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Received: 14 December 2021 | Revised: 5 January 2022 | Accepted: 18 January 2022

DOI: 10.1002/rmv.2333

REVIEW

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Aedes mosquitoes in the emerging threat of urban yellow fever transmission

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Funding information

Agence Nationale de la Recherche, Grant/Award Number: DSP-2021-269/ARS; Horizon 2020 Framework Programme, Grant/Award Numbers: 731060, 734548; Integrative Biology of Emerging Infectious Diseases, Grant/Award Number: ANR-10-LABX-62-IBEID

Abstract

This last decade has seen a resurgence of yellow fever (YF) in historical endemic regions and repeated attempts of YF introduction in YF-free countries such as the Asia-Pacific region and the Caribbean. Infected travellers are the main entry routes in these regions where competent mosquito vectors proliferate in appropriate environmental conditions. With the discovery of the 17D vaccine, it was thought that YF would be eradicated. Unfortunately, it was not the case and, contrary to dengue, chikungunya and Zika, factors that cotribute to YF transmission remain under investigation. Today, all the signals are red and it is very likely that YF will be the next pandemic in the YF-free regions where millions of people are immunologically naïve. Unlike COVID-19, YF is associated with a high case-fatality rate and a high number of deaths are expected. This review gives an overview of global YF situation, including the non-endemic Asia-Pacific region and the Caribbean where Aedes aegypti is abundantly distributed, and also proposes different hypotheses on why YF outbreaks have not yet occurred despite high records of travellers importing YF into these regions and what role Aedes mosquitoes play in the emergence of urban YF.

KEYWORDS

Aedes mosquitoes, risk assessment, yellow fever

1 | INTRODUCTION

Yellow fever (YF) has been a historical arboviral threat following massive populations displacements from its cradle of origin in Africa into the New World since the 17th century.[1] The discovery by Carlos Finlay and Walter Reed of yellow fever virus (YFV) transmission by the mosquito *Aedes aegypti* brought hope in the control of YF outbreaks in the Americas at the beginning of the 20th century.[2,3] Thus, vector control was the first attempt to eradicate urban YF transmission before the discovery of a YF vaccine. Unfortunately, relaxation of vector control measures and vaccine supply shortage hinder the control of YF. With the growing geographical expansion of *Ae. aegypti*, YF continues to be a burden for human health, causing each year, 51,000–380,000 severe cases and a very high in-hospital case fatality rate (20%–60%),[4,5] with an estimated global disability-adjusted life year of 314 (95% uncertainty interval [UI] [67.2–900])

Abbreviations: CI, confidence interval; Crl, credible interval; CHIKV, chikungunya virus; DALY, disability-adjusted life year; DENV, dengue virus; ISV, insect-specific virus; JEV, Japanese encephalitis virus; NHP, non-human primate; PAHO, Pan-American Health Organisation; UI, uncertainty interval; YF, yellow fever; YFV, yellow fever virus; ZIKV, Zika virus.

All authors contributed equally to this work.

in 2017.[6] Although the current YF epidemics are still restricted to Africa and South America, the past history of YF in the Caribbean and Mediterranean Europe has shown that the sporadic exportation of YF to the non-endemic regions could lead to local outbreaks in the presence of competent vector,[7-9] particularly in the Caribbean islands which experienced deadly YF epidemics during the colonial era, and with a still on-going sylvatic YF circulation in Trinidad.[10] On the contrary, even though YF has never struck the Asia-Pacific region, the region remains at high risk of emergence as it hosts millions of immunologically naive people living at close proximity with urban mosquitoes competent for YFV.[11] These two essential factors for YF urban transmission, along with expanding global transportation raise fears of YF occurrence in cities and its arrival in the Asia-Pacific region. This review compiles the current knowledge on YF and describes the entomological factors which might contribute to YF resurgence and emergence.

2 | DISCOVERY OF *AEDES AEGYPTI*-MEDIATED YELLOW FEVER VIRUS TRANSMISSION

Between 1881 and 1889, YF caused thousands of deaths during the construction of the Panama Canal until the transmission mode of YFV was elucidated.[12] In 1881, Carlos Finlay hypothesised that YF was transmitted by *Ae. aegypti* (which was then called *Culex fasciatus*). Finlay inoculated 102 healthy volunteers with YFV-infected mosquitoes, and found that volunteers could develop YF symptoms.[2] However, the theory of transmission by mosquitoes was not very well accepted as some experimental designs could be improved, such as unstandardised criteria for mild YF diagnosis, and incorrect assumption on mosquito vector competence.[2,13] The mosquito-mediated YFV transmission was verified in 1900. Walter Reed and colleagues confirmed Finlay's hypothesis with improved experimentations; two members of Reed's research team, James Carroll and Jesse Lazare volunteered for self-experimentation with YFV-infected mosquitoes and developed into severe and lethal symptoms.[14] The death of Jesse Lazare brought enough attention and a more rigorous experimentation was carried out thereafter. After several tests with human volunteers and YFV-infected mosquitoes, Reed proved the route of YFV transmission by mosquitoes.[3] In these experiments, YF symptoms could be observed in the volunteers exposed to *Ae. aegypti* having become infected 14–25 days after feeding on symptomatic patients.[3] These findings opened a new era in the control of infectious diseases through controlling mosquito vectors.

3 | YELLOW FEVER VIRUS GENOME

YFV was first isolated in 1927, from a symptomatic patient in Ghana.[15,16] Belonging to the family *Flaviviridae*, YFV is an enveloped virus with an icosahedral capsid of 40–60 nm diameter. The genome of YFV is a positive sense, single-stranded RNA molecule. Except the highly structured 5′ and 3′ untranslated regions that are essential for virus replication, the 11 kb YFV genome contains a single open reading frame encoding for three structural proteins (capsid [C], matrix [M], and envelope [E]) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5). All the viral proteins have a defined role to allow infecting the host cells and escape the immune system.[17]

4 | YELLOW FEVER VIRUS GENOTYPES IN AFRICA AND AMERICA

There are seven YFV genotypes identified: five African genotypes (West Africa I, West Africa II, Angola, East Africa, and East/Central Africa) and two American genotypes (South America I and South America II) (Figure 1). Phylogenetic studies have suggested that among the five African genotypes, the Angola, East Africa, and East/Central Africa genotypes are genetically more heterogeneous than the West Africa genotypes I and II.[18] While the two American genotypes are closely related to each other, the two West African genotypes were less diverged than the other African genotypes to the American genotypes, suggesting that West Africa is the possible origin of the YFV strains circulating in America.[19] Evidence suggests that the West Africa II and East/Central Africa genotypes are enzootic YFV in Africa, whereas the West Africa genotype I might be circulating among human populations, even though nucleotide and amino acid sequence variations between West Africa genotypes I and II are close. Interestingly, the Angola genotype is the most divergent genotype compared to the other African genotypes, however, it does not present significant differences in amino acids sequence; the sequence variation between YFV Angola and East Africa genotype is only 0.4%–0.9% in amino acids but 16.7%–17.4% in nucleotides.[18] In South America, the YFV phylodynamic data suggests that the recent YFV epidemics were initiated by different genotypes originating from different regions. The last outbreaks were mainly caused by the America genotype I from Trinidad and Tobago, which was imported from Northern Brazil in the 1950s and responsible for the outbreaks before the 1990s. The most recent genotype belongs to the America genotype II which can be traced back to 1956; this genotype spread from Peru to the neighbouring countries of Bolivia, Ecuador, Northern Brazil, Trinidad and Tobago, where only sylvatic YFV transmissions were reported.[20]

5 | YELLOW FEVER VIRUS TRANSMISSION

5.1 | Sylvatic, rural, and urban cycles of yellow fever virus

Three transmission cycles are classically described; they involve different vectors and hosts in different ecological environments. In the sylvatic cycle, the virus is circulating only between NHPs (playing the role of amplification hosts) and zoophilic mosquito species. In the intermediate cycle, the virus can be passed from NHPs to humans

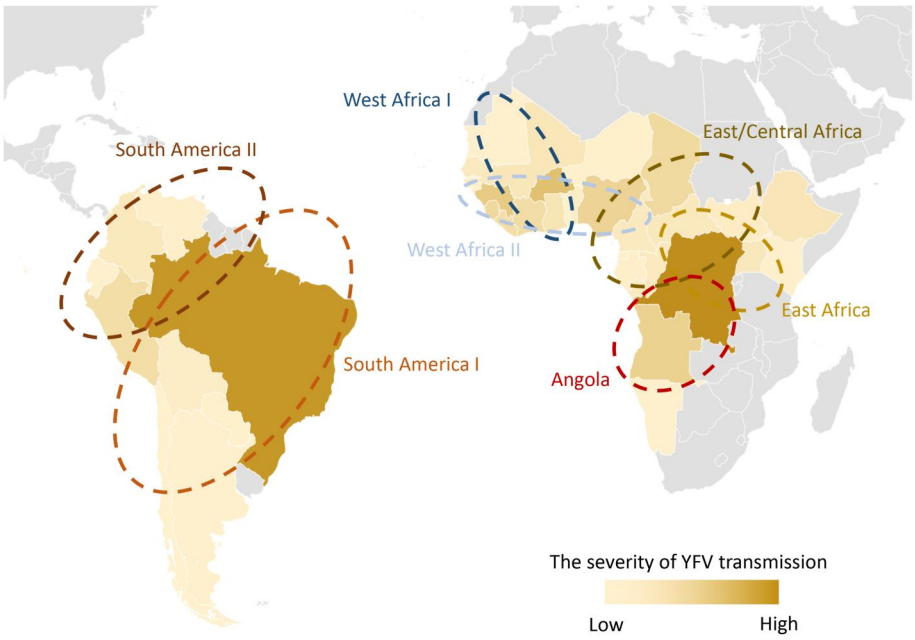

FIGURE 1 Africa and America yellow fever (YF) epidemics from 2000 to 2020 and circulating genotypes. The severity of YF virus transmission was calculated with the annual reported cases that weighted by the year of outbreak, the more recent the heavier. Data were extracted from Global Healthy Observatory, WHO (https://www.who.int/data/gho/data/indicators/indicator-details/GHO/yellow-fever---number-of-reported-cases); the map was created by Microsoft PowerPoint

through the transmission by an anthropo-zoophilic mosquito; increasing human activities at the fringe between the forest and the human dwellings accentuate spill over events (emergence zone). The urban cycle occurs when infected people are repeatedly confronted to bites of anthropophilic YFV-infected mosquitoes. Up to date, YFV circulation is restricted only in sub-Saharan Africa and South America.

5.2 | *Aedes aegypti* as the main epidemic vector of urban yellow fever virus

A competent mosquito can become a vector by ingesting the virus from an infected host, and being able to transmit the virus to other hosts through the bite. In a mosquito, the ingested virus infects and replicates in mosquito midgut epithelial cells. After several days of incubation, virions are produced and released in the mosquito general cavity named hemocele. With the haemolymph, viral particles disseminate and infect several internal organs and tissues. Finally, the virus reaches the salivary glands where it replicates and is excreted with saliva during blood feeding. Among many mosquito vectors that are able to transmit human pathogens, *Ae. aegypti* is a major vector for various arboviral diseases. As it is highly adapted to artificial containers, has an anthropophilic behaviour, and limited flight range, *Ae. aegypti* proliferates in human habitats where it intervenes in urban epidemics. *Ae. aegypti* is mainly present in tropical and subtropical regions of Africa, Asia, and America,[21] with a trend of rapid expansion due to the eggs resistance to desiccation[22] that facilitates long-distance transportation; it also contributed to the establishment of *Ae. aegypti* in Mediterranean Europe during the early 17th century to the mid-20th century, until its disappearance after 1950.[8] *Ae. aegypti* is an efficient vector for YFV transmission; accumulating studies have indicated that its vector competence for YFV depends on the combination of virus genotype and mosquito population.[23] In general, in the YFV epidemic regions, it is believed that African *Ae. aegypti* (from Kenya, South Africa, Guinea, and Capo Verde) were less susceptible to African YFV strains[24-27] compared to American *Ae. aegypti* (Brazil, Venezuela, and the USA) that are more susceptible to American genotypes.[26,28,29]

5.3 | *Aedes albopictus* as a potential vector of rural yellow fever virus transmission

YFV can be transmitted by *Aedes albopictus*; like *Ae. aegypti*, *Ae. albopictus* is also an invasive species. Native to Asia, *Ae. albopictus* has invaded the Americas from 1985 through two main routes: *via* Japan to North America, and *via* Southeast Asia (Cambodia, Vietnam, and Thailand) to South America. *Ae. albopictus* has similar geographical distribution to *Ae. aegypti* but can also be found in temperate regions.[21] In Caribbean countries, the presence of *Ae. albopictus* was firstly reported in the Dominican Republic in 1993,[30] and has reached several Caribbean countries since then, including Barbados,[31] Cayman Islands,[32] Cuba,[33] Haiti,[34] Jamaica,[35] and Trinidad.[36] Similar to those of *Ae. aegypti*, eggs of *Ae. albopictus* are resistant to desiccation, but in contrast to those of *Ae. aegypti*, eggs of *Ae. albopictus* are able to diapause ensuring a dispersion over long distances and a survival at low winter temperatures[37,38] In addition, *Ae. albopictus* is

able to colonize artificial and small natural breeding sites, and to feed on animals in the absence of humans as a blood source,[39] whereas *Ae. aegypti* is highly anthropophilic and adapted to artificial containers. Therefore, owing to its great ecological and physiological plasticity, *Ae. albopictus* is able to colonize both tropical and even temperate regions. Moreover, *Ae. albopictus* from Africa and America can transmit different strains of YFV.[26,28,40] On the field, YFV-infected *Ae. albopictus* was found at the edge of a forest in Brazil,[41] suggesting that *Ae. albopictus* has the potential to act as a bridge vector allowing YFV spillover events from the sylvatic cycle to the urban cycle where *Ae. aegypti* is predominant.

5.4 | Yellow fever virus transmission in Africa

Africa has been the historical epicentre of YF,[42] and is still contributing to more than 90% of clinical cases worldwide each year; in 2018, approximately 100,952 (95% credible interval [CrI] [63,001–158,362]) severe infections and 47,318 (95% CrI [29,126–74,981]) deaths were reported.[16,43,44] Although the mortality rate of YF in Africa is lower than in South America,[45] the recent massive YF outbreak in Angola during 2015–2016 still caused 375 deaths, and was then spread to countries such as Democratic Republic of Congo, Uganda, and even China.[46,47] In Africa, several *Aedes* spp. mosquito species are responsible for sylvatic, rural, and urban YFV transmission cycles, which increase the complexity of YFV control by breaking the transmission between each cycle. Forest canopy dwelling *Aedes* spp. mosquitoes such as *Aedes africanus*, *Aedes furcifer*, *Aedes taylori*, *Aedes luteocephalus*, and *Aedes opok*, are the major vectors for YFV transmission between NHPs in the jungle, whereas *Ae. aegypti*, *Ae. furcifer*, *Aedes vittatus*, *Aedes bromeliae*, and *Aedes keniensis* that feed on both NHPs and humans, are bridge vectors helping YFV to spill out of the sylvatic cycle.[48] Among these last mosquitoes, *Ae. aegypti* is the only species able to survive in urban areas and mediate YFV transmission among human populations. The situation has been worsened with climate change; an estimation of YF sylvatic spillover transmission based on a YF occurrence model and environmental factors in Africa, indicated that there will be 93.0%(95% confidence interval [CI] [92.7%, 93.2%]) chance of annual deaths to increase in 2050.[49]

5.5 | Yellow fever virus transmission in South America

In South America, *Haemagogus* spp. and *Sabethes* spp. are the mosquitoes that transmit YFV among NHPs in the sylvatic cycle,[50,51] and the major source of human infections come from a YFV sylvatic transmission in Brazil.[52] The recent YF epizootic in Brazil between 2016 and 2019 that initiated in Minas Gerais state, affected more than 15,000 NHPs in the forest and even caused 2251 human infections.[52] Evidence suggested that humans were infected from the sylvatic cycle only 4 days after an epizootic was declared.[53] Vaccination is still the prevention measure against YFV infection in South America, particularly in high-risk areas, even though it still cannot stop YFV sylvatic transmission during epizootics.[53,54] Unlike Africa, the rural cycle at the boundary between rural and urban cycles has an unclear status in South America. A competent mosquito vector could act as a bridge vector for a transmission of YFV from one transmission cycle to another. *Ae. albopictus* can play this role because of its both anthropophilic and zoophilic behaviour. This species can experimentally transmit YFV.[28] However, since the mosquito eradication campaigns organised in the early 20th century by the Rockefeller Foundation followed by the Pan-American Health Organization,[55] which likely had held off YFV urban transmission, YF only persists in a sylvatic cycle and no urban epidemics have been reported up to date.[53]

5.6 | Yellow fever virus transmission in the Caribbean

Vector-borne diseases played a significant geopolitical role during the colonial era in the Caribbean region. Started from Barbados in 1647, the Caribbean islands suffered from massive urban YF outbreaks.[1] It spread to Cuba, Guadeloupe, Jamaica, Martinique, and Saint Kitts.[1] From 1793 to 1798, in the British-dominated Santo Domingo (today Haiti) island, tropical diseases caused the death of about 12,700 British troops, and mostly were believed to be YF.[56] Later on, in 1804, the French troops lost 50,000–55,000 of soldiers in the island during the most serious epidemic of YF in the Caribbean history, leading to Santo Domingo's independence.[57] Concomitantly, YF indirectly led to the sale of Louisiana by Napoleon Bonaparte to the United States because of high human losses due to malaria and YF. Although the current YFV transmission in the Caribbean is still restricted to Trinidad where a sylvatic YFV transmission is ensured by *Haemagogous janthinomys* and *Sabethes chloropterus*,[10] growing exchanges between the Caribbean islands increase the risk of urban YFV. Moreover, the risk of YFV spillover transmission is also increased by the abundant distribution of *Ae. aegypti* and newly invaded *Ae. albopictus* in Trinidad.[36,58] Thus, YFV circulating in Trinidad was the cause of YFV epizootic in America in 1978–1980.[20]

5.7 | Yellow fever raged in Europe

The history of European YF epidemics has demonstrated the risk of YFV transmission in temperate regions with the presence of competent vectors. In the 19th century, Europe was affected by YF like in the Caribbean. Both YFV and *Ae. aegypti* were introduced as early as 18th century in Europe, mainly in port cities surrounding the Mediterranean Sea.[55] Outbreaks were reported in Spain (Barcelona, Gibraltar, Sevilla, Cadiz, Malaga), Portugal (Lisbon, Porto), France (Marseille, Brest, Saint-Nazaire, Rochefort, Bordeaux), and Italy (Livorno).[59] More than 3500 people died in Barcelona in 1821, and

more than 6000 in Lisbon in 1857.[60] After the 1950s, better management of water collections in cities and vector control with DDT, along with decrease in maritime traffic between harbours of Mediterranean countries could have contributed to eradicate *Ae. aegypti* from Europe.[7] Its last record was reported in Italy in 1971.[61] However, the mosquito can still be found in South Russia, West Georgia, and North Turkey,[62-64] with gaining ground towards the West.[63] Nonetheless, the estimation on the suitability of *Ae. aegypti* in the European region is low, as the minimum temperature and humidity do not reach the requirements of *Ae. aegypti* to establish sustainable populations.[65] The risk of YFV transmission carried out by *Ae. aegypti* in Europe is considerably low.

6 | THE EXCEPTION OF THE ASIA-PACIFIC REGION

6.1 | The Asian paradox

Even though 75% of global dengue disease burden are reported in the Asia-Pacific region in the last century,[66] YFV has never settled in Asia despite several opportunities of introduction. While historical records trace more clearly the introduction of YF in America *via* the slave trade, past interactions between Africa and Asia received much less attention.[67,68] The history of the slave trade from Africa to Asia can be traced back to 2900 B.C. in Egypt.[69] From the 17th to the 19th century when YFV was introduced into America, there were more than five million slaves transported to Asia, mostly to countries of the Indian Ocean and South Asia.[69] Furthermore, after the completion of the Panama Canal in the early 1900s which shortened the duration of travel between Latin America and Asia, many cities in the Asia-Pacific region were considered at high YFV transmission risk.[70] However, the concern regarding to YFV introduction through the Panama Canal to Asia was discussed, but no confirmed incident was ever reported except of a non-laboratory confirmed YF-like outbreak in Hong Kong in 1865–1866.[71] In 2016, 11 YFV-infected workers returned to China from Angola where a YFV outbreak was active.[72] Although these incidents were properly managed in China, the probability of priming an epidemic hitting millions of immunologically naive people caught the attention of the scientific community as experienced today with the COVID-19 pandemic.[73]

6.2 | Mosquito vectors in the Asia-Pacific region

Mosquito species should not be an obstacle for YFV transmission in the Asia-Pacific region where both *Ae. aegypti* and *Ae. albopictus* are abundant. Vector competence of Asian *Ae. aegypti* for YFV was successfully demonstrated in laboratory conditions early in 1929.[74] *Ae. aegypti* mosquitoes collected in Indonesia were susceptible to YFV from West Africa, and able to transmit YFV from an infected patient to monkeys. More recent studies showed that *Ae. aegypti* mosquitoes from Cambodia and Vietnam were more susceptible than Brazilian populations to the South America genotype I,[26] and an *Ae. aegypti* colony from Laos was also able to transmit the West Africa genotype I.[75] Moreover, a more extensive study analysing *Aedes* spp. from the Asian-Pacific region indicated that both *Ae. aegypti* and *Ae. albopictus* were susceptible to the West Africa genotype I; the *Ae. aegypti* from Cambodia, Vietnam, Laos, Thailand, Singapore, Taiwan, New Caledonia, and French Polynesia were able to transmit YFV, corroborating the status of competent vector assigned to *Ae. aegypti* from the Asia-Pacific region. On the contrary, *Ae. albopictus* mosquitoes from the region were less susceptible to YFV.[11]

7 | MOSQUITO MICROBIOTA CAN INFLUENCE MOSQUITO VECTOR COMPETENCE

Different mosquito genetic backgrounds in various geographical locations cannot solely explain the absence of YF in Asia-Pacific region, factors other than mosquito genetics that cause regional differences in endemic arboviral diseases are to be elucidated. The impact of mosquito microbiota in non-YF endemic regions on vector competence for YFV, is the next to be investigated to access the future risk of YFV transmission.

Accumulating studies have suggested mosquito microbiota can either directly or indirectly affect mosquito vector competence for arboviruses. From larval to adult stages, *Ae. aegypti* and *Ae. albopictus* acquire microbes vertically or from the environment, and harbour them in gut or other organs/tissues.[76-80] The composition of microbiota (mainly viruses and bacteria) changes with mosquito age, probably resulting from competition among symbionts for resources[77,81] or mosquito immunity[82] with effects on vector competence. Although the molecular mechanisms still need to be elucidated, accumulating evidence has indicated that insect-specific viruses (ISVs) influence mosquito immunity, with effects directly on viral replication and indirectly on mosquito microbiota leading to shape vector competence for arboviruses.[83-88] An example is Nhumirim virus (*Flaviviridae*) that was originally found in *Culex chidesteri*,[89] was able to reduce Zika virus (ZIKV) transmission but not chikungunya virus (CHIKV) in *Ae. aegypti*, suggesting a species-dependent manner for the interaction between ISVs and arboviruses in mosquitoes. Although not necessarily vertically transmitted, arboviruses are also part of mosquito virome and can also influence the vector competence.[90] *Ae. aegypti* is able to co-transmit CHIKV, DENV and ZIKV simultaneously, but the effects of one arbovirus on transmission of the other are not significant.[91] On the contrary, the impact of bacteria on mosquito vector competence has been extensively studied. Mosquito bacteria affect vector competence by inducing immune responses,[80,92-94] competing for nutritive resources,[95,96] producing secondary metabolites,[97,98] and even triggering RNAi immunity.[99,100] Among all mosquito symbionts, *Wolbachia* is the most intensively studied bacteria that suppresses YFV replication in *Ae. aegypti*,[101,102] even though the molecular mechanism is still unclear. The interactions between mosquito microbiota and arbovirus depends on the composition of microbiota

that a mosquito acquired from different environments. Thus, the microbiota diversity among geographic populations could be another factor that shapes the mosquito vector competence, and subsequently limiting the spreading of YFV.[103,104]

8 | DISCUSSION

Although competent vectors are abundantly present, the Asia-Pacific and Caribbean regions are still free of YF urban transmission. However, the growing international exchanges have once again raised the risks of YF spreading, threatening immunologically naïve populations. It is believed that to establish persistent transmission cycles, both sylvatic and urban, and repeated introductions of YF are critical as experienced in the past between Africa and America (Figure 2). The global expansion of the urban vector, *Ae. aegypti* has challenged the current prevention systems for YF in South America and the Caribbean, threatening them with urban YF outbreaks like in the past. In Trinidad, YFV circulates within a sylvatic cycle and has proved in the past to be able to escape from this jungle cycle.[20] This viral strain is responsible for the large outbreaks currently observed in South America, making this scenario more real than ever. In Asia, the air traffic between China and African nations has grown significantly in the last decades. The risk of YFV importation into China is considerably high as Guangzhou airport welcomes millions of passengers including those from YFV endemic countries, such as Ethiopia and Kenya.[105] Moreover, Guangzhou is the city where *Ae. albopictus* is abundantly distributed and has caused dengue fever outbreaks since 2013.[106] Fortunately, even though the environment favours YFV transmission, the YFV importation in 2016 did not lead to any autochthonous transmission. However, Guangzhou remains a city in Southeast Asia possessing the highest probability of YFV outbreaks.[107] Moreover, the distribution of the main YF vector *Ae. aegypti* is moving north and has reached southern China, in a region only 500 km away from Guangzhou.[108] As it is predicted that the environmental conditions in Guangzhou will become more suitable for *Ae. aegypti* in a few decades,[108] this renders the scenario more realistic than in 2016, and likely more possible than ever. Notably, *Ae. aegypti* and *Ae. albopictus* from the Asia-Pacific region are experimentally competent to transmit YFV. Thus, vector populations are seemingly not a brake to the emergence of YF in the region.[11] Likewise, in Asia, all the ingredients to fuel a sylvatic cycle are gathered with *Macaca* spp. monkeys being able to play the role of a YFV amplification host.[74,109,110] The establishment of a wild cycle could be a prerequisite for spillovers and human infections in Asia as it has been shown in South America (Figure 3).[53]

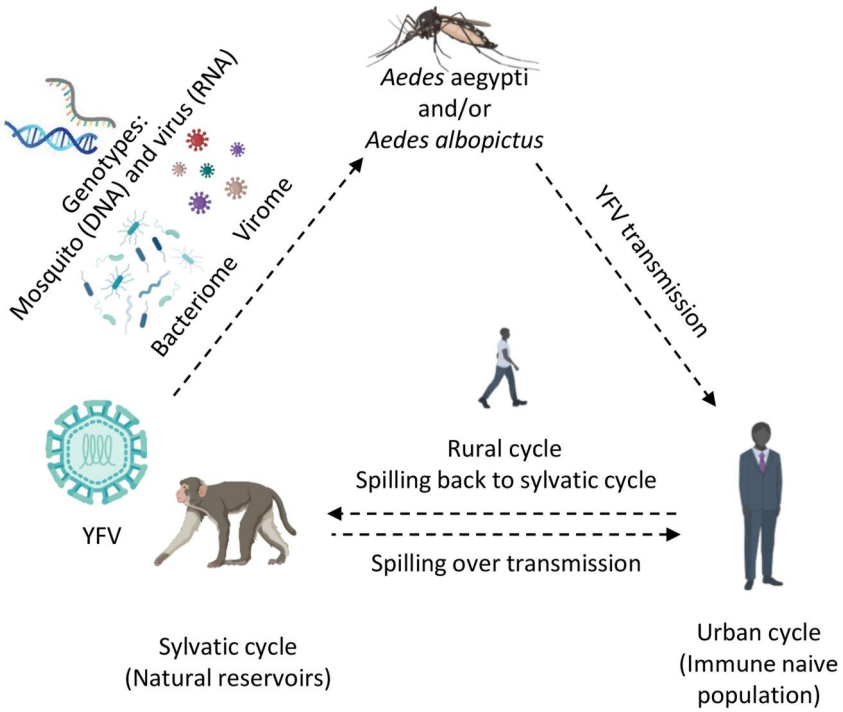

FIGURE 2 The mode of yellow fever (YF) sporadic urban outbreaks. *Aedes* mosquitoes are pivotal to initiate YF virus (YFV) urban outbreaks in non-epidemic areas, and potentially playing the role of bridge vector in rural areas, spilling YFV back to sylvatic cycle. YFV could be therefore circulating between mosquitoes and natural amplification hosts, until it spills over to rural and urban cycles to initiate a persistent outbreak. Mosquito and virus genotypes, bacteriome, and virome are factors that influence the risk of YFV urban transmission and are important targets for surveillance systems to prevent YF outbreak in a non-epidemic area. Icons in this figure were created with BioRender.com, or acquired from science clipart PNG designed by Morphart with Pngtree.com

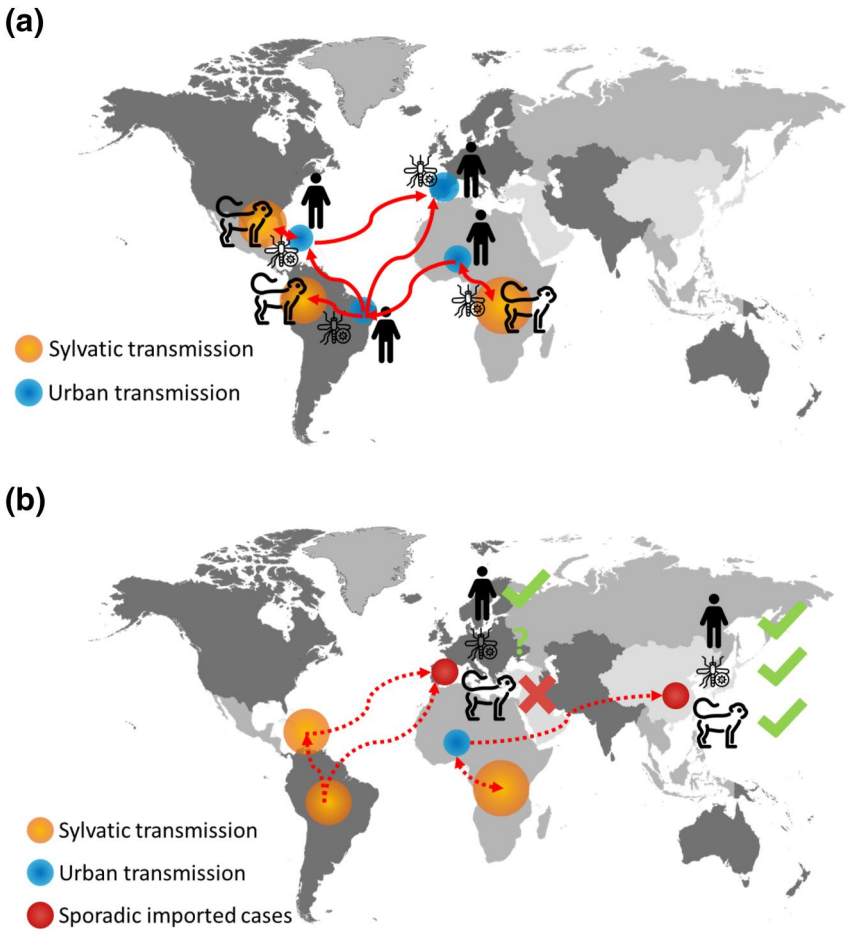

FIGURE 3 Yellow fever (YF) transmission cycles. (a) Past dynamics of transmission. (b) Risk of YF outbreaks in the future. Yellow fever virus (YFV) has two transmission cycles described in Africa and America: sylvatic and urban (the intermediate cycle being described only in Africa). The sylvatic cycle (also named jungle cycle) involves the transmission of YFV between non-human primates and zoophilic mosquitoes. The urban cycles involve the transmission of YFV between humans and anthropophilic mosquitoes, primarily *Aedes aegypti*. Today, outside Africa, only persists a sylvatic cycle in America. However, all components likely to favour YFV circulation in Asia are there, immunologically naïve human populations, competent mosquito vectors, and susceptible natural reservoir hosts, in contrast with Europe where there is no reservoir hosts and limited number of competent vectors for YFV. Solid arrows: the direction of YFV spreading in the past. Dashed arrows: the current risk of YFV spreading. The size of circles represents the probability of each transmission cycle to occur: the sylvatic transmission is more likely to occur than the urban and sporadic imported cases. World map in this figure is adapted from freepnglogos.com; the icons were designed by Voysla, Freepik, and kerismaker from Flaticon

Globalisation is changing the landscape of global arboviral diseases transmission and challenging the current circulation zone of each arbovirus. Therefore, local endemic viruses might have the chance to interact with introduced viruses from distinct geographic regions, which could change the virome of local mosquito populations, and subsequently affect the vector competence. YFV endemic to Africa and South America and Japanese encephalitis virus exclusively present in Asia, are both *Flaviviruses* that could be transmitted by *Ae. aegypti* in the Asia-Pacific region. Co-infections can occur either simultaneously or sequentially in mosquitoes with an outcome depending on interactions between arboviruses and ISV and microbial communities.

To conclude, the growth of international traffic and expansion of *Ae. aegypti* geographical distribution have posed YF urban outbreaks as a global threat to public health. While vaccination against YF remains the most effective method to limit YFV in endemic areas in response to an ongoing outbreak, mosquito vector surveillance and control are still playing a decisive role to break YFV transmission chain, before or even at the beginning of an outbreak. Information regarding the factors that are affecting mosquito vector competence for YFV could be more widely assessed and monitored as a component of a national surveillance programme. Insecticides are currently the main approach for mosquito control programme despite several other alternatives proposed to reduce the size of the

target population or replace the target population with a pathogen refractory strain. This can be achieved with *Wolbachia*-carrying and genetically modified mosquito control approaches.[111] To prevent a foreseeable urban YFV transmission, more investment should be made in mosquito vector surveillance and control programme, and vaccine development, in response to different YF transmission scenarios in the future.

ACKNOWLEDGMENTS

We thank Patricia Smiley for correcting English. This work was supported by the European Union's Horizon 2020 research and innovation program under (grant number 731060) (Infravec2, Research Infrastructures for the control of vector-borne diseases; http://infravec2.eu/), the Laboratoire d'Excellence "Integrative Biology of Emerging Infectious Diseases" (grant number ANR-10-LABX-62-IBEID), the European Union's Horizon 2020 research and innovation program under ZIKAlliance (grant number 734548), and the "Agence régionale de Santé de Martinique" (grant number DSP-2021-269/ARS Martinique).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Gaelle Gabiane contributed to the writing. Pei-Shi Yen was involved in the conceptualization and writing. Anna-Bella Failloux contributed to the conceptualization and writing.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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How to cite this article: Gabiane G, Yen P-S, Failloux A-B. Aedes mosquitoes in the emerging threat of urban yellow fever transmission. *Rev Med Virol*. 2022;e2333. https://doi.org/10.1002/rmv.2333