vector of urban yellow fever transmission. The combination of sustained introduction of viraemic travellers, an ecology conducive to local transmission, and an unimmunized population raises the possibility of a yellow fever epidemic in Asia. This represents a major global health threat, particularly in the context of a depleted emergency vaccine stockpile and untested surveillance systems in the region. In this review, the potential for a yellow fever outbreak in Asia is discussed with reference to the ecological and historical forces that have shaped global yellow fever epidemiology. The limitations of surveillance and vector control in the region are highlighted, and priorities for outbreak preparedness and response are suggested.

1. A yellow fever outbreak emerges in Africa

On January 22, 2016, the internet-based disease outbreak reporting system of the International Society for Infectious Diseases – ProMED – posted an alert of 23 cases of yellow fever (YF) amongst locals, as well as Congolese and Eritreans, in a heavily populated suburb of Luanda, the Angolan capital.[1] This was based on an official Angolan Ministry of Health announcement. Three days later, the number of suspected cases had grown to 99 (26 confirmed), including eight deaths. On January 29, ProMED reported additional cases in southern Huila Province nearly 1000 km from Luanda.[2] Over the following weeks, a major urban YF epidemic unfolded in Angola, and by April 10, a total of 1751 suspected cases (582 laboratory-confirmed) with 242 deaths had been reported. The outbreak is widespread, involving 59 districts in 12 of the 18 provinces in the country, including the capital Luanda, which has recorded 406 confirmed cases. Three confirmed cases in neighbouring Democratic Republic of Congo have been connected with the Angolan outbreak,[3] and infected travellers have been reported in Kenya.[4]

Of major concern, the first YF cases have been reported in Asia, occurring in infected travellers from Angola. By April 10, 10 laboratory-confirmed cases had been imported into China, including six in Fujian Province, an area where dengue transmission has occurred.[5] With a large expatriate Chinese community in Angola, it is likely that additional undetected cases may have been imported. If ongoing introduction of cases occurs in areas with a high density of the urban YF mosquito vector, *Aedes aegypti*, it is possible that local transmission could occur in China and potentially spread to Southeast Asia.

Approximately two billion people live in *Ae aegypti*-infested countries in Asia. The prospect of a YF introduction into this unvaccinated population poses a major global health threat. In this review, the potential for a YF outbreak in Asia is discussed in the context of the ecological and historical forces that have shaped global YF epidemiology. The aim is to draw attention to this emerging epidemic and to provide impetus for the necessary public health response.

PubMed was searched for papers written in English with the search terms "yellow fever" and "Aedes aegypti", and all articles that focused on epidemiology, recent outbreaks, and control and

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prevention were selected. The World Health Organization (WHO) website and Google Scholar were also searched for epidemiological reports. The bibliographies of review articles and other selected articles were scanned for other relevant references.

2. The ecology and clinical manifestations of yellow fever

YF is a viral haemorrhagic fever transmitted by mosquitoes. The YF virus (YFV) is the prototype virus of the family *Flaviviridae*, a group that includes the epidemic arthropod-borne viruses causing dengue, Japanese encephalitis (JE), and Zika, amongst others. YF is enzootic in rainforests of Africa and South America, and is maintained in sylvatic transmission cycles between monkeys and arboreal mosquitoes. Sporadic human infection can occur after intrusion into this 'jungle cycle' through occupational or recreational exposure to infected mosquitoes, resulting in single cases or limited sylvatic outbreaks. In South America, this may spill over into nearby towns to enter an inter-human urban cycle. In the wet African savannah, where mosquito vectors reach high densities in the rainy season and overlap with areas of human activity, there is intense enzootic transmission with increased risk of human infection. Inter-human transmission that occurs as a result of these epizootics is usually self-limited, but can lead to the emergence of rural epidemics. This is known as the intermediate cycle, or 'zone of emergence,' because extension of an epizootic into dry savannah areas with larger human and domestic vector populations may establish an urban epidemic cycle that can lead to explosive outbreaks.

Ae aegypti is the vector for urban YF epidemics in both Africa and South America, and is also the main vector for dengue and Zika virus transmission. It is exquisitely well-adapted for this purpose: *Ae aegypti* breeds in man-made containers of water, feeds predominantly on human blood and bites multiple individuals in a single blood meal, lives in close association with human dwellings, and efficiently transmits YFV in its saliva.

The clinical manifestations of YF range from asymptomatic infection to multi-organ failure and death. Most infections are asymptomatic. Most symptomatic cases experience a self-limiting febrile illness associated with myalgia, back pain, and prostration. The fever, which lasts about 4 days, is accompanied by high levels of viraemia, increasing the risk for mosquito infection during a blood meal.[6] Approximately 15–25% of infected individuals enter a 'period of intoxication' after a brief remission of fever. This is a multisystem disease dominated by hepato-renal failure, profound jaundice, and a bleeding diathesis. Death occurs in 20–50% of these cases.[6] This is a much higher mortality than dengue, which causes death in 5% of patients, and as low as 1% in settings with experience in dengue management.[7] Morbidity in survivors is substantial, with a prolonged convalescent phase characterized by weakness and fatigue.

3. Epidemiology

YFV almost certainly originated in Africa.[8] Its initial spread to Central and South America, along with *Ae aegypti*, was a consequence of the trans-Atlantic slave trade.[9–12] The appalling conditions on slave ships supported an intense and sustained introduction of YFV into the Americas: hundreds of thousands of West Africans were transported together with domesticated *Ae aegypti* mosquitoes, which presumably set up breeding and transmission cycles during the long voyages,[13] delivering a critical mass of viraemic hosts and vectors into a receptive environment. This allowed for the establishment of enzootic YF in the forests surrounding slave ports and its rapid dissemination throughout the continent to become the most important epidemic disease in the region for three centuries.[14] Yellow fever epidemics had significant impact as far north as Philadelphia in the 18th century. The conditions for YF introduction into the Americas are not dissimilar to the current scenario in Angola, where thousands of foreign workers are rapidly transported via air to Asian cities that have dense infestations of *Ae aegypti* vectors and unvaccinated populations.

Epidemic YF in the Americas was successfully controlled in the mid 20th century through mass vaccination and vector reduction programmes.[14,15] However, sporadic cases and small, limited outbreaks continue to occur, associated with forest exposure.[16] After a major resurgence in the region in the late 20th century,[17] there now appears to be a downward trend of reported cases.[18] Between 1985 and 2012, there were an estimated 4066 reported cases and 2351 deaths from YF (58% case fatality rate) in the Americas. Failure to sustain vector control and vaccination programmes has led to the reinvasion of *Ae aegypti* across large swaths of the Americas, as evidenced by ongoing chikungunya and Zika outbreaks. If sufficient YF cases occur in cities to facilitate urban transmission, we may yet see YF epidemics again in the Americas.

In Africa, YF continues to place an enormous burden on communities living in endemic areas. Between 1980 and 2012, 150 yellow fever outbreaks in 26 African countries were reported to the WHO, and over 90% of the estimated 200 000 annual global cases occur on the continent. However, field studies suggest that the actual number of cases may be 10 to 500 times higher.[19,20] This is supported by a recent modelling study, which showed that YF may infect up to 1.8 million individuals in Africa annually, resulting in 180 000 (95% confidence interval 51 000–380 000) cases and 78 000 (95% confidence interval 19 000–180 000) deaths;[21] this accounts for 0.8% of all-cause mortality in endemic regions, and up to 3% in West Africa where most cases occur.[21] Although complete eradication of YF is not possible due to the sylvatic reservoir, significant progress has been made with the introduction of YF vaccine into routine child immunization programmes.[22] Mass vaccination has led to a 27% reduction in overall annual burden and a 57% reduction in cases in targeted countries.[21] However, according to WHO and United Nations Children's Emergency Fund (UNICEF) estimates, only 41% of the target population had received YF vaccination in 2014,[23] well below the recommended 80% threshold for the prevention of an epidemic. In Angola, the YF vaccine coverage of 77% in 2014 (dropping to 70% in 2015), has clearly been inadequate to prevent the current outbreak.

4. Re-emergence of yellow fever in the Americas and Africa: implications for Asia

In dengue-endemic areas, the basic reproduction numbers (R_0) of YF and dengue are closely connected, suggesting that the introduction of a single YF-infected individual has the potential to trigger an urban YF epidemic.[24] This has been a concern in South American countries where there has been a reinvasion by *Ae aegypti* in most large cities.[16,25,26] Although the last urban YF outbreak in South America occurred in 1942 in Brazil, further cases of spill-over with documented urban transmission have been reported in Bolivia[27] and Paraguay.[28] Both of these outbreaks were limited in space and time: in Paraguay, a rapid national response with mass vaccinations and surveillance terminated the outbreak.[29]

A similar situation exists in Africa, where there are regular large epidemics involving partially immune populations living at the forest–urban interface. This occurs mainly in West Africa, but even Kenya has experienced a recent large sylvatic outbreak.[30] During urban epidemics in Africa, the incidence of infection is as high as 20%. Up to 40% of the affected population demonstrate serological evidence of recent YF infection, which may reflect partial