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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

immunity from prior vaccination or infection.[31] This incidence highlights the devastating potential of a YF introduction into a completely non-immune population.

With increasing volumes of air travel, the international spread of emerging and vector-borne infections has become a substantial risk.[29] This risk is particularly acute in the Asia-Pacific region, where systems for YF surveillance and detection are largely untested, and YF vaccination is limited to travellers.[14,16] The volume of south-to-south travel – between Asia and South America, or between Asia and Africa – has been less well-documented. This has now become an important consideration, as underscored by the chikungunya and Zika experience. For YF, Africa, with over 90% of global YF cases, is the most likely source for YF importations into Asia. The 10 YF cases reported in China suggests that not all travellers were effectively vaccinated despite Chinese public health regulations. The current confluence of a significant urban YF outbreak in Angola together with a large expatriate Chinese workforce (estimated at 20 000) with suboptimal vaccination levels may provide the ideal ecological conditions for the introduction and urbanization of YFV in China and other Asian countries. These reports of imported cases from Angola in China therefore need to be taken extremely seriously.

5. Barriers to yellow fever introduction into Asia

Despite an abundance of people, monkeys, and *Ae aegypti* throughout tropical and subtropical latitudes, yellow fever virus has not previously been reported in Asia. In contrast, dengue virus has established an urban transmission cycle in large populations in the region, where it is now hyperendemic with major public health and economic impacts. The failure of YF to become established in the Asia-Pacific is unexpected, given the closely shared disease ecology with dengue. The actual epidemiological difference suggests that local factors in the Asia-Pacific have prevented YF from gaining a foothold in the region, and may provide some reassurance that there are sufficient barriers to prevent the establishment of YF in the Asia-Pacific.

Urban outbreaks of YF are much less common in East Africa, and are associated with enzootic YFV genotypes transmitted by sylvatic mosquito vectors, rather than *Ae aegypti*.[32] This suggests that the East African *Ae aegypti* mosquitoes are less favourable vectors for human disease and may therefore have limited adaptation to human environments, reducing the possibilities for survival during the long trade crossings by boat to Asia historically.[33] Phylogenetic data suggest that *Ae aegypti* may eventually have reached Asia from the West, and not via the East African trade route, and Asia thus probably became infested with *Ae aegypti* later than the Americas.[32,33]

Additionally, there is some evidence of geographical variation in *Ae aegypti* susceptibility to YF,[34] raising the possibility that Asian strains may be less competent YF vectors.[8,26] Notwithstanding the above limitations, there may have been importations of YF into Asia after its widespread infestation with *Ae aegypti*, potentially during the large African epidemics in Sudan,[35] Ethiopia,[36] and Kenya.[30] But, these would have involved few cases from isolated rural and remote regions amongst populations unlikely to travel by commercial airlines, and thus had a low potential for sustained or transcontinental transmission.[6,8,26,37] Together with delayed historical introduction, this low risk of importation of viraemic YF individuals to Asia has been the dominant explanation for the absence of the disease in the region. However, it is less compelling in the contemporary context of a large outbreak in a major urban centre such as Luanda with direct flight connections to *Aedes*-infested cities in Asia.

The delayed and limited introduction of YF into Asia may have left open an ecological niche for the establishment and dominance of dengue and other flaviviruses in the region through the native *Aedes albopictus*, and later the well-adapted *Ae aegypti* mosquito. This may have impacted on the ecology of YF in Asia in two key ways. First, dengue virus may out-compete YFV within *Ae aegypti*,[37] either preventing co-infection or reducing infectiousness by induction of a latently infected state.[38,39] Second, the high population seroprevalence of dengue and JE in Asia may provide cross-protective immunity and act as a barrier to the establishment of YF.[6]

In strong support of this hypothesis, experimental animals with previous heterologous flavivirus exposure experience lower levels of viraemia and less severe disease when challenged with YFV.[40,41] Thus, although the presence of heterotypic flavivirus antibody does not lower the risk of infection, dengue-immune individuals who become infected with YF may be less likely to transmit YF to mosquitoes. Using a mathematical transmission model, Amaku and colleagues showed that YF prevalence is strongly affected by cross-immunity, and that this best accounted for the absence of YF in Asia compared with other competing hypotheses.[42] This raises the possibility that areas that are endemic but not hyperendemic for dengue, such as southern China or Hong Kong and Singapore, may be vulnerable to YF outbreaks, as the level of dengue and JE immunity in the population may not be as complete as in other parts of Southeast Asia. However, these findings do not explain the presence of both dengue and urban YF in Africa, suggesting that additional factors may have a role in the failure of YF to become a dominant flavivirus in Asia.

These other factors may relate to the YFV itself and its transmission dynamics. YF has lower peak viral loads compared to dengue,[25] limiting its transmission potential in dengue-endemic environments. And unlike dengue, YF has maintained is sylvatic character. Urban transmission is thus always initiated by spill-over from the jungle or savannah,[26] and consequently may have a lower risk of occurring in urban centres in Asia. The higher mortality of YF may further limit its introduction and persistence in an urban cycle and allow dengue to dominate in Asia.

A virological explanation for the lower frequency of YF outbreaks in East Africa, and its absence in Asia, may be the observed regional differences in YF viral genotypes,[43] which potentially influence virulence phenotypes in humans and non-human primates.[31,32] The genetic differences between geographic strains of *Ae aegypti* influence its competence as a YF vector,[44] and it has been suggested that this also contributes to a lower YF transmission risk in Asia.[8,14,26] Finally, although it is possible that humans and non-human primates in Asia have a lower genetic susceptibility to YF, this has never been demonstrated.

6. Factors conducive to yellow fever entry into Asia

In the face of the above limitations, there is a modern precedent for large-scale introduction of other *Aedes*-borne viral infections into receptive populations. In 2004, a Kenyan outbreak of the alphavirus chikungunya (CHIKV) spread via the India Ocean basin to India and Southeast Asia, leading to an explosive epidemic involving millions of people from populations with historical CHIKV exposure.[45] The same epidemic strain, which is spread by *Ae aegypti*,[46] is causing an ongoing chikungunya epidemic in the Americas, and has already led to 39 000 infections this year. The WHO has recently declared a Public Health Emergency of International Concern in response to the Zika virus (ZIKV) outbreak in the same region. Like YFV, ZIKV is a flavivirus that originated in Africa and is mainly transmitted by *Ae aegypti*. It entered South America via the Pacific in 2014, and has rapidly spread to infect over a million people, with autochthonous cases reported from 26 countries[47,48] by early April 2016. The Zika and chikungunya epidemics provide powerful counterpoints to the most important

putative limitations for YF introduction into Asia, namely that a shared vector and prior population exposure do not necessarily constrain the entry of a new arbovirus into dengue-endemic regions.

In the particular case of YF there are a number of other contemporary factors that, when taken together, represent the ideal conditions for an Asian epidemic. These are summarized in Table 1. First, and perhaps the most critical, is the volume of travellers entering the region on commercial airlines. This allows for the introduction of symptomatic individuals during the period of maximal viraemia, as well as those incubating the virus or asymptomatically infected, raising the potential for transmission to mosquito vectors. The Asia-Pacific region will represent the largest regional market for air transport in 2016,[49] accounting for a third of global passengers. Even a limited YF outbreak in China could therefore rapidly disseminate to the higher risk regions of India or Southeast Asia though air travel. Second, the ongoing importation of YF-infected individuals into China in April 2016 is nearing the peak period of dengue transmission, starting in July.[5] The very high vector densities during this time may overcome other barriers to YF urbanization, including the theoretical possibility that Asian strains of *Ae aegypti* are less competent than their African counterparts.[50] Third, there appears to be low effective vaccination coverage of Chinese workers in Angola. The risk of illness for an unimmunized person spending 2 weeks in an area of epidemic activity has been estimated at one in 267,[51] translating into a substantial number of potential cases amongst returning workers, with the consequence of sustained regional YF exposure. Finally, there is a strong possibility that widespread epidemic transmission could occur in Asia before it is recognized.[16] This is related to the difficulty in YF diagnosis due to serological cross-reactivity with prevalent flaviviruses such as dengue and JE, and a similar clinical presentation to other endemic diseases such leptospirosis, typhoid fever, rickettsiosis, malaria, and viral hepatitis.

Using the successful introduction and threats of re-emergence of YF in South America as a historical model, there appear to be four main conditions that need to be fulfilled to support YF introduction into a new population: (1) sufficient migratory flow of viraemic individuals from YF-endemic/epidemic areas (i.e., intense and sustained introduction), (2) a high density of competent vectors in receptive ecological conditions, (3) a susceptible or partially susceptible human and monkey population, and (4) inadequate surveillance with delayed recognition leading to ineffective vaccination programmes. Current conditions in many parts of Asia therefore appear to be favourable for the introduction of YF and the establishment of a transmission cycle in the region[12] (Figure 1). In this context, the occurrence of YF cases from the Angolan outbreak imported to China creates a situation primed for an Asian epidemic, and demands an adequate response.

7. Responses to prevent yellow fever introduction into Asia

Actions in Central and South America in the early 20th century demonstrated that urban YF epidemics can be successfully prevented and controlled. As with other arboviruses, the tenets underlying YF prevention are surveillance, vaccination, and vector control. This should be coupled with the development of systems that can support a rapid outbreak response. These include strengthening laboratory capacity, the ability to carry out epidemiological and entomological investigations, and emergency measures to interrupt transmission, such as mass vaccination, destruction of urban mosquito breeding sites, education about mosquito avoidance, use of ovitraps, and domiciliary residual spraying.[57–60]

The extent and nature of *Ae aegypti* infestation in Asia prohibits the use of vector elimination as a feasible short-term intervention for outbreak prevention,[60] and so the urgent focus needs to be on coordinated programmes of surveillance and vaccination of travellers. Unfortunately, the high proportion of asymptomatic infections and the non-specific nature of the mild clinical disease limit the usefulness of passive surveillance to detect YF introduction into a new population. In the event of an outbreak in Asia, even active case finding will be challenging in the context of overlapping clinical presentation with other endemic infections and the limitations in diagnostic tests described above. To mitigate these limitations, governments could consider enforcing a 7-day quarantine for returning travellers from endemic countries without YF vaccination certificates. Most countries in the Asia-Pacific require proof of YF vaccination for travellers arriving from countries with a risk of YF transmission,[61] and this clearly needs to be more strictly enforced after the importation of YF-infected travellers to China. In response to this, the WHO has recommended the reinforcement of vaccination requirements in China, and the Chinese government has deployed teams to Angola to provide vaccination to its citizens there. However, there is a delay of

Table 1
Factors supporting the introduction of yellow fever into Asia

Risk factor	Comments
Favourable local ecology	Abundance of the primary mosquito vector, high human population density, and forested areas with monkey hosts. This will support both an enzootic cycle and urban transmission.
Large numbers of returning travellers from an active outbreak in Angola	There are an estimated 20 000 Chinese workers in Angola, plus many from other Asian countries, including India. This could support sustained, high volume YF introduction into Asia.
High volumes of passenger air travel between an active epidemic and China, and with other Asian countries	Air travel allows the introduction into China of viraemic cases or of people incubating YF, and facilitates subsequent dissemination within Asia.
Possibly low vaccine coverage of Chinese workers	Unimmunized travellers increase the risk of infection and subsequent importation.
Importation of cases during *Aedes aegypti* breeding season, starting July	This will coincide with peak vector densities, increasing the risk for local transmission.
YF cases imported into dengue-endemic areas	Six cases have been reported from Fujian Province, where the local transmission of dengue occurs with high *Aedes aegypti* concentrations.
Difficulty in recognition of imported cases	Overlapping clinical presentation with other endemic infections and cross-reactivity of YF serology with other endemic flaviviruses may delay the recognition of an incipient epidemic.
Inadequate vaccine stocks	The current vaccine supply would not support a full outbreak response in Asia.
Poor surveillance structures	Asian laboratories are not geared for YF detection, airport screening is not sufficiently sensitive for passive surveillance (misses cases in the incubation period, fever masked by antipyretics), and there are limited numbers of travel medicine experts.[52]

YF, yellow fever.

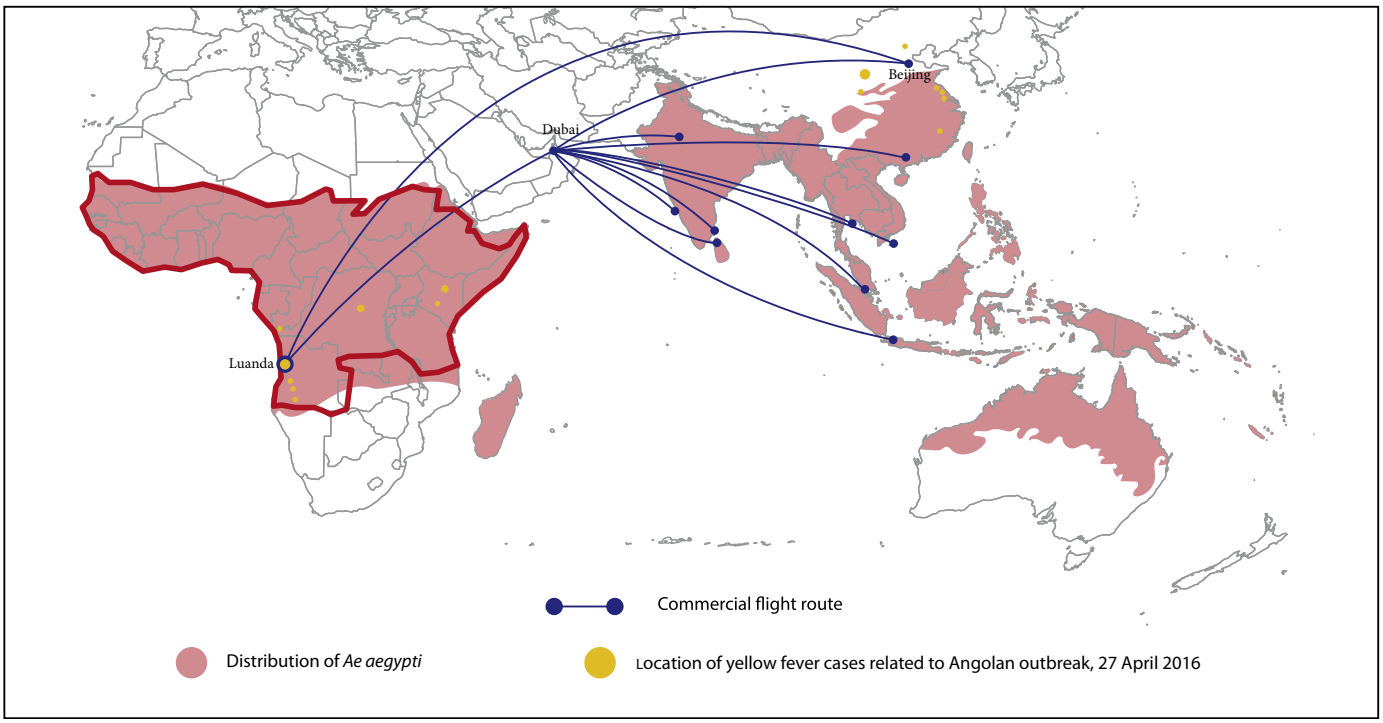

Figure 1. Map showing the distribution of *Ae aegypti* across Africa and the Asia-Pacific region[53] (areas shaded pink). The red outline delineates yellow fever-endemic regions.[54] Yellow dots represent the location of yellow fever cases related to the Angolan outbreak (source: HealthMap).[55] Commercial flight routes with direct connections between Luanda and Beijing and indirect connections from Luanda to South and Southeast Asia via Dubai (source: FLIRT)[56] are also represented.

10 days until the development of protective immunity after vaccination, and surveillance for imported cases in Asia should be ongoing. Unofficial disease reporting systems, such as ProMED, are becoming increasingly useful for the early detection and communication of new cases in emerging outbreaks, and have an important role in raising situational awareness.

The most powerful tool in YF control is vaccination. Mass vaccination campaigns are extremely effective at reducing the YF burden in populations with low immunity, both in the prevention of enzootic spill-over and in the rapid control of urban epidemics.[14,17,21] As of April 10, the Angolan government, together with international partners, had administered 5.9 million doses of YF vaccine in the Luanda province (accounting for 90% of the city's population); preparations for mass vaccination in Huambo and Benguela provinces are underway. However, the global emergency YF vaccine stockpile is depleted, and there is currently not enough vaccine to cover Angola's population. The production of new vaccine using the current method of embryonated chicken eggs is slow and limits capabilities to rapidly produce large vaccine quantities in response to an outbreak. It is therefore highly unlikely that sufficient YF doses would be available for an effective emergency YF outbreak response in Asia, further emphasizing the vulnerability of the situation. Much lower doses of YF vaccine are likely to be as effective as the currently used full-dose vaccine,[62] and it has been suggested that a fifth of the current dose should be administered to expand vaccine stockpiles in the context of the global threat posed by the current outbreak.[63] This should be considered seriously and implemented as a matter of urgency.

8. Conclusions

There is no single factor that accounts for the absence of YF in Asia, and it is likely that a complex combination of virological, environmental, and social processes have shaped the current global epidemiology of YF restricting the disease to Africa and the Americas. The current scenario of a YF outbreak in Angola, where there is a large community of non-immune foreign nationals, coupled with high volumes of air travel to an environment conducive to transmission in Asia, is unprecedented in history. These conditions raise the alarming possibility of a YF epidemic, with a case fatality of up to 50%, in a region with a susceptible population of two billion people and where there is extremely limited infrastructure to respond effectively. The growing number of imported cases in China shows how critical it is to recognize this risk now in order to take adequate pre-emptive action so that a global catastrophe can be averted.

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